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Workers' Compensation Board

Medical Treatment Guidelines

Work-Related Depression and Depressive Disorders

Effective May 2, 2022

Contributors

The NYS Workers' Compensation Board would like to thank the members of the New York Workers' Compensation Board Medical Advisory Committee (MAC). The MAC served as the Board's advisory body to adapt the American College of Occupational and Environmental Medicine (ACOEM) Practice Guidelines to a New York version of the Medical Treatment Guidelines (MTG). In this capacity, the MAC provided valuable input and made recommendations to help guide the final version of these Guidelines. With full consensus reached on many topics, and a careful review of any dissenting opinions on others, the Board established the final product.

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A. General Guideline Principles

The principles summarized in this section are key to the intended application of the New York State Medical Treatment Guidelines (MTG) and are applicable to all Workers' Compensation Medical Treatment Guidelines.

A.1 Medical Care

Medical care and treatment required as a result of a work-related injury should be focused on restoring functional ability required to meet the patient's daily and work activities with a focus on a return to work, while striving to restore the patient's health to its pre-injury status in so far as is feasible.

A.2 Rendering Of Medical Services

Any medical provider rendering services to a workers' compensation patient must utilize the Treatment Guidelines as provided for with respect to all work-related injuries and/or illnesses.

A.3 Positive Patient Response

Positive results are defined primarily as functional gains which can be objectively measured. Objective functional gains include, but are not limited to, positional tolerances, range of motion, strength, endurance, activities of daily living (ADL), cognition, psychological behavior, and efficiency/velocity measures which can be quantified. Subjective reports of pain and function may be considered and given relative weight when the pain has anatomic and physiologic correlation in proportion to the injury.

A.4 Re-Evaluate Treatment

If a given treatment or modality is not producing positive results within a well-defined timeframe, the provider should either modify or discontinue the treatment regime. The provider should evaluate the efficacy of the treatment or modality 2 to 3 weeks after the initial visit and 3 to 4 weeks thereafter. These timeframes may be slightly longer in the context of conditions that are inherently mental health issues, and shorter for other non-musculoskeletal medical conditions (e.g. pulmonary, dermatologic etc.). Recognition that treatment failure is at times attributable to an incorrect diagnosis a failure to respond should prompt the clinician to reconsider the diagnosis in the event of an unexpected poor response to an otherwise rational intervention.

A.5 Education

Education of the patient and family, as well as the employer, insurer, policy makers and the community should be a primary emphasis in the treatment of work-related injury or illness. Practitioners should develop and implement effective educational strategies and skills. An education-based paradigm should always start with communication providing reassuring information to the patient. No treatment plan is complete without addressing issues of individual and/or

group patient education as a means of facilitating self-management of symptoms and prevention of future injury.

Time Frames

A.6 Acuity

Acute, Subacute and Chronic are generally defined as timeframes for disease stages:

- Acute – Less than one month
- Subacute - One to three month, and
- Chronic - greater than three months.

A.7 Initial Evaluation

Initial evaluation refers to the acute timeframe following an injury and is not used to define when a given physician first evaluates an injured worker (initial encounter) in an office or clinical setting.

A.8 Diagnostic Time Frames

Diagnostic time frames for conducting diagnostic testing commence on the date of injury. Clinical judgment may substantiate the need to accelerate or decelerate the time frames discussed in this document.

A.9 Treatment Time Frames

Treatment time frames for specific interventions commence once treatments have been initiated, not on the date of injury. It is recognized that treatment duration may be impacted by disease process and severity, patient compliance, as well as availability of services. Clinical judgment may substantiate the need to accelerate or decelerate the time frames discussed in this document.

A.10 Delayed Recovery

For those patients who fail to make expected progress 6-12 weeks after an injury and whose subjective symptoms do not correlate with objective signs and tests, reexamination in order to confirm the accuracy of the diagnosis and re-evaluation of the treatment program should be performed. When addressing a clinical issue that is not inherently a mental health issue, assessment for potential barriers to recovery (yellow flags/psychological issues) should be ongoing throughout the care of the patient. At 6-12 weeks, alternate treatment programs, including formal psychological or psychosocial evaluation should be considered. Clinicians must be vigilant for any pre-existing mental health issues or subsequent, consequential mental health issues that may be impacting recovery. For issues that are clearly and inherently mental health issues from the outset (i.e. when it is evident that there is an underlying, work-related, mental health disorder as part of the claim at issue), referral to a mental health provider can and should occur much sooner. Referrals to mental health providers for the evaluation and management of delayed recovery do not indicate or require the establishment of a psychiatric or psychological condition. The evaluation and management of

delayed recovery does not require the establishment of a psychiatric or psychological claim.

Treatment Approaches

A.11 Active Interventions

Active interventions emphasizing patient responsibility, such as therapeutic exercise and/or functional treatment, are generally emphasized over passive modalities, especially as treatment progresses. Generally, passive and palliative interventions are viewed as a means to facilitate progress in an active rehabilitation program with concomitant attainment of objective functional gains.

A.12 Active Therapeutic Exercise Program

Active therapeutic exercise program goals should incorporate patient strength, endurance, flexibility, range of motion, sensory integration, coordination, cognition and behavior (when at issue) and education as clinically indicated. This includes functional application in vocational or community settings.

A.13 Diagnostic Imaging And Testing Procedures

Clinical information obtained by history taking and physical examination should be the basis for selection of imaging procedures and interpretation of results. All diagnostic procedures have characteristic specificities and sensitivities for various diagnoses. Usually, selection of one procedure over others depends upon various factors, which may include: relative diagnostic value; risk/benefit profile of the procedure; availability of technology; a patient's tolerance; and/or the treating practitioner's familiarity with the procedure.

When a diagnostic procedure, in conjunction with clinical information, provides sufficient information to establish an accurate diagnosis, a second diagnostic procedure is not required. However, a subsequent diagnostic procedure including a repeat of the original (same) procedure can be performed, when the specialty physician (e.g. physiatrist, sports medicine physician or other appropriate specialist) radiologist or surgeon documents that the initial study was of inadequate quality to make a diagnosis. Therefore, in such circumstances, a repeat or complementary diagnostic procedure is permissible under the MTG.

It is recognized that repeat imaging studies and other tests may be warranted by the clinical course and/or to follow the progress of treatment in some cases. It may be of value to repeat diagnostic procedures (e.g., imaging studies) during the course of care to reassess or stage the pathology when there is progression of symptoms or findings, prior to surgical interventions and/or therapeutic injections when clinically indicated, and post-operatively to follow the healing process. Regarding serial imaging, (including x-rays, but particularly CT scans), it must be recognized that repeat procedures result in an increase in cumulative radiation dose and associated risks.

A given diagnostic imaging procedure may provide the same or distinctive

information as obtained by other procedures. Therefore, prudent choice of procedures(s) for a single diagnostic procedure, a complementary procedure in combination with other procedures(s), or a proper sequential order in multiple procedures will ensure maximum diagnostic accuracy, minimize the likelihood of adverse effect on patients, and promote efficiency by avoiding duplication or redundancy.

A.14 Surgical Interventions

Consideration of surgery should be within the context of expected functional outcome. The concept of "cure" with respect to surgical treatment by itself is generally a misnomer. All operative interventions must be based upon positive correlation of clinical findings, clinical course and imaging and other diagnostic tests. A comprehensive assimilation of these factors must lead to a specific diagnosis with positive identification of pathologic condition(s). For surgery to be performed to treat pain, there must be clear correlation between the pain symptoms and objective evidence of its cause. In all cases, shared decision making with the patient is advised. The patient should be given the opportunity to understand the pros and cons of surgery, potential for rehabilitation as an alternative where applicable, evidence-based outcomes, and specific surgical experience.

A.15 Pre-Authorization

All diagnostic imaging, testing procedures, non-surgical and surgical therapeutic procedures, and other therapeutics within the criteria of the Medical Treatment Guidelines and based on a correct application of the Medical Treatment Guidelines are considered authorized, with the exception of the procedures listed in section 324.3(1)(a) of Title 12 NYCRR. These are not included on the list of pre-authorized procedures. Providers who want to perform one of these procedures must request pre-authorization from the carrier before performing the procedure.

Second or subsequent procedures (the repeat performance of a surgical procedure due to failure of, or incomplete success from the same surgical procedure performed earlier, if the Medical Treatment Guidelines do not specifically address multiple procedures) also require pre-authorization.

A.16 Psychological/Psychiatric Evaluations

In select patients, mental health evaluations are essential to make, secure or confirm a diagnosis. Of course, the extent and duration of evaluations and/or interventions by mental health professionals may vary, particularly based on whether: the underlying clinical issue in the claim is inherently a mental health issue; or there is a mental health issue that is secondary or consequential to the medical injury or illness that is at issue in the claim in question; or there is a pre-

existing, unrelated mental health issue that has been made worse by, or is impeding the recovery from (or both) the medical injury or illness that is at issue in the claim in question.

Tests of psychological function or psychometric testing, when indicated, can be a valuable component of the psychological evaluation in identifying associated psychological, personality and psychosocial issues. Although these instruments may suggest a diagnosis, neither screening nor psychometric tests are capable of making a diagnosis. The diagnosis should only be made after careful analysis of all available data, including from a thorough history and clinical interview.

A professional fluent in the primary language of the patient is strongly preferred. When such a provider is not available, services of a professional language interpreter must be provided.

Frequency: When assessing for a pre-existing, unrelated mental health issue that has been made worse by, or is impeding the recovery from (or both) a work-related, medical injury or illness, then a one-time visit for initial psychiatric/psychological encounter should be sufficient, as care would normally be continued by the prior treating provider. If psychometric testing is indicated by findings in the initial encounter, time for such testing should not exceed an additional three hours of professional time. For conditions in which a mental health issue is a central part of the initial claim, or in which there is a mental health issue that is secondary or consequential to the work-related, medical injury or illness, that is part of the claim in question, then more extensive diagnostic and therapeutic interventions may be clinically indicated, and are discussed in detail in the Medical Treatment Guidelines for such mental health conditions.

A.17 Personality/Psychological/Psychosocial Intervention

Following psychosocial evaluation, when intervention is recommended, such intervention should be implemented as soon as possible. This can be used alone or in conjunction with other treatment modalities. For all psychological/psychiatric interventions, there must be an assessment and treatment plan with measurable behavioral goals, time frames and specific interventions planned**.**

- Time to produce effect: two to eight weeks.
- Optimum duration: six weeks to three months.
- Maximum duration: three to six months.
- Counseling is not intended to delay but rather to enhance functional recovery.

For PTSD Psychological Intervention:

- Optimum duration three to six months.
- Maximum duration: nine to twelve months.

For select patients, longer supervision and treatment may be required, and if further treatment is indicated, documentation of the nature of the psychological factors, as well as projecting a realistic functional prognosis, should be provided by the authorized treating practitioner every four weeks during the first six months of treatment. For treatment expected to last six to twelve months, such documentation should be provided every four to eight weeks. For long-term treatment beyond twelve months, such documentation should be provided every eight to twelve weeks. All parties should strive for ongoing and continuous communications, in order to facilitate seamless, continuous and uninterrupted treatment.

A.18 Functional Capacity Evaluation (FCE)

Functional capacity evaluation is a comprehensive or more restricted evaluation of the various aspects of function as they relate to the patient's ability to return to work. Areas such as endurance, lifting (dynamic and static), postural tolerance, specific range-of-motion, coordination and strength, worker habits, employability, as well as psychosocial, cognitive, and sensory perceptual aspects of competitive employment may be evaluated. Components of this evaluation may include: (a) musculoskeletal screen; (b) cardiovascular profile/aerobic capacity; (c) coordination; (d) lift/carrying analysis; (e) job-specific activity tolerance; (f) maximum voluntary effort; (g) pain assessment/psychological screening; (h) non-material and material handling activities; (i) cognitive and behavioral; (j) visual; and (k) sensory perceptual factors.

In most cases, the question of whether a patient can return to work can be answered without an FCE.

An FCE may be considered at time of MMI, following reasonable prior attempts to return to full duty throughout course of treatment, when the treating physician is unable to make a clear determination on work status on case closure. An FCE is not indicated early during a treatment regime for any reason including one to support a therapeutic plan.

When an FCE is being used to determine return to a specific job site, the treating physician is responsible for understanding and considering the job duties. FCEs cannot be used in isolation to determine work restrictions. The authorized treating physician must interpret the FCE in light of the individual patient's presentation and medical and personal perceptions. FCEs should not be used as the sole criteria to diagnose malingering.

A.19 Return To Work

For purposes of these guidelines, return to work is defined as any work or duty that the patient is able to perform safely. It may not be the patient's regular work. Ascertaining a return to work status is part of medical care, and should be included in the treatment and rehabilitation plan. It is normally addressed at every outpatient visit. A description of the patient's status and task limitations is part of any treatment plan and should provide the basis for restriction of work activities when warranted. Early return to work should be a prime goal in treating

occupational injuries. The emphasis within these guidelines is to move patients along a continuum of care and return to work, since the prognosis of returning an injured worker to work drops progressively the longer the worker has been out of work.

A.20 Job Site Evaluation

The treating physician may communicate with the employer or employer's designee, either in person, by video conference, or by telephone, to obtain informationregarding the individual or specific demands of the patient's pre-injury job. This may include a description of the exertional demands of the job, the need for repetitive activities, load lifting, static or awkward postures, environmental exposures, psychological stressors and other factors that would pose a barrier to re-entry, risk of re-injury or disrupt convalescence. When returning to work at the patient's previous job tasks or setting is not feasible, given the clinically determined restrictions on the patient's activities, inquiry should be made about modified duty work settings that align with, the patient's condition in view of proposed work activities/demands in modified duty jobs. It should be noted, that under certain circumstances, more than one job site evaluation may be indicated.

Ideally, the physician would gain the most information from an on-site inspection of the job settings and activities; but it is recognized that this may not be feasible in most cases. If job videos/CDs/DVDs are available from the employer, these can contribute valuable information, as can video conferences, conducted from the worksite and ideally workstation or work area.

Frequency: one or two contacts

- 1st contact: Patient is in a functional state where the patient can perform some work.
- 2nd contact: Patient has advanced to state where the patient is capable of enhanced functional demands in a work environment.

The physician shall document the conversation.

Other

A.21 Guideline Recommendations And Medical Evidence

The Workers' Compensation Board and its Medical Advisory Committee have not independently evaluated or vetted the scientific medical literature used in support of the guidelines, but have relied on the methodology used by the developers of various guidelines utilized and referenced in these Guidelines.

A.22 Experimental/Investigational Treatment

Medical treatment that is experimental/investigational and not approved for any purpose, application or indication by the FDA is not permitted under these Guidelines.

A.23 Injured Workers As Patients

In these Guidelines, injured workers are referred to as patients recognizing that in certain circumstances there is no doctor-patient relationship.

A.24 Scope Of Practice

These Guidelines do not address scope of practice or change the scope of practice.

Work-Related Depression and Depressive Disorders

Effective date will coincide with the launch of OnBoard: Limited Release

B. Introduction to Work-Related Depression and Depressive Disorders

Work-related depression and depressive disorders (DDD) may include a wide array of diagnoses, including but not necessarily limited to Major Depressive Disorder, Depressive Disorder Due to Another Medical Condition, Adjustment Disorder and Substance/Medication-Induced Depressive Disorder.

Each of these conditions have distinguishing characteristics, and inclusion of all of them in this guideline (for purposes of thoroughness) is not intended to imply that they are all the same, or that they can all be treated in exactly the same manner. Rather, these guidelines will provide the definitions of each of these disorders, briefly explain their distinctions, and then provide a discussion of various diagnostic and therapeutic modalities that may prove clinically effective, if applied appropriately in the given context.

The essential features of a major depressive episodes are a period of at least two weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. A diagnosis based on a single episode is possible, although the disorder is generally recurrent.

Major Depressive Disorder (MDD) involves multiple symptoms of depression that persist and significantly interfere with normal social and/or occupational functioning. Examples of symptoms include depressed mood, reduced interests or pleasure, weight changes, sleep disruption, fatigue, and reduced ability to think. Suicidal thoughts or attempts may occur.

Depressive Disorder Due to Another Medical Condition is characterized by: a prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture; evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition; no evidence that the disturbance is not better explained by another mental disorder; the disturbance does not occur exclusively during the course of a delirium; and the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The DSM-5 defines **Adjustment Disorder** as “the presence of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within three months of the onset of the stressor(s).” (American Psychiatric Association, 2013)

The DSM-5 Diagnostic Criteria for **Substance/Medication-Induced Depressive Disorder** include: prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities; evidence from the history, physical examination, or laboratory findings of BOTH onset of the depressive symptoms during or soon after substance intoxication or withdrawal or after exposure to a medication, AND the involved substance/medication is capable of producing the symptoms; the disturbance is not better explained by a depressive disorder that is not substance/medication-induced; the disturbance does not occur exclusively during the course of a delirium; and the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

B.1 History and Examination

Establishing a working diagnosis in a patient with depressive symptoms entails a focused clinical interview, physical examination, and pertinent laboratory and other testing with an eye toward identifying remediable co-occurring conditions or alternative diagnoses. DSM-5 criteria should be used to diagnose DDD. Co-occurring conditions or experiences do not preclude a diagnosis of DDD yet are important in treatment planning. Physical examination supports the clinical interview and mental status exam with attention to any neurologic deficits, evidence of endocrine or other metabolic disease or systemic illness. Laboratory testing is performed as clinically indicated. Useful tests may include thyroid studies (thyroid-stimulating hormone [TSH]), complete blood count (CBC), chemistry profile, pregnancy screen, and/or toxicology panel. Use of a structured instrument such as the Patient Health Questionnaire (PHQ) 9 can facilitate the collection of information required to diagnosis DDD based on DSM criteria, establishing a quantifiable baseline severity of symptoms that can also be used for tracking treatment response.

B.2 Diagnosis

Table 1: DSM 5 Diagnostic Criteria for Major Depressive Disorder (MDD)
Criterion A: Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Note: Do not include symptoms that are clearly attributable to another medical condition.
Criterion B: The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Criterion C: The episode is not attributable to the physiological effects of a substance or to another medical condition.
Criterion D: The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
Criterion E: There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.
Note: Criterion A through C represent a major depressive episode

Table 2: DSM 5 Diagnostic Criteria for Depressive Disorder Due to Another Medical Condition
Criteria A: A prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture.
Criteria B: There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
Criteria C: The disturbance is not better explained by another mental disorder (e.g., adjustment disorder, with depressed mood, in which the stressor is a serious medical condition).
Criteria D: The disturbance does not occur exclusively during the course of a delirium.
Criteria E: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. *Specifically, if:* • **With depressive features**: Full criteria are not met for a major depressive episode. • **With major depressive-like episode**: Full criteria are met (except criterion C) for a major depressive episode. • **With mixed features:** Symptoms of mania or hypomania are also present but do not predominate in the clinical picture.
Differential Diagnosis
Depressive disorders not due to another medical condition Determination of whether a medical condition accompanying a depressive disorder is causing the disorder depends on a) the absence of an episode(s) of depressive episodes prior to the onset of the medical condition, b) the probability that the associated medical condition has a potential to promote or cause a depressive disorder, and c) a course of the depressive symptoms shortly after the onset or worsening of the medical condition, especially if the depressive symptoms remit near the time that the medical disorder is effectively treated or remits.
Medication-induced depressive disorder An important caveat is that some medical conditions are treated with medications (e.g., steroids or alpha-interferon) that can induce depressive or manic symptoms. In these cases, clinical judgement, based on all the evidence in hand, is the best way to try to separate the most likely and/or the most important of two etiological factors (i.e., association with the medical condition vs. a substance-induced syndrome).
Adjustment disorders It is important to differentiate a depressive episode from an adjustment disorder, as the onset of the medical condition is in itself a life stressor that could bring on either an adjustment disorder or an episode of major depression. The major differentiating elements are the pervasiveness the depressive picture and the number and quality of the depressive symptoms that the patient reports or demonstrates on the mental status examination. The differential diagnosis of the associated medical conditions is relevant but largely beyond the scope of the present manual.

Table 3: DSM 5 Diagnostic Criteria for Adjustment Disorders
Criteria A: The development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).

Criteria B: These symptoms or behaviors are clinically significant, as evidenced by one or both of the following:

1. Marked distress that is out of proportion to the severity or intensity of the stressor, taking into account the external context and the cultural factors that might influence symptom severity and presentation.
2. Significant impairment in social, occupational, or other important areas of functioning.

Criteria C: The stress-related disturbance does not meet the criteria for another mental disorder and is not merely an exacerbation of a preexisting mental disorder.

Criteria D: The symptoms do not represent normal bereavement.

Criteria E: Once the stressor or its consequences have terminated, the symptoms do not persist for more than an additional 6 months.

Specify whether:

- **With depressed mood**: Low mood, tearfulness, or feelings of hopelessness are predominant.
- **With anxiety**: Nervousness, worry, jitteriness, or separation anxiety is predominant.
- **With mixed anxiety and depressed mood**: A combination of depression and anxiety is predominant.
- **With disturbance of conduct**: Disturbance of conduct is predominant.
- **With mixed disturbance of emotions and conduct**: Both emotional symptoms (e.g., depression, anxiety) and a disturbance of conduct are predominant.
- **Unspecified**: For maladaptive reactions that are not classifiable as one of the specific subtypes of adjustment disorder.

Differential Diagnosis

Major depressive disorder
If an individual has symptoms that meet criteria for a major depressive disorder in response to a stressor, the diagnosis of an adjustment disorder is not applicable. The symptom profile of major depressive disorder differentiates it from adjustment disorders.

Posttraumatic stress disorder and acute stress disorder
In adjustment disorders, the stressor can be of any severity rather than of the severity and type required by Criterion A of acute stress disorder and posttraumatic stress disorder (PTSD). In distinguishing adjustment disorders from these two posttraumatic diagnoses, there are both timing and symptom profile considerations. Adjustment disorders can be diagnosed immediately and persist up to 6 months after exposure to the traumatic event, whereas acute stress disorder can only occur between 3 days and 1 month of exposure to the stressor, and PTSD cannot be diagnosed until at least 1 month has passed since the occurrence of the traumatic stressor. The required symptoms profile for PTSD and acute stress disorder differentiates them from the adjustment disorders. With regard to symptoms profiles, an adjustment disorder may be diagnosed following a traumatic event when an individual exhibits symptoms of either acute stress disorder or PTSD that do not meet or exceed the diagnostic threshold for either disorder. An adjustment disorder should also be diagnosed for individuals who have not been exposed to a traumatic event but who otherwise exhibit the full symptom profile of either acute stress disorder or PTSD.

Personality disorders
With regard to personality disorders, some personality features may be associated with a vulnerability to situational distress that may resemble an adjustment disorder. The lifetime history of personality functioning will help inform the interpretation of distressed behaviors to aid in distinguishing a long-standing personality disorder from an adjustment disorder. In addition to some personality disorders incurring vulnerability to distress, stressors may also exacerbate personality disorder symptoms. In the presence of a personality disorder, if the symptom criteria for an adjustment disorder are met, and the stress-related disturbance exceeds what may be attributable to maladaptive personality disorder symptoms (i.e., Criterion C is met), then the diagnosis of an adjustment disorder should be made.

Psychological factors affecting other medical conditions In psychological factors affecting other medical conditions, specific psychological entities (e.g., psychological symptoms, behaviors, other factors) exacerbate a medical condition. These psychological factors can precipitate, exacerbate, or put an individual at risk for medical illness, or they can worsen an existing condition. In contrast, an adjustment disorder is a reaction to the stressor (e.g., having a medical illness).
Normative stress reactions When bad things happen, most people get upset. This is not an adjustment disorder. The diagnosis should only be made when the magnitude of the distress (e.g., alterations in mood, anxiety, or conduct) exceeds what would normally be expected (which may vary in different cultures) or when the adverse event precipitates functional impairment.

Table 4: DSM 5 Diagnostic Criteria for Substance/Medication Induced Depression
Criteria A: A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.
Criteria B: There is evidence from the history, physical examination, or laboratory findings of both (1) and (2): 1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication. 2. The involved substance/medication is capable of producing the symptoms in Criterion A.
Criteria C: The disturbance is not better explained by a depressive disorder that is not substance/medication-induced. Such evidence of an independent depressive disorder could include the following: • The symptoms preceded the onset of the substance/medication use. • The symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication. • There is other evidence suggesting the existence of an independent non-substance/medication-induced depressive disorder (e.g., a history of recurrent non-substance/medication-related episodes).
Criteria D: The disturbance does not occur exclusively during the course of a delirium.
Criteria E: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Notes
Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention. **Note**: If a mild substance use disorder is comorbid with the substance-induced depressive disorder, the clinican should record "mild [substance] use disorder" before the substance-induced depressive disorder (e.g., mild cocaine use disorder with cocaine-induced depressive disorder"). If a moderate or severe substance use disorder is comorbid with the substance-induced depressive disorder, the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder, then the clinician should record only the substance-induced depressive disorder. *Specify* if:

- **With onset during intoxication**: If criteria are met for intoxication with the substance and the symptoms develop during intoxication.

- **With onset during withdrawal**: If criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.

Recording Procedures

The name of the substance/medication-induced depressive disorder begins with the specific substance (e.g., cocaine, dexamethasone) that is presumed to be causing the depressive symptoms. In cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word "with," followed by the name of the substance-induced depressive disorder, followed by the specification on onset (i.e., onset during intoxication, onset during withdrawal). For example, in the case of depressive symptoms occurring during withdrawal in a man with a severe cocaine use disorder, the diagnosis is severe cocaine use disorder with cocaine-induced depressive disorder, with onset during withdrawal. A separate diagnosis of the comorbid severe cocaine use disorder is not given. If the substance-induced depressive disorder occurs without a comorbid substance use disorder (e.g., after a one-time heavy use of the substance), no accompanying substance use disorder is noted (e.g., phencyclidine-induced depressive disorder, with onset during intoxication). When more than one substance is judged to play a significant role in the development of depressive mood symptoms, each should be listed separately (e.g., severe methylphenidate use disorder with methylphenidate-induced depressive disorder, with onset during withdrawal; dexamethasone-induced depressive disorder, with onset during intoxication).

Differential Diagnosis

Substance intoxication and withdrawal
Depressive symptoms occur commonly in substance intoxication and substance withdrawal, and the diagnosis of substance-specific intoxication or withdrawal will usually suffice to categorize the symptom presentation A diagnosis of substance-induced depressive disorder should be made instead of a diagnosis of substance intoxication or substance withdrawal when the mood symptoms are sufficiently severe to warrant independent clinical attention. For example, dysphoric mood is a characteristic feature of cocaine withdrawal. Substance/medication-induced depressive disorder should be diagnosed instead of cocaine withdrawal only if the mood disturbance is substantially more intense or longer lasting than what is usually encountered with cocaine withdrawal and is sufficiently severe to be a separate focus of attention and treatment.

Primary depressive disorder
A substance/medication-induced depressive disorder is distinguished from a primary depressive disorder by the fact that a substance is judged to be etiologically related to the symptoms.

Depressive disorder due to another medical condition
Because individuals with other medical conditions often take medications for these conditions, the clinician must consider the possibility that the mood symptoms are caused by the physiological consequences of the medical condition rather than the medication, in which case depressive disorder due to another medical condition is diagnosed. The history often provides the primary bases for such a judgement. At times, a change in the treatment for the other medical condition (e.g., medication substitution or discontinuation) may be needed to determine empirically whether the medication is the causative agent. If the clinician has ascertained that the disturbance is a function of both another medical condition and substance use or withdrawal, both diagnoses (i.e., depressive disorder due to another medical condition and substance/medication-induced depressive disorder) may be given. When there is insufficient evidence to determine whether the depressive symptoms are associated with substance (including a medication) ingestion or withdrawal or with another medical condition or are primary (i.e., not a function of either a substance or another medical condition), a diagnosis of other specified depressive disorder or unspecified depressive disorder would be indicated.

B.2.a DSM-IV versus DSM-5: Clinical Practice Guideline Implications

When the diagnosis of DDD has been made under the DSM-IV criteria, prior to the publication of DSM-V criteria, these DDD Treatment Guidelines apply to the care of the worker.

Diagnosis of DDD subsequent to the publication of the DSM-V criteria must be consistent with the DSM-V criteria.

Summary: An injured worker with a prior diagnosis of DDD under DSM-IV maintains the diagnosis of DDD and should receive care consistent with these guidelines

B.3 Overview – Evaluation and Management

B.3.a Screening and Monitoring

While there are other tools, the PHQ-9 is an acceptable, cross- culturally validated and easy to use tool for screening, measuring and monitoring of severe depression.

Additionally, PHQ-9 can be utilized for screening patients with DDD for suicide risk and the potential need for urgent/emergent mental health intervention. When screening or monitoring with the PHQ-9, attention should be paid to the last item ("Thoughts that you would be better off dead or of hurting yourself in some way?"), as it has been associated with increased risk for a suicide attempt.

Table 5:
Nine Symptom Checklist (PHQ-9)

	Over the last two weeks, how often have you been bothered by any of the following?	Not at all	Several days	More than half the days	Nearly every day
A	Little interest or pleasure in doing things?	0	1	2	3
B	Feeling down, depressed, or hopeless	0	1	2	3
C	Trouble falling or staying asleep, or sleeping too much?	0	1	2	3
D	Feeling tired or having little energy?	0	1	2	3
E	Poor appetite or overeating?	0	1	2	3
F	Feeling bad about yourself – or that you are a failure or have let yourself or your family down?	0	1	2	3
G	Trouble concentrating on things, such as reading the newspaper or watching television?	0	1	2	3
H	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual?	0	1	2	3
I	Thoughts that you would be better off dead or of hurting yourself in some way?	0	1	2	3
For office coding: Total Score=_____+_____+_____+_____					

Table 6: Classification of MDD Symptoms Severity and Risk Factors

Total Score	Depression Severity
1-4	Minimal Depression
5-9	Mild Depression
10-14	Moderate Depression
15-19	Moderately Severe Depression
20-27	Severe Depression

From Kroenke K, Spitzer RL, Psychiatric Annals 2002; 32:509-521

Clinical monitoring should include assessment of symptomatology adherence to medication and psychotherapy, emergence of adverse effects, symptom breakthrough, suicidality, psychosocial stress and the completion of the PHQ-9.

The PHQ-9 is utilized to monitor clinical depression over time. The results can be discussed with the patient to demonstrate improvement in symptoms.

Psychometric testing may follow a positive result from a screen. While screening and psychometric tests may suggest a diagnosis, neither are capable of making a diagnosis. The diagnosis should only be concluded after careful analysis of all available data, including from a thorough history and/or clinical interview.

B.3.b Treatment Overview

In general, first-line treatment for acute uncomplicated DDD is either cognitive behavioral therapy or pharmacotherapy with anti-depressants. For DDD due to other medical conditions, substances or medications, it is critical that the underlying cause of the DDD be addressed.

Combined CBT and antidepressant treatment may be indicated; (1) when therapy with either CBT or an antidepressant does not result in improvement or resolution of symptoms in acute, mild/ moderate uncomplicated or severe DDD, or (2) in severe (i.e., PHQ-9 >20) or complicated DDD. ECT may be indicated in treatment resistant DDD. If a given treatment approach has not resulted in improvement in depressive symptoms, the treatment plan should be reevaluated.

B.3.b.i Cognitive Behavioral Therapy (CBT)

Cognitive-behavioral therapy (CBT) is one of the established nonpharmacological treatments for major depressive disorder. It is been demonstrated that a 12 to16 weeks course of individual CBT has efficacy comparable to antidepressant pharmacotherapy for mild to moderate depressive episodes, with fewer relapses after treatment is stopped. CBT also may significantly improve treatment outcomes when used in combination with pharmacotherapy, especially for patients with more severe or treatment-resistant depressive disorders. Despite compelling justification for use of CBT, there are

significant barriers to providing this form of therapy including limited availability and access to trained therapists. These limitations help explain why antidepressant pharmacotherapy, not CBT, continues to be the most commonly used treatment for depressive disorders.

CBT must address workplace issues/barriers and set RTW goals as part of the treatment plan. It includes a variety of component therapies such as Acceptance and Commitment Therapy (ACT), Mindfulness, Behavioral Therapy/Behavioral Activation (BT/BA) and Interpersonal Therapy.

Treatment frequency and duration may vary, based on case-specific circumstances. The healthcare provider must provide medical explanation and/or justification for deviation in frequency/duration from these guidelines. While this documentation is typically provided on a monthly basis during the acute phase of illness, for patients who have transitioned to a long-term, chronic phase of illness, and who are stable on existing treatment, this medical documentation can be provided every two to three months, in conjunction with regular clinical follow-up at those intervals. Care should be taken that such longer periods between clinic visits and reporting do not result in gaps in care.

B.3.b.ii Pharmacotherapy

Note: It is vitally important that prescribers appreciate the potential for drug-drug interactions and the potential for just one new prescription to significantly increase the likelihood that a patient will experience adverse side-effects when multiple medications are being prescribed. This particularly true for any medication that is potentially sedating, a respiratory depressant, habit forming or addictive. Therefore, extreme caution should be exercised whenever one is considering prescribing more than one medication with these properties.

Note: For patients with certain long-term psychiatric illnesses, who are on stable doses of ongoing pharmacologic therapy, stable and uninterrupted dosing can be critical. Therefore, when clinically appropriate, prescribers may consider writing prescriptions with two to six monthly refills, in order to reduce the likelihood of prescriptions expiring in-between monthly to tri-monthly follow-up appointments.

The major classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCAs),

atypical antidepressants, and monoamine oxidase inhibitors (MAOIs). TCAs and MAOIs are older antidepressants. They are effective however their tolerability, adverse effects, and safety profiles, often make them less acceptable than first-line antidepressants, such as the SSRIs or SNRIs.

There is no evidence to suggest that one antidepressant drug class is superior to another for the treatment of DDD in terms of response and remission rates. Initial monotherapy with an SNRI, or an SSRI provides the best options for patients who do not have contraindications to these medications. The therapeutic benefits of these medications typically take two to four weeks to appear. The choice of anti-depressants should be based on safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses and concurrently prescribed medications.

B.4 Screening and Testing

B.4.a Screening Tools

Recommended – PHQ-9 for the identification of potential depressive disorders.

Indications - Patients at risk of depressive disorders PHQ9 may not be necessary if clinical judgement is sufficient to establish the diagnosis.

Benefits - Earlier identification of potential depressive disorders, assists with directing the patient to appropriate mental health services that include diagnostic confirmation and suicide prevention.

Frequency/Dose/Duration - Generally only one administration. Repeat screening may be clinically indicated if there is a change in symptoms. However, routine screening is not recommended.

Clinical correlation is required. While screening tools may suggest a diagnosis of DDD, neither screening nor psychometric tests are capable of making a diagnosis. The diagnosis can only be made after careful evaluation of all available data, including a thorough history and clinical interview.

Evidence for the Use of Screening Tools

B.4.a.i Monitoring

Recommended: PHQ-9, combined with clinical indicators, to monitor treatment progress (assess depressive symptoms and symptom severity) in DDD.

Indication - After initiation of therapy or a change in treatment, patients with DDD should be monitored at least monthly to track response/progress until remission is achieved.

Remission is defined as a PHQ-9 score of four or less, maintained for at least one month. In patients who reach remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence, and potential suicide risk.

Rationale - Since treatment is guided by the severity of depression, the PHQ-9 score can be very helpful to the clinician in monitoring the response to treatment. At minimum, monitoring should include an assessment of symptoms, completion of PHQ-9, adherence to medication and psychotherapy, and emergence of adverse effects.

B.4.b Psychometric Testing

Recommended – for individuals presenting with signs and symptoms consistent with DDD, where, in the judgement of the clinician, an evaluation indicates the potential for comorbid psychiatric conditions such as anxiety disorders, bipolar, substance use disorders.

Indication- to identify those patients with signs and symptoms of DDD and potential relevant comorbid psychiatric conditions and to assist in directing the patient to appropriate mental health services.

Benefits - Provide psychometric evidence as a component of an evaluation regarding potential for depressive disorders and for other mental health disorder(s).

Frequency/Dose/Duration - One-time testing unless otherwise indicated (e.g. significant changes in symptoms). Requires administration by a professionally trained mental health professional.

Rationale - Clinical correlation is required. While these instruments may suggest a diagnosis, neither screening nor psychometric tests are capable of making a diagnosis. The diagnosis can only be made after careful clinical evaluation of all available data, including a thorough history and clinical interview.

Evidence for the Use of Psychometric Testing

B.4.c Pharmacogenomics Testing

Recommended – for select patients with Major Depressive Disorders (MDD).

Indications - Select patients with moderate or severe MDD who are resistant to treatment despite the prior use of multiple antidepressants and/or have repeated intolerance of anti-depressant side-effects.

Frequency/Dose/Duration - One assessment, especially to assess CYP2D6 and CYP2C19.

B.5 Treatment Recommendations

B.5.a Psychological Interventions

B.5.a.i Cognitive Behavioral Therapy

Recommended – for the treatment of patients with depressive disorders.

Dosage/Frequency/Duration – 12 to16 week course of weekly individual CBT.

Evidence for the Use of Cognitive Behavioral Therapies

B.5.a.ii Acceptance and Commitment Therapy (ACT)

Recommended– for the treatment of patients with depressive disorders.

Rationale - A key feature of these interventions is acceptance rather than avoidance of emotional pain. This acceptance is thought to reduce affective symptom severity.

B.5.a.iii Behavioral Therapy/Behavioral Activation (BT/BA)

Recommended– for the treatment of patients with depressive disorders.

Rationale - BT for major depression refers to a class of psychotherapy interventions which treat DDD by teaching patients to increase rewarding activities. Patients learn to track their activities and identify the affective and behavioral consequences of those activities. Patients then learn techniques to schedule activities to improve mood. BT emphasizes training patients to monitor their symptoms and behaviors to identify the relationships between them. BA is a

particular version of BT which targets the links between avoidant behavior and depression and expands the treatment component of BT

B.5.a.iv Interpersonal Psychotherapy (IPT)

Recommended – for the treatment of patients with depressive disorders.

Rationale - IPT is derived from attachment theory and treats DDD by focusing on improving interpersonal functioning and exploring relationship-based difficulties. IPT addresses the connection between patients' feelings and current difficulties in their relationships with people in their life by targeting four primary areas: (1) interpersonal loss, (2) role conflict, (3) role change, and (4) interpersonal skills.

B.5.a.v Mindfulness-Based Cognitive Therapy (MBCT)

Recommended – for patients with depressive symptoms

Rationale - MBCT integrates traditional CBT interventions with mindfulness-based skills, including mindfulness meditation, imagery, experiential exercises, and other techniques that aid patients in experiencing affect without necessarily attempting to change it. With regard to cognitions, unlike cognitive therapy, MBCT does not so much seek to modify or eliminate dysfunctional thoughts as to become more detached and able to observe thoughts as objects.

Evidence for the Use of Mindfulness Therapy

B.5.a.vi CBT / Antidepressant Combined Use

Recommended – for the treatment of patients with moderately severe /severe or complicated depressive disorders.

Recommended – When monotherapy with either CBT or an antidepressant does not result in improvement or resolution/partial resolution of symptoms in acute, mild/ moderate uncomplicated DDD.

B.5.a.vii Short-Term Psychodynamic Psychotherapy

Recommended – for the treatment of patients with depressive disorders.

Indications - Short-term psychodynamic psychotherapy may be first line treatment and is often used in addition to

antidepressants. For severe depressive disorders, is generally used as adjunctive to medications [rather than as a stand-alone treatment.

Frequency/Dose/Duration - Begin at eight sessions. May need additional blocks of eight sessions based on incremental functional gain.

Evidence for the Use of Short Term Psychodynamic Psychotherapy

B.5.b Medications

B.5.b.i Antidepressants

Recommended – for the treatment of patients with depressive disorders.

Indications - Depressive disorder where medication is clinically indicated. May be prescribed as monotherapy or in conjunction with other treatments including CBT and psychotherapy.

There are many classes of anti-depressant medications used to treat depressive disorders. These include selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors and atypical anti-depressants.

There is no evidence to suggest that one antidepressant drug class is superior to another for the treatment of DDD in terms of response and remission rates.

All SSRIs, *except fluvoxamine*, may be used as first-line agents in the treatment of adults with DDD. Fluvoxamine is not a Food and Drug Administration (FDA) approved drug for the treatment of DDD.

Selection of an anti-depressant is typically dependent on several factors, including concomitant symptoms to potentially address simultaneously (e.g.sleep disturbance), anticipated potential for adverse effects, prior adverse effects, co-morbid psychiatric /medical illnesses, concurrently prescribed medication

Frequency/Dose/ Duration - Providers should ensure that an appropriate dose titration and target dose range has been achieved and an adequate trial period allowed (a minimum of

four to six weeks) prior to considering discontinuing an antidepressant as a treatment failure.

Patients with DDD who have received an adequate trial of initial pharmacotherapy or psychotherapy monotherapy but have achieved partial or no response should be reassessed for possible diagnostic error, the presence of co-occurring conditions, and treatment adherence. Once diagnosis and treatment adherence are confirmed, treatment should be adjusted to achieve remission.

In general, monotherapy with first-line antidepressants (e.g. SSRIs, SNRIs, bupropion, mirtazapine) is preferable to combination treatment with two antidepressants because of the increased potential drug-drug interactions and adverse effects. Therefore, it is reasonable to consider switching to another first-line antidepressant (either within-class or out-of-class), or augmenting current pharmacological therapy with psychotherapy, or switching to psychotherapy in the absence of a partial response or no response to initial antidepressant monotherapy

The return of symptoms of depression after a remission is common. Patients who achieve remission with antidepressant medication should have the medication continued for at least 6 months after remission of DDD symptoms to decrease risk of relapse. Some patients may need to continue antidepressants indefinitely.

Discontinuation of Antidepressant Therapy - Should be done with a slow taper since discontinuation done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms. Relapse is common.

Evidence for the Use of Antidepressants

B.5.b.ii Fluvoxamine

Not Recommended – for the treatment of patients with depressive disorders.

Rationale - Fluvoxamine, is not a Food and Drug Administration (FDA) approved drug for the treatment of DDD.

B.5.b.iii Antipsychotics

Recommended for augmentation of antidepressants in treating Major Depressive Disorder (MDD).

Indication - Second generation antipsychotics should be considered only when other strategies have failed because of their significant side effects.

Recommended - in select patients with psychosis

Indications - Treatment of depressive disorders with psychotic characteristics include:

1. Serious delusions (e.g., fixed false beliefs)
2. Visual or (typically) auditory hallucinations
3. Confusion (incoherence)
4. Catatonic behavior (e.g., motoric immobility or excessive agitation)
5. Extreme negativism or mutism
6. Peculiar movements
7. Inappropriate effect of a bizarre or odd quality
8. Severe symptoms

B.5.c Electroconvulsive Therapy (ECT)

Recommended – for patient with treatment resistant Major Depressive Disorder (MDD) and any of the following conditions:

1. Catatonia
2. Psychotic depression
3. Severe suicidality
4. A history of a good response to ECT
5. Need for rapid, definitive treatment response on either medical or psychiatric grounds
6. Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative)
7. A history of a poor response to multiple antidepressants
8. Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety)

Frequency/Dose/Duration - One administration. Generally not repeated unless severe Major Depressive Disorder (MDD) recurs and is again treatment resistant.

Evidence for the Use of Electroconvulsive Therapy

B.5.d Adjunctive Therapies

B.5.d.i Exercise

Recommended – for the treatment of patients with depressive disorders.

Indications – Exercise may be used as adjunctive treatment to first line therapies such as CBT and/or medication.

Frequency/Dose/Duration – Aerobic exercise based on clinical assessment

Rationale – Improvement in depressive symptoms, increased physical function and overall well-being.

Evidence for the Use of Exercise

B.5.d.ii Yoga

Recommended – in select patients with depressive symptoms

Indications – Yoga may be used as adjunctive treatment to first line therapies such as CBT and/or medication.

Rationale – Improvement in depressive symptoms, increased physical function and overall well-being.

Evidence for the Use of Yoga

B.5.d.iii Acupuncture

Not Recommended – for the treatment of patients with depressive disorders.

Evidence for the Use of Acupuncture

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Appendix Two – Evidence Tables

Evidence for the Use of Screening Tools

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Wada 2007 (score=8.0)	Center for Epidemiologic Studies Depression Scale (CES-D), Psychological Interview	Screening Tools	No mention of COI or sponsorship.	N = 2,219 Japanese manufacturing company workers	Mean age: 42.0 years; 1,868 males, 315 females	Major depressive disorder (MDD)	Mini International Neuropsychiatric Interview (MINI) vs. Center for Epidemiologic Studies Depression Scale (CES-D). All participants received both screening tools	Area under ROC curve for CES-D = 0.96 (95% CI [0.94-0.99]). Optimal cutoff score = 19 for CES-D.	"The validity of CES-D is confirmed and it is a valid instrument for detecting MDD in working populations in Japan."	Data suggests CES is a valid workplace MDD screening tool.
Olden 2009 (score=8.0)	Hamilton Depression Rating Scale (HAMD), Psychological Interview	Screening Tools	Sponsored by the National Institute of Nursing Research and the American Foundation for Suicide Prevention. No mention of COI.	N = 422 terminally ill cancer patients with a life expectancy of less than 6 months.	Mean age: 65.8 years; 239 males, 183 females	Major Depressive Disorder	Structured Clinical Interview (DSM-IV criteria) vs. the Hamilton Depression Rating Scale (HAM-D17). All participants received both measurements	72 patients met the criteria for a current major depressive episode (MDE) according to the DSM-IV. 4 HAM-D factors were correlated with MDE diagnoses: Anxiety ($p<0.001$), depression ($p<0.001$), insomnia ($p<0.001$) and somatic ($p<0.001$). The strongest correlations were with suicidal ideation, desire for	"[T]his study provides empirical support for the Hamilton Depression Rating Scale in a large sample of terminally ill cancer patients. Further research is needed to help clarify the relationship between depression	Data suggest the HAM-D is both valid and reliable for measuring depression in terminally ill cancer patients.

								hastened death, optimistic thinking, hopelessness, and spiritual well-being (p <0.001 for all).	and anxiety at the end of life."	
Lamoureux 2010 (score=8.0)	Quick Inventory of Depressive Symptomology (QIDS-SR), Psychological Interview	Screening Tools	No mention of COI. Sponsored by the Ohio Board of Regents.	N = 155 participants recruited from a public hospital medical center	Mean age: 39 years; 32 males, 123 females	Major depressive disorder	Quick Inventory of Depressive Symptomology (QIDS-SR16) vs. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID). All participants completed all measures	Area under the curve for QIDS-SR16 (AUC) = 0.82 (p < 0.00001)	"Findings from the present study provide support for the use of the QIDS-SR16 as a screening measure for identifying primary care patients who will meet diagnostic criteria for MDD based on clinician assessment."	Data suggest QIDS-SR16 appears to be an effective MDD screening tool.
Mogge 2008 (score=8.0)	Personality Assessment Inventory, Zung Depression Scale, Beck Depression Inventory	Screening Tools	No mention of COI or sponsorship	N = 96 participants who were referred due to psychiatric concerns	Mean age: 47.52 years; 48 males, 48 females	Depression	Assessment Depression Inventory Depression Scale (Dep) vs. Beck Depression Inventory – II (BDI II) vs. Zung Self-rating Depression Scale (ZSDS) vs. Personality Assessment Inventory (PAI). All participants took all assessments	ADI Dep scale correlated with the PAI Dep scale, BDI – II, and ZSDS significantly (p < 0.01).	"Results of this study suggest that the ADI, as a measure of depression, may have utilitarian value in an outpatient setting."	Data suggest high correlation between ADI and ZSDS, BDI II and PAI depression scales.

Volker 2016 (score=7.5)	Patient Health Questionnaire, Psychological Interview	Screening Tools	Sponsored by the Netherlands organization for Health Research and Development (ZonMw) and by Achmea SZ. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 170 participants consisting of employees on sick leave between 4 and 26 weeks	Mean age: 45.4 years; 85 males, 85 females	Major depressive disorder	Patient Health Questionnaire-9 (PHQ-9) vs. MINI-International Neuropsychiatric Interview (MINI). All participants received both measurements	Optimal cut-off for PHQ-9 = 10, with sensitivity = 86.1% [95% CI (69.7–94.8)] and specificity = 78.4% [95 % CI (70.2–84.8)]. Via ROC analysis, area under the curve for PHQ-9 = 0.90 [SE = 0.02; 95% CI (0.85–0.94)]	"The PHQ-9 shows good sensitivity and specificity as a screener for MDD within a population of employees on sickness leave."	Data suggests PHQ-9 exhibits good sensitivity and specificity as a screening tool for MDD in employees who are on sick leave.
Phelan 2010 (score=7.5)	Patient Health Questionnaire, Psychological Interview	Screening Tools	Sponsored by the Center for HealthCare improvement for	N = 71 participants aged 65 years	Mean age: 78 years; 27 males, 44 females.	Major and minor depression	Patient Health Questionnaire-9 (PHQ-9) vs. 15-item Geriatric Depression Scale (GDS) vs. Structured	Area under the curve (AUC) for PHQ-9 = 0.87 [95% CI (0.74-1.00)], PHQ-2 = 0.81 (0.64-0.98), GDS = 0.81 (0.70-0.91) (p = 0.551) for major	"Based on AUC values, the PHQ-9 performs comparably to the PHQ-2 and the 15-item GDS in identifying	Data show PHQ-9 performs similar to PHQ-2 and GDS in the identification

			Addictions, Mental Illness, and Medically vulnerable Populations (CHAMMP), and the Harborview Medical Center, University of Washington. No COI.	or older			Clinical Interview for Depression (SCID). All participants underwent all measurements	depression. AUC for PHQ-9 = 0.85 (0.73-0.96), PHQ-2 = 0.80 (0.68-0.93), GDS = 0.71 (0.55-0.87) (p = 0.187)	depression among primary care elderly."	of depression in the elderly.
Ritsher 2001 (score=7.0)	Minnesota Multiphasic Personality Inventory, Hamilton Depression Rating Scale (HRDS)	Screening Tools	Sponsored by International Research and Exchanges Boards, U.S. Department of State, the Academy for Educational Developm	N = 180 adult participants diagnosed with depression according to the ICD-10 (50%), Moscow-	No mention of mean age, 46% under 26 years old; 94 males, 86 females	Depression	Hamilton Rating Scale for Depression (HRSD): 26 item questionnaire vs Minnesota Multiphasic Personality Inventory (MMPI) vs the Rorschach-Comprehensive System vs ICD-10	MMPI scales appeared to have greater validity compared to Rorschach hit rates between 44-48%. DEPI scale prediction of depression was OR=0.50 (95% CI 0.22-1.2, p=0.11), compared to OR=0.71 (95% CI 0.32-1.6, p=0.40) in ICD-10, and OR=1.6 (95% CI 0.64-4.2, p=0.30) in HRSD	"In this Russian clinical sample, the MMPI functioned more accurately than the Rorschach in detecting depression, regardless of how it was defined."	In this sample of Russian patients, MMPI was the better indicator of depression as Rorschach components were poorly associated with more established measures of depression. MMPI is the older version

			ent, National Security Education Program, the Open Society Institute, the National Institute of Mental Health, and the Departme nt of Veterans Affairs Health Services Research and Developm ent Service and Mental Health Strategic Healthcare Group. No mention of COI.	ICD-9 (72%) and Snezhn evsky (63%).						of the MMPI-2.

Henkel 2004 (score=7.0)	Psychological Interview, Patient Health Questionnaire	Screening Tools	Sponsored by the German Federal Research Ministry. No mention of COI.	N = 448 adults recruited from primary care facilities	Mean age: 52.85 years; 161 males, 287 females	Major Depression, Minor Depression, Dysthymic Disorder	Composite International Diagnostic Interview (CIDI) vs the depression module of the Brief Patient Health Questionnaire (B-PHQ) vs the WHO-5 Well Being Index vs the General Health Questionnaire twelve (GHQ-12). All completed all measures.	Brief Patient Health Questionnaire (B-PHQ) – standard cut-off ≥ 2: sensitivity = 0.79, specificity = 0.86, false-negative rate (FN) = 0.21, positive predictive value (PPV) = 0.55, negative predictive value (NPV) = 0.95, positive likelihood ratio (PLR) = 5.47, negative likelihood ratio (NLR) = 0.24. General Health Questionnaire-12 (GHQ-12) – standard cut-off ≥ 2: sensitivity = 0.85, specificity = 0.63, FN = 0.15, PPV = 0.34, NPV = 0.95, PLF = 2.30, NLF = 0.23. WHO-5 Well-Being Index Questionnaire – standard cut-off ≤ 13: sensitivity = 0.94, specificity = 0.65, FN = 0.06, PPV = 0.37, NPV = 0.98, PLR = 2.69, NLR = 0.09	"Superiority of one screening tool over the other depends on the subgroup considered. Gender, age, form (subtype), and severity of depression influence the test characteristics of a screening tool…the benefit of routine screening also depends on efforts made for treatment and monitoring of patients in whom depression was diagnosed."	Data suggest routine screening for depression via a brief depression screening tool is only valuable if followed up carefully with accepted treatment and monitoring.
Iverson 2004 (score=7.0)	Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 130 adult participants.	Mean age: 45.9 years; 46	Major Depression	Structured Clinical Interview for DSM-IV (SCID-I) (n=130) vs	Using a cut-off of 9/10 had 0.92 sensitivity, 0.99 specificity, 0.98 positive predictive power, and 0.93	"The sensitivity, specificity, and predictive power of the test to depression in this	Data suggest the BC-Major Depression Inventory has both high

				62 with depression (criteria not given), referred by their psychiatrist, and 68 control subjects.	males, 84 females		British Columbia (BC) Major Depression Inventory (n=130). All participants completed both measures.	negative predictive power. The mean score was 1.2 for the control subjects, and 20.3 for patients with depression ($p<0.0001$)	study were very high."	sensitivity and specificity and appears useful.
Furlanetto 2005 (score=6.5)	Beck Depression Inventory (BDI), Psychological Interview	Screening Tools	Sponsored by CAPES, CNPq, and FAPERJ/ Brazil. No mention of COI.	N = 155 patients admitted to an adult medical ward	Mean age: 49.5 years; 73 male, 82 female	Moderate and severe depression	International Classification of Diseases, 10th edition (ICD-10) interview vs. Beck Depression Inventory – Short Form (BDI-SF). All participants received both measurements.	When the cut-off point of 9/10 was used, sensitivity was 100%, specificity was 83%, positive predictive value was 59.6%, negative predictive value was 100%, and overall misclassification (false positives) was 40.4%. When the 13/14 cut-off point was used, sensitivity was 90.3%, specificity was 96%, positive predictive value was 84.8%, negative predictive value was 97.5, and overall	"The BDI-SF is a valid instrument for detecting moderate and severe depression in medical inpatients. For screening purposes, a 9/10 cut-off is indicated, but if a high specificity is desired, a 13/14 cut-off score is warranted."	Data suggest BDI may be used to detect moderate and severe depression.

								misclassification (false positives) was 14.7%.		
Stuart 2014 (score=6.5)	Psychological Interview	Screening Tools	Sponsored by the National Health and Medical Research Council of Australia. No mention of COI.	N = 1,977 adults participating in the Geelong Osteoporosis Study	Mean age: not given; 891 males, 1,086 females	Depression	Self-reported depression by answering the question "Have you ever suffered by depression" (n=1,977) vs Structured Clinical Interview for DSM-IV-TR research version, non-patient edition (SCID-I/NP) used to assessed self-reported past and current mood disorders (n=1,977)	Of the 431 participants identified as having a lifetime history of depression with the SCID-I/NP, 263 self-reported depression. Of the 1546 participants who did not meet the SCID-I/NP criteria for depression, 162 self-reported depression. There was a discrepancy between diagnosis and self-report of depression for 330 participants.	"The SCID-I/NP remains the gold standard for identifying depression; however, given the moderate level of agreement between the self-report questionnaire and SCID-I/NP in our current study, we conclude that the simple self-report methods can be used to identify depression with some degree of confidence."	Data suggest self-report screening method with a fair degree of confidence but the Clinical SCID-I/NP is the gold standard.
Cuijpers 2007 (score=6.5)	Psychological Interview	Screening Tools	No mention of sponsorship. No COI.	N = 258 psychiatric outpatients	Mean age: 36.45 years; 111 males, 142 females, 5 missing data	Major Depressive Disorder (MDD)	The 12-item Major Depression Inventory (MDI) vs the depression and anxiety subscales of the Symptomology Check List -90 (SCL-90). All patients completed all measures. (n=258)	The correlation between MDI scores and SCL depression subscale was 0.79 ($p<0.001$). The correlation between MDI scores and SCL anxiety subscales 0.57 ($p<0.001$).	"The MDI is an attractive, brief depression inventory, which seems to be a reliable tool for assessing depression in psychiatric outpatients."	Data suggest the MDI self-report tool moderately agrees with the clinical diagnosis of depression made by a psychiatrist.

Surís 2016 (score=6.5)	Quick Inventory of Depressive Symptomology (QIDS-SR), Psychological Interview	Screening Tools	No mention of COI or sponsorship.	N = 240 participants from three different randomized clinical trials, veterans with combat-related PTSD	Mean age: 43.78 years; 127 males, 113 females	Current major depressive episode (MDE)	Quick Inventory of Depressive Symptomology (QIDS-SR16) vs. Structured Clinical Interview for DSM-IV-TR Axis I Disorders OR Diagnostic Interview Schedule for DSM-IV for major depressive disorder. All participants completed the QIDS-SR16 and one of the two structured interviews	Optimal cutoff for QIDS-SR16 = 13, sensitivity = 77.55%, specificity = 56.25%. ROC analysis resulted in area under the curve (AUC) = 0.73	"The QIDS-SR16 can be effectively utilized in military veterans with comorbid PTSD."	Population of military veterans with PTSD. Data supports the use of QIDS-SR16 in military veterans with PTSD for a valid screening tool for MDD.
Cameron 2013 (score=6.0)	Quick Inventory of Depressive Symptomology (QIDS-SR), Hamilton Depression Rating Scale (HAMD)	Screening Tools	No COI. Sponsored by NHS Quality Improvement Scotland and Tenovus Scotland.	N = 286 participants recruited from general practices and were diagnosed with depress	Mean age: 49.5 years; 91 males, 195 females	Depressive disorder	Quick Inventory of Depressive Symptomatology (QIDS-SR16) vs. 17-item Hamilton Rating Scale for Depression (GRID-HAMD)	QIDS-SR16 exhibited internal consistency (Cronbach's alpha=0.86). This highly correlated with the HRSD-17 (r = 0.79). Differed significantly in categorizing depressive severity relative to HRSD ($p < 0.001$)	"In conclusion, psychometric properties of the QIDS-SR16 were found to be strong in terms of internal consistency, factor structure and convergent and discriminant validity. Using conventional scoring and conversion	Data suggest the QIDS-SR16 was highly correlated with the HRSD-17 but differed in categorization of depression severity.

				ion via general practitioner					methods the scale was found not to concur with the HRSD-17 in categorising the severity of depressive symptoms."	
Zimmerman 2012 (score=6.0)	Psychological Interview, Clinically Useful Depression Outcome Scale (CUDOS), Hamilton Depression Rating Scale (HAMD), Quick Inventory of Depression Symptomatology-self report	Screening Tools	Sponsored by Lilly USA, LLC. No mention of COI.	N = 274 depressed outpatients ongoing treatment for DSM-IV diagnosed Major Depressive Disorder (MDD)	Mean age: 49 years; 87 males, 187 females	Remission from Depression	Quick Inventory of Depressive Symptomatology (QIDS) (n=274) vs the Clinically Useful Depression Outcome Scale (CUDOS) (n=274) vs the 17-item Hamilton Depression Rating Scale (HAM-D). All patients completed all measures.	Correlation between CUDOS scores and QIDS scores was 0.86 ($p<0.001$). Correlation between HAM-D scores and CUDOS scores was 0.65 ($p<0.001$). Correlation between HAM-D scores and QIDS scores was 0.63 ($p<0.001$).	"The CUDOS and the QIDS were equally related to the HAM-D definition of remission. The CUDOS takes less time to complete than the QIDS and, therefore, may be preferable to use in routine clinical practice."	Data suggest CUDOS has higher specificity than the QIDS and takes less time to complete.

	(QIDS-SR)									
Sanchez-Villegas 2008 (score=6.0)	Psychological Interview	Screening Tools	Sponsored by the Spanish Ministry of Health & the Navarra Regional Govemment. No COI.	N = 104 participants in the SUN Study	Mean age: 43 years; 30 males, 74 females	Major Depressive Disorder	Structured Clinical Interview for DSM-IV (SCID-I) (n=104) vs Self-Reported depression, asked whether they had every received a depression diagnosis by a physician (n=104). All participants received both measures.	46/62 (74.2%) participants who self-reported depression had a true positive diagnosis in the SCID-I. 34/42 (81%) participants who self-reported no depression had a true negative diagnosis in the SCID-I.	"The validity of a self-reported diagnosis of depression in the SUN cohort is adequate. Thus, this question about depression diagnosis could be used in further investigations regarding this disease in this graduate cohort study."	Data suggest in the SUN study, self-reported depression in a cohort of participants adequately correlated to the DSM-IV (SCID-1).
McIntyre 2002 (score=6.0)	Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by the Centre for Addiction and Mental Health Foundation, Janssen Ortho, Eli Lilly, and GloxoSmithKline. COI, one or more of the	N = 292 patients with unipolar non-psychotic major depressive disorder treated at a Depres	Mean age: not mentioned; 107 males, 185 females	Major Depressive Disorder	Hamilton Depression Rating Scale (HAM-D17) vs. Bech Melancholia Scale (items 1, 2, 7, 8, 10, 13), Gibbons Global Depression Severity Scale (items 1, 2, 3, 7, 9, 10, 11, 14), and Maier and Philip Severity Scale (items 1, 2,	The items from the 17-HAM-D that were reported most frequently with the most sensitivity to change were included in the Toronto HAM-D7: depressed mood, guilt, suicide, work and interests, psychic anxiety, somatic anxiety, and general somatic. The Toronto HAM-D7 was comparable to the HAM-D17 for	"Seven items with the greatest frequency of occurrence and sensitivity to change with treatment were identified and designated as the Toronto HAM-D. A score of 3 or less on the Toronto HAM-D was found to correlate with the 17-item HAM-D definition of full	Data suggest a 7-item version of the 17-item HAM-D showed greatest sensitivity to change with treatment and a score of 3 or less appeared to correlate to the full remission of depression definition.

			authors have received or will receive benefits for personal or professional gain.	sion Clinic in Toronto according to DSM-IV criteria			7, 8, 9, 10) HAM-D Subscales. All participants received all measurements	predicting remission of depressive symptoms with: cut-off score = 3.04; sensitivity=0.95; specificity=0.84; positive predictive power=0.94; negative predictive power=0.86.	remission (i.e., score of 7 or less)."	
Aalto 2012 (score=6.0)	Beck Depression Inventory (BDI), Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 5,561 adults under 80 from a Finish cluster sample and completed the Composite International Diagnostic Interview	Mean age: 50.6 years; 2,583 male, 2,978 female	Depressive disorders	Beck Depression Inventory (BDI) 21-item vs. BDI 13-item vs. BDI 6-item vs. General Health Questionnaire (GHQ) vs. Composite International Diagnostic Interview (CIDI). All participants received all measurements	Cut-off points were assessed by the Youden index. For the BDI-21, a cut-off of 9/10 and 8/9 had the highest Youden index (Y=0.50). For the BDI-13, the cut-off of 4/5 and 5/6 had the highest Youden's index (Y=0.50). For the GHQ-12, a cut-off of 2/3 had the highest Youden index (Y=0.50). For the BDI-6, a cut-off of ½ had the highest Youden index (Y=0.50).	"[V]arious versions of the BDI and the GHQ-12 are useful in detecting depressive disorders in the general population. Even the 6-item version of the BDI showed acceptable criterion validity."	Data suggest all 4 versions of the GHQ and BDI (even the 6 item BDI) are useful in the detection of depression.
Cheng 2005 (score=6.0)	Center for Epidemiologic	Screening Tools	No mention of COI or	N = 398 participants	Mean age: 69.97 years;	Major depression, dysthymia	Center for Epidemiologic Studies Depression Scale	Optimal threshold: CESD-10 = 12, CESD-20 = 22. Sensitivity, specificity, positive	"The ten-item version can be used in lieu of the 20-item version, and a	Data suggest the CESD-10 can be used in place of

	Studies Depression Scale (CES-D)		sponsorship.	referred for psychiatric assessment by physician	141 males, 257 females	, adjustment disorder with depression mood, dementia with depression	20-item version (CESD-20) vs. Center for Epidemiologic Studies Depression Scale 10-item version (CESD-10). All participants received both screening tools	predictive value, and negative predictive value, respectively: CESD-10 – 0.76, 0.55, 0.57, 0.74, CESD-20 – 0.75, 0.51, 0.55, 0.72	dichotomous response format would probably work as well as the original four-point format, in order to simplify administration for elderly persons."	CESD-20 as there were similar performance indices in elderly Chinese individuals.
Turk 1994 (score=6.0)	Center for Epidemiologic Studies Depression Scale (CES-D)	Screening Tools	No mention of COI or sponsorship.	N = 100 physician-referred patients who were evaluate at a pain evaluation and treatment institute. 50 being diagnosed with depression via	Mean age: 41.96 years; 34 males, 66 females	Affective disorders, depression, somatic symptoms, pain severity, disability levels	Center for Epidemiological Study-Depression Scale (CES-D) vs. Multidimensional Pain Inventory (MPI) vs. Oswestry Disability Scale (ODS). All participants received all screening tools	Using cut-off of 16 for CES-D resulted in 50% of those with depression being classified with depression. Using cutoff score of 19 produced reduction in sensitivity but a 12% increase in specificity.	"The results of this study demonstrate that the CES-D is a valid self-report, screening instrument to assess depression in chronic pain patients."	Data suggest use of CES-D with a cutoff point of 19 versus 16 should be used in screening depression in chronic pain patients.

				DSM-III criteria, 50 without a diagnosis						
Geisser 1997 (score=6.0)	Center for Epidemiologic Studies Depression Scale (CES-D), Beck Depression Inventory (BDI)	Screening Tools	No mention of COI or sponsorship.	N = 132 chronic pain patients, with 44 who met DSM-IV major depression criteria	Mean age: 40.7 years; 38 males, 94 females	Major depressive disorder	Beck Depression Inventory (BDI) vs. Center for Epidemiologic Studies-Depression Scale (CES-D). All participants received both screening tools	Optimal cut-off score for BDI = 21 and CES-D = 27 via discriminant function analysis. Hit rates at these cut-off scores were comparable between groups. CES-D has better sensitivity (81.8% vs. 68.2%) while BDI had better specificity (78.4% vs. 72.7%)	"The results suggest that both questionnaires have good predictive validity among chronic pain patients, and decisions regarding the use of one questionnaire rather than the other may depend upon the goals of the user and the setting within which the questionnaire is used."	Data suggest both the BDI and the CES-D appear to be good depression screening tools among persons with chronic pain.
Tuunainen 2001 (score=6.0)	Center for Epidemiologic Studies Depression Scale (CES-D), Psycholo	Screening Tools	Sponsored by the National Institutes of Health. Author Tuunainen received grants from the	N = 436 post-menopausal women	Mean age: 67.8 years; 0 males, 436 females	Major depression, dysthymia, lifetime major, lifetime mood	Burnam screen (shortened version of Center for Epidemiologic Studies-Depression Screen) vs. Structured Clinical	Burnam screen had sensitivity of 74% and specificity of 87% for current major depression and dysthymia and positive predictive value of 20%. Overall error rate was 14%	"These results re-emphasize the difficulty of using a one-stage screen to detect accurately a depressive diagnosis."	Data suggest use of a one-stage screen to detect depression are convenient but miss a portion of cases. It is suggested that these types of

	gical Interview		Academy of Finland, the Finnish Cultural Foundation, the Finnish Medical Foundation, the Jalmari and Rauha Ahokas Foundation, and the Paulo Foundation.				Interview for DSM-IV Axis I Disorders, non-patient edition. All participants received both screening tools			abbreviated screens may serve as a first line screening tool to be followed up with a second line screening tool. Study performed only on post-menopausal female patients.
Lyness 1997 (score=6.0)	Center for Epidemiologic Studies Depression Scale (CES-D), Psychological Interview	Screening Tools	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 130 patients attending 3 primary care internists' practices	Mean age: 71.0 years; 53 males, 77 females	Major depression	Center for Epidemiologic Studies-Depression Scale (CES-D) vs. Geriatric Depression Scale (GDS) vs. Shortened version of Geriatric Depression Scale vs. Structured Clinical Interview for	CES-D: optimum cut-off score = 21, sensitivity = 92%, specificity = 87%. GDS: optimum cut-off score = 10, sensitivity = 100%, specificity = 84%. Shortened GDS: optimum cut-off score = 5, sensitivity = 92%, specificity = 81%	"The CES-D and the GDS have excellent properties for use as screening instruments for major depression in older primary care patients. Because the GDS's yes or no format may ease administration, primary care clinicians should consider its routine	Data suggest both the GDS and CES-D are good screening tools for depression but the GDS has a simpler format of yes/no making it simpler to use.

							DSM-III-R criteria. All participants were given all three screening tools		use in their practices."	
Schueller 2015 (score=6.0)	Patient Health Questionnaire, Hamilton Depression Rating Scale (HAMD)	Screening Tools	No mention of sponsorship or COI.	N = 487 participants who met DSM-IV criteria for major depressive disorder (MDD) or PHQ-9 scores indicating a depression diagnosis	Mean age: 48 years; 112 males, 375 females	Major depressive disorder	Participants received 18 weeks of telephone and face-to-face cognitive behavioral therapy (CBT) (N=279) or participants received 8 weeks of web-delivered CBT (N=208). All participants received the patient health questionnaire-9 (PHQ-9) and the Hamilton Rating Scale for Depression (HAM-D)	Optimal cutoff points suggest the following cutoff values for the PHQ-9: ≥17 at 4 weeks, ≥13 at 9 weeks, ≥9 at 14 weeks	"Consistent specified cut points were found within trials included. These cut points may be valuable for algorithms to support clinical decision-making."	Data suggests PHQ-9 cut points positively correlate to depressive symptoms.
Nyklíček 2004 (score=6.0)	Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 951 women around menop	Mean age: 51 years; 0 males,	Depressive Symptomology,	Edinburgh Depression Scale (EDS): questionnaire administered	When comparing the two time points at each cut-off, specificity and negative predictive value (NPV) did not	"In conclusion, the 10-item EDS is a reliable, valid and valuable screening instrument. When	Data suggest the EDS is a valid first line screening tool

				ausal age diagnosed with depression on the EDS scale	951 females	clinical depression	twice, 18 months apart vs. Research Diagnostic Criteria (RDC): structured clinical interview to diagnose depression, administered once. All participants completed both tests.	have significant change (92.2%-98.0%; 92.8%-88.8%). Sensitivity dropped 64.9%-48.5% at each cut-off. Positive predictive value (PPV) increased at each time point (43.8%-61.8%).	employed repeatedly, a more stable depression may be tapped, which can be of substantial value for both epidemiological research and clinical practice."	for clinical depression.
Zausznie wski 2012 (score=5.5)	Psychological Interview, Center for Epidemiologic Studies Depression Scale (CES-D)	Screening Tools	No sponsorship or COI.	N = 629 patients	Mean age: 35 years; 189 males, 440 females	Clinical depression	Depressive Cognitive Scale (DCS): one time, self-administered eight-item scale vs. Center for Epidemiologic Studies Depression Scale (CES-D): 20-item scale, administered once All participants completed both test.	Participants scored 7.59 and 15.45 on the DCS and CES-D measures. A cutoff of 7-8 on DCS = 73.9% sensitivity and 75.3% specificity; PPV of 88.3%. Cut-off point of 6-7 (sensitivity=76.6%) was also considered to minimize false negatives. Optimal cutoff score for DCS was deemed to be 7.	"Although findings indicate that the DCS may overidentify risk for clinical depression, the instrument is useful for screening and assessment, with possible initiation of psychological treatment to prevent clinical depression."	Data suggest the DCS may over identify depression risk. It is useful for first line screening.
Albani 2006 (score=5.5)	Psychological Interview, Patient Health	Screening Tools	No mention of sponsorship or COI.	N = 536 adult patients with	Mean age: 53 years; 520 males,	Depression	Mental Health Diagnostic Interview Schedule (DIS): short interview,	Sensitivity and specificity ranged from 72.6%-96.6% and 56.9%-90.0% in all five samples. >97%	"Overall, it seems that the two-question screening are well suited for the exclusion of a	All published 2-question screens have NPVs of 79.7%. Data

	Question naire			a DSM-III diagnosis for depression.	16 females		administered once (n=536) vs. Composite International Diagnostic Interviews (CIDI): oral questionnaire, administered once (n=421) vs. Structure Clinical Interview DSM-III-R (SCID): questionnaire and phone interview, administered once (n=580) vs. Structure Clinical Interview DSM-IV (SCID): administered once (n=520) vs. Patient Health Questionnaire (PHQ-9): questionnaire, administered once (n=2036)	negative predictive value, 17.8%-38.5% positive predictive value was demonstrated through all five studies.	major depression. It is possible that regular screening could further lower the percentage of undiagnosed cases."	suggest a two question depression screen likely excludes a positive screen for MD suggesting cutoffs may need to be lowered.
Patten 2015 (score=5.5)	Patient Health Questionnaire, Center	Screening Tools	Sponsored by Calgary Health Trust, the	N = 152 participants recruite	Mean age: 50 years; 34 males,	Major depression	Patient Health Questionnaire (PHQ) 9 vs. PHQ-2 vs. Center for	All scales had an area under the ROC of >90%. PHQ-9 optimal cutoff = 10, specificity (SP) = 85.9%,	"While all of the scales performed well in terms of their sensitivity and specificity, the	Data suggests that while all 4 screening tools were similar, the

	for Epidemiological Studies Depression on Rating Scale (CES-D), Psychological Interview		Hotchkiss Brain Institute, and Alberta Innovates Health Solutions. No COI.	d from a multiple sclerosis (MS) clinic	118 females		Epidemiological Studies Depression rating scale (CES-D) vs. Hospital Anxiety and Depression Scale (HADS-D) vs. Structured Clinical Interview, DSM-IV (SCID). All participants completed all measurements.	sensitivity (SEN) = 95.0%, positive predictive value (PPV) = 51.4%. PHQ-2 optimal cutoff = 3, SP = 93.0%, SEN = 80.0%, PPV = 64.0%, HADS-D optimal cutoff = 8, SP = 82.2%, SEN = 85.0%, PPV = 42.5%, CES-D optimal cutoff = 16, SP = 73.1%, SEN = 94.7%, PPV = 33.9%	availability of the PHQ-9 in the public domain and its brevity may enhance the feasibility of its use."	brevity of the PHQ-9 makes use more attractive.
Spitzer 1999 (score=5.5)	Patient Health Questionnaire	Screening Tools	Sponsored by Pfizer US Pharmaceuticals Inc. No mention of COI.	N = 3,632 participants recruited from 8 primary care sites	Mean age: 46 years; 603 males, 2,397 females	Any psychiatric diagnosis, mood disorder – major depressive disorder, other depressive disorder	Self-administered Primary Care Evaluation of Mental Disorders (PRIME-MD) vs. Clinician-administered PRIME-MD. All participants completed the self-administered PRIME-MD however only 585 patients had an interview with a mental health professional	When used to diagnosis major depression, self-administered PRIME-MD has sensitivity = 73%, specificity = 98%, overall accuracy = 93% and clinician-administered PRIME-MD has sensitivity = 57%, specificity = 94%, overall accuracy = 92% (kappa: 0.54 vs. 0.61, not significantly different)	"Our study suggests that the PHQ has diagnostic validity comparable to the original clinician-administered PRIME-MD, and is more efficient to use."	Data suggest PHQ comparable in validity to PRIME-MD and was more efficient to use as it was far less time consuming for both patient and clinician interpretation.
Zimmerman 2014	Clinically Useful Depression	Screening Tools	No sponsorship or COI.	N = 773 patients with	Mean age: 41.1 years;	Major depressive disorder	Clinically Useful Depression Outcome Scale-Anxious Distress	All item-scale correlations substantial (mean r=0.79, p<.001). 58 subjects examined	"In the present study of a large sample of psychiatric	Data suggest CUDOS-A appears reliable and

(score=5.5)	Outcome Scale (CUDOS), Psychological Interview			DSM-5 diagnosis of major depressive disorder	272 males, 501 females		Specifier (CUDOS-A): take-home questionnaire booklet, completed once vs. Structured Clinical Interview for DSM-IV (SCID): one-time interview with a trained diagnostic rater to assess the severity of symptoms. All participants completed both measurements.	for test-retest reliability with total scale (r=0.89) and all items significant (r=0.78). 204 patients examined for discriminant and convergent validity. Correlation of CUDOS-A vs. anxiety symptoms or nonanxious symptoms demonstrated; anxiety rating significantly higher than depressed mood rating (p<.01) and significantly higher than irritable mood item (p<.01). All patients examined for association with psychiatric diagnosis. Across all, CUDOS-A mean score = 11 (SD=5.0); patients with anxiety disorder (n=513) scored higher than without (n=260) (p<.001). CUDOS-A used to subtype patients who did not meet DSM-5 requirements. Higher scores on CUDOS-A associated with global rating of functional impairment,	outpatients, the CUDOS-A was a fillable and valid measure of the DSM-5 anxious distress specifier for major depressive disorder."	valid in the measurement of DSM-5 anxious distress for those with MDD.

								reduced satisfaction of life, and poorer physical and mental health (r=0.41, p<.001; r=0.31, p<.001; r=0.33, p<.001; r=0.27, p<.001; r=0.18, p<.001).		
Lasa 2000 (score=5.5)	Beck Depression Inventory (BDI), Psychological Interview	Screening Tools	Sponsored by the European Commission's Biomed 2 Programme and the Spanish Ministry of Health. One or more of the authors has received or will receive benefits for personal or professional use.	N = 1250 adult (18-64 years old) individuals randomly selected from the municipal census of Santander, Cantabria	Mean age: not given; 623 male, 627 female	Depressive disorders	Phase 1: Depressive disorders identified using the Beck Depression Inventory (BDI) with a threshold of 12/13 chosen to screen (n=1250) vs Phase 2: A random 5% of total sample Phase 1 participants with BDI score less than 13 diagnosed with structured clinical psychiatric interview (n=44) all participants underwent the BDI. Those with a score greater than or equal to 13 were then	For a cut-off of 12/13 has 100% sensitivity, 99% specificity, 0.72 positive predictive value, 1.0 negative predictive power, and overall diagnostic value of 98%. For a cut-off of 13/14 has 90% sensitivity, 99% specificity, 0.80 positive predictive value, 0.99 negative predictive power, and overall diagnostic value of 99%. For a cut-off of 14/15 has 90% sensitivity, 99% specificity, 0.82 positive predictive value, 0.99 negative predictive power, and overall diagnostic value of 99%. For a cut-off of 15/16 has 84% sensitivity, 99% specificity, 0.81 positive predictive	"We conclude that the BDI is a good instrument for screening depressive disorders in community surveys."	Data suggest BDI is a good screening tool for the general population.

							assessed with clinical interview	value, 0.99 negative predictive power, and overall diagnostic value of 98%. No differences in terms of age or gender.		
Cho 1993 (score=5.5)	Center for Epidemiologic Studies Depression Scale (CES-D), Psychological Interview	Screening Tools	Sponsored by the Interagency Agreement. No mention of COI.	N = 808 Cuban Americans and 1,200 Puerto Ricans who were participants of the Cuban Americans and Puerto Rican responders to the Hispanic Health and Nutrition Examination	No mean age reported; 17 males, 61 females	Major depression	Center for Epidemiologic Studies-Depression Scale (CES-D) vs. the National Institute of Mental Health Diagnostic Interview Schedule (DIS). All participants received both screening tools.	Measurements taken at baseline, 2 weeks, 1 and 6 months. CES-D optimal cutoff scores were 17 for Cuban Americans, 20 for Puerto Ricans. Sensitivity and specificity values at all four time points, respectively: Cuban Americans = 91.7 & 90.5, 91.7 & 90.5, 84.6 & 90.4, 72.2 & 90.6, Puerto Ricans = 98.3 & 73.3, 97.0 & 73.7, 95.6 & 73.7, 88.6 & 73.9	"In conclusion, we suggest that the CES-D performs well in identifying current DIS major depression, with relatively high concordance between the two instruments."	Data suggest good agreement between CES-D and DIS suggesting CES-D as a recommended first line screening tool for depression measures in Hispanic individuals, although cutoff points were different between Puerto Ricans and Cuban Americans.

				Survey (HHANES)						
Irwin 1999 (score=5.5)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	Sponsored by National Institute on Alcohol Abuse and Alcoholism, National Institute of Health, and Merck Research Laboratories. No mention of COI.	N = 151 depressed patients (n=40), comparison controls (n=43) and adults from the community (n=68)	Mean age: 57.1 years; 78 males, 73 females.	Late life depression	The 20-item Center for Epidemiological Studies Depression Scale (CES-D) vs. the 10-item CES-D. Study 1 had a sample of middle-aged depressed patients and a control group (n=83). Study 2 tested the accuracy of the cutoff score in adults 60 years and older from the community (n=68).	The optimal cutoff score found was 4. There was a 97% sensitivity, 84% specificity, 85% positive predictive value in study 1. Study 2 gave 100% sensitivity, 93% specificity, and 38% positive predictive value.	"The 10-item CES-D has excellent properties for use as a screening instrument for identification of major depression in older adults.	Data suggest to 10-item CES-D is useful for screening depression in middle aged and older adults.
Nishiyama 2009 (score=5.5)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	No mention of sponsorship or COI.	N = 86 outpatients in the psychiatric department.	Mean age: 47 years; 30 males, 56 females.	Major depression	20-item Center for Epidemiological Studies Depression Scale (CES-D) vs 10-item CES-D. All participants completed both measures.	The 20-item CES-D gave 91% sensitivity and 76% specificity. The 10-item CES-D gave 88% sensitivity and 81% specificity	"The 10-item CES-D is the better instrument to use because of the higher feasibility than the 20-item CES-D in psychiatric outpatient settings"	Data support use of 10-item CES-D as it is more feasible to use than the 20-item version with almost identical reliability and validity.

Furukawa 1997 (score=5.5)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	Sponsored by Nervous and Mental Disorders from the Ministry of Health and Welfare. No mention of COI.	N = 591 first-visit patients to psychiatric hospitals and clinics.	Mean age: 36.9 years; 268 males, 323 females.	Depression	Conventional Likert method vs. Presence method vs. GHQ method vs. Persistence method vs. 10-item version vs. 5-item version vs. Item 6. All participants completed all measures.	Area under the curve (AUC) for Likert method, Presence method, GHQ method, Persistence method, 10-item version, 5-item version, and Item 6 (AUC=0.75; 0.73; 0.75; 0.70; 0.74; 0.71; 0.69). GHQ and Likert model showed superiority to the persistence method.	"In conclusion, the traditional Likert scoring method of the full CES-D appeared to perform best in screening for major depressive episodes among first-visit psychiatric patients."	Data suggest the full CES-D performs best as a screening tool for MD and the GHQ presence method and shortened 10-item CES-D had similar results. The persistence method, the 5-item CES-D and single-item version performed significantly worse.
Schneibel 2012 (score=5.5)	Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD)	Screening Tools	No mention of sponsorship or COI.	N = 105 hospitalized patients with DSM-IV diagnosed major depressive	Mean age: 41.6 years; 34 male, 71 female	Major depressive disorder	Severity of depression assessed by clinician-rated 17-item Hamilton Rating Scale for Depression (HAMD) (n=105) vs. Severity of depression assessed with self-rated Beck Depression	HAMD had an effect size of 2.51. The BDI had an effect size of 1.86. The somatic items of the HAMD showed greater changes during the course of treatment than psychological items ($p<0.001$). The psychological items showed grater change than the somatic items in the BDI ($p<0.001$).	"The HAMD and the BDI should be regarded as two complementary rather than redundant or competing instruments as the discrepancy is associated with personality characteristics. Attributing large effect sizes solely	Data suggest there are differences between the HAM-D and BDI but should generally be regarded as two complementary depression screening tools.

				disorder			Inventory (BDI) (n=105). All participants were assessed by both measures pre-treatment and post-treatment at 5 weeks		to effective treatment and a sensitive measure may be misleading."	
Rush 2003 (score=5.5)	Quick Inventory of Depressive Symptomology (QIDS-SR), Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by Bristol-Myers Squibb Pharmaceuticals, the National Institute of Health, National Institute of Mental Health, the Betty Jo Hay Distinguished Chair in Mental Health, Rosewood Corporation Chair in Biomedical Science, the Sara M. and Charles E.	N = 596 outpatients with chronic, nonpsychotic, major depressive disorder via DSM-IV criteria, current MDD superimposed upon a preexisting dysthymic	Mean age: 43.6 years; 212 males, 384 females	Major depressive disorder	30-item Inventory of Depressive Symptomatology (IDS) vs. Self-Report 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16) vs. Hamilton Rating Scale for Depression (17-, 21-, and 24-item versions) vs. Patient Global Impression-Improvement scale (PGI-I)	High internal consistencies for four scales at study end (QIDS-SR16 = 0.86, IDS-SR30 = 0.92, HAM-D17 = 0.83, HAM-D21 = 0.84, HAM-D24 = 0.88). QIDS-SR16 total scores correlated with IDS-SR30 (r = 0.96) and HAM-D24 (r = 0.86)	"The QIDS-SR16 was as sensitive to symptom change as the IDS-SR30 and HAM-D24, indicating high concurrent validity for all three scales."	Data suggest QIDS-SR16 was sensitive to symptom changes and showed internal consistency to the IDS-SR30 and HAM-D24.

			Seay Center for Basic and Applied Research in Psychiatry, and the Mental Health Connections. Mention of COI.	disorder, or recurrent MDD with history of incomplete remission between episodes						
Gabrys 1985 (score=5.5)	Zung Depression Scale	Screening Tools	No mention of sponsorship or COI.	N = 760 family escorts (n=173), nondepressed (n=218), and depressed patients (n=369).	Mean age: 30.1 years; 280 males, 307 females. Genders were not provided for the escort group.	Depression	Depression profiles using Zung Self-Rating Depression scale. All participants completed the checklist and then an interview.	There is a significant difference in total Zung scores between depressed and nondepressed patients ($p<0.001$). Family escorts were more depressed than family escorts ($p<0.01$) and depressed patients ($p<0.001$).	"It is concluded that the present findings support the scale's reliability by judge or self-report and the predictive and discriminant validities with functionally diverse groups."	Data suggest Zung self-rating depression scale measured individual perception of well-being or lack thereof.

Lin 2014 (score=5.0)	Zung Depression Scale, Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by Kai-Syuan psychiatric hospital and the Ministry of Science and Technology. No COI.	N = 112 patients with major depressive disorder.	Mean age: 45.6 years. Genders were not provided.	Depression	Patients were given 20 mg of fluoxetine daily for 6 weeks. Depression symptoms measure via: Hamilton Depression Rating Scale-17 vs. Zung Self-Rating Depression scale. All participants received both measurements at baseline and post treatment.	The correlation between both groups increased after 6 weeks ($p<0.001$). The correlation between global assessment of functioning (GAF) and work and social justice scale (WSAS) scores were correlated post treatment ($p<0.001$).	"We concluded that self-rating scales should not displace physician-rating scales.42 Depression is a private subjective experience. Physician-rating scales may lend some apparent objectivity and reliability but often ignore feelings"	Data suggest better sensitivity with physician rating scales versus self-rating scales for detection of symptom and/or functional changes.
Zung 1965 (score=5.0)	Zung Depression Scale	Screening Tools	No mention of sponsorship or COI.	N = 56 patients diagnosed with depressive disorder.	Age and gender of the sample were not provided.	Depression	Pervasive, physiological, and psychological characteristics for diagnosis. All participants completed the self-rating Sung depression inventory.	Patients with depressive disorder had a mean score of 0.74 for the Self-Rating Depression Scale while patients with other disorders had a mean of 0.53. After treatment, the mean Self-Rating Depression Scale index for patients with depressive disorders and patients with other disorders decreased to 0.39 and 0.33, respectively.	"A self-rating depression scale was devised as an attempt to quantitate the symptoms of depression, using the diagnostic criteria of the presence of a pervasive depressed affect, and its physiological and psychological concomitants as test items."	Data suggest a high degree of correlation between self-rated depressive induces, EEG responses during sleep, and the clinical evaluation of patients with regards to depression.

Bellino 2005 (score=5.0)	Zung Depression Scale, Psychological Interview, Hamilton Depression Rating Scale (HAMD)	Screening Tools	No mention of sponsorship or COI.	N = 119 patients with personality disorder and MDD.	Mean age: 37.2 years; 45 males, 74 females.	Major depressive disorder (MDD)	Characteristics between patients with borderline personality disorder (BPD) and MDD (n=45) vs. patients with only MDD (n=74). All patients completed DSM-IV interviews, Hamilton scale, Zung SDS, social and occupational functioning assessment scale, Sheehan disability scale, and the revised childhood experiences questionnaire.	Patients with BPD had a higher rate of mood and anxiety disorders in relatives (p=0.016), axis 1 comorbidity (p=0.042), and self-mutilating behaviors (p=0.0005). Patients with BPD had MDD at an earlier age (p=0.025). The Zung SDS was significantly related to criteria for BPD patients (p=0.0005).	"Patients with comorbid MDD and BPD present differential characteristics that indicate a more serious and impairing condition with a stronger familial link with mood disorders than is shown by depression patients with other Axis II codiagnoses."	Data suggest MDD individuals with BPD likely have earlier onset of depression, more aggressiveness, severe social impairment and familial mood disorders association.
Rush 2006 (score=5.0)	Quick Inventory of Depressive Symptomology (QIDS-SR), Hamilton Depression Rating	Screening Tools	Sponsored by the National Institute of Mental Health and the National Institutes of Health. No	N = 1120 outpatient participants with nonpsychotic major depressive	Mean age: 40.8 years; 410 males, 710 females	Major depressive disorder	Clinician-rating Quick Inventory of Depressive Symptomatology (QIDS-C16) vs. Self-report QIDS-SR16 vs. Automated, interactive voice response QIDS-IVR16 vs. 17-item Hamilton	Differences between all three QIDS measurements were statistically different [F(2, 1162) = 48.13, p = 0.001) but had a small effect size (n2 = 0.01)	"In nonpsychotic MDD outpatients without overt cognitive impairment, clinician assessment of depression severity using either the QIDS-C16 or HRSD17 may be successfully	Data suggest QIDS-C26 or HRSD may be replaced by either the self-reported QIDS-SR26 or the IVR version of the QIDS.

	Scale (HAMD)		mention of COI.	disorder, enrolled in the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial			Rating Scale for Depression (HRSD17)		replaced by either the self-report or IVR version of the QIDS."	
Oliver 1984 (score=5.0)	Beck Depression Inventory (BDI), Psychological Interview	Screening Tools	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 298 individual participants randomly selected from a pool of English-speaking adults	Mean age: 37.9 years; 117 male, 181 female	Major depressive disorder	Depressive symptoms assessed with Diagnostic Interview Schedule (DIS) Version 3 (n=298) vs. Depressive symptoms assessed with Beck Depression Inventory (BDI) 21-item (n=298). All participants were assessed with both the DIS and the BDI, administered in a	A BDI cut-off score of 9/10 had 100% sensitivity, 86% specificity, 0% false negatives, and 13.7% false positives. Using a cut-off score of 21/22 reduced false positives to 1.4%, and increased false negatives to 52.4%. A cut-off score of 18/19 yielded an unbiased estimate of the prevalence of depression as diagnosed by the DSM-III.	"The BDI may be adapted as a screening instrument for clinical research, if it is followed by a second measure to further characterize depression yielding a more homogeneous group."	Data suggest the BDI is a good depression screening instrument but needs further testing to further characterize depression.

							counterbalanced order			
Haringsma 2004 (score=5.0)	Center for Epidemiological Studies Depression Scale (CES-D), Psychological Interview	Screening Tools	Sponsored by The Dutch Health Research and Development Council. No mention of COI.	N = 318 subjects with a clinical diagnostic of DSM-IV for Major Depressive Disorder (MDD)	Mean age: 65.5 years; 87 males, 231 females	Major depressive disorder (MDD), Clinically relevant depression (CRD)	The Center for Epidemiologic Studies Depression scale (CES-D) vs. Mini International Neuropsychiatric Interview (MINI). Baseline questionnaire was completed at home. Diagnostics was two weeks later, done by researchers. All participants completed the questionnaires.	For MDD, the optimal cut-off score was 25, (sensitivity 85%, specificity 64%, and positive predicted value of 63%). For Clinically Relevant Depression (CRD), the optimal cut-off was 22 (sensitivity 84%, specificity 60%, and positive predicted value 77%)	"The criterion validity of the CES-D for MDD and CRD was satisfactory in this semi-clinical sample of elders. Subjects scoring >25 constitute a target group for further diagnostic assessment in order to determine appropriate treatment."	Data suggest CES-D has satisfactory screening ability for depression in older individuals.
Beekman 1997 (score=5.0)	Center for Epidemiological Studies Depression Scale (CES-D), Psychological Interview	Screening Tools	Sponsored by the Ministry of Health, Welfare and Sports of The Netherlands. No mention of COI.	N = 487 subjects with major depression according to DSM-III	No mention of mean age; 205 males, 282 females	Major depression	The Center for Epidemiologic Studies Depression scale (CES-D) vs. Diagnostic Interview Schedule (DIS). All participants completed the questionnaires.	For CES-D, the weighted sensitivity was 100%; specificity 88%; and positive predictive value was 13±2%.	"We conclude that the criterion validity of the CES-D for major depression was very satisfactory in this sample of older adults."	Data suggest the CES-D is a valid screening tool for MDD in older individuals from the Netherlands.
Boey 1999	Center for Epidemio	Screening Tools	No mention of	N = 554 elderly	Mean age: 76.6	Depressive symptoms	The Center for Epidemiologic Studies	Cronbach a=0.78±0.79) for CESD-10. The CESD-10 had	"The CESD-10 attained satisfactory content	Data suggest a high degree of internal

(score=5.0)	logical Studies Depression Scale (CES-D)		sponsorship or COI.	subjects who were or were not clinically depressed.	years; 264 males, 287 females		Depression scale (CES-D) (n=554) vs. 10-item short form of the CES-D (CESD-10) (n=61). The CESD-10 was used as a small scale validation study.	comparable accuracy to the original CES-D in cases with depressive symptoms (k=0.84, p<0.01).	and temporal reliability. Its construct and concurrent validity were established. With its brevity, it should prove a useful mental health measure for the elderly."	consistency between the CESD-10 to the CESD-20 in screening depression in in Chinese elderly individuals.
Santen 2008 (score=5.0)	Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by GlaxoSmithKline, UK. No COI.	N = 765 patients diagnosed with Major Depressive Disorder (diagnostic criteria not mentioned) that previously participated in 1 of 2 studies	Mean age and gender of participants not mentioned	Major Depressive Disorder	Hamilton Depression Rating Scale (HAM-D) Subset 1: Seven items on the HAM-D17 scale identified as sensitive to response over time were depressed mood, feelings of guilt, suicide, work and interest, retardation, anxiety psychic, and anergia vs. HAM-D Subset 2: Seven items on the HAM-D17 scale identified as sensitive to response over	For Study 1: Analysis of the effects of paroxetine vs placebo on depression using the HAM-D17 was p=0.0566; with the HAM-D subset 1 p=0.0154; with the HAM-D subset 2 p=0.025 (p<0.05). For Study 2: Analysis of the effects of paroxetine vs placebo on depression using the HAM-D17 was p=0.0595; with the HAM-D subset 1 p=0.0063; with the HAM-D subset 2 p=0.0199 (p<0.05).	"[T]his study provides further evidence that not all items of the HAM-D17 scale are equally sensitive to detect responding patients in a clinic trial. A HAM-D7 scale is proposed consisting of the HAM-D6 and the suicide item. This response-based subscale increases the signal-to-noise ration and could reduce failure rate in efficacy trials with antidepressant drugs."	Data suggest not all HAM-D items are equally sensitive for detection responding patients who are in a clinical trial. (Not sensitive to treatment effects)

				measuring the effect of paroxetine to treat depression			time were depressed mood, feelings of guilt, work and interest, anxiety psychic, insomnia late, insomnia middle, and anergia. All participants were analyzed by both HAM-D subsets			
Kroenke 2001 (score=5.0)	Patient Health Questionnaire	Screening Tools	No mention of COI. Sponsored by the Pfizer US Pharmaceuticals.	N = 6,000 patients from 8 primary care and 7 obstetrics-gynecology clinics	Mean age: 38.5 years; 1,020 males, 4,980 females	Major depression, mild/moderate/moderately severe/severe depression	Patient Health Questionnaire-9 (PHQ-9) vs. 20-item Short-Form General Health Survey. All participants completed both measurements	PHQ-9 cutoff score ≥ 10 had sensitivity = 88% and specificity = 88% for major depression	"In addition to making criteria-based diagnoses of depressive disorders, the PHQ-9 is also a reliable and valid measure of depression severity. These characteristics plus its brevity make the PHQ-9 a useful clinical and research tool."	Data suggest PHQ-9 makes reliable and valid assessments of depression severity and is shorter making it more useful.
Henkel 2004 (score=5.0)	Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 487 adults with diagnosed with depression	Mean age, number of males, and number of females is not	Depression	Single-item World Health Organization Well Being Index (WHO-5): five-item scale, administered once vs. Two-item World Health	Single-item screening questions were deemed inadequate. There was no significant difference between the Areas under the curve (AUC) values of both tests (0.85, 95% CI 0.79-0.92 vs 0.86, 95% CI 0.81-0.91).	"The PHQ is a good screening instrument to use when a quick diagnosis is needed and computer scoring methods are not available, and when missing	Data suggest depression screening may be able to be performed by two questions for increasing ease of labor both by the administrator

					reported.		Organization Well Being Index (WHO-5): five-item scale, administered once All participants completed both tests.		some cases is acceptable."	and the patient.
Burnam 1988 (score=5.0)	Psychological Interview, Center for Epidemiologic Studies Depression Scale (CES-D)	Screening Tools	Supported by the Robert Wood Johnson Foundation, Kaiser Family Foundation, Pew Memorial Trust, and NIMH. No COI.	N = 3132 patients from the Los Angeles Epidemiologic Catchment Area Study (ECA) and Psychiatric Screening Questionnaires for Primary Care	Mean age: 41 years; 1472 males, 1660 females	Clinical depression	Center for Epidemiologic Studies Depression Scale (CES-D): 20-item questionnaire vs. Diagnostic Interview Schedule (DIS): two items from DIS considered All participants completed both tests, all tests administered once.	Maximal sensitivity for all but one sample was at a cutoff of 0.009. The screener had high sensitivity (89%) and good positive predictive value (PPV) at a cutoff of 0.060, only slightly lower than the highest achievable for the given range of sensitivity.	"The high predictive utility of the screener, in combination with its brevity, suggest that it may be a useful tool for screening for depression in health care settings."	Data suggest development of a shorter 8 item screening tool may be useful for screening depression in health care settings due to high predictive ability.

				Patients (PSP)						
Whooley 1998 (score=5.0)	Psychological Interview, Center for Epidemiologic Studies Depression Scale (CES-D), Beck Depression Inventory (BDI)	Screening Tools	Supported by the University of California, San Francisco School of Medicine and the Department of VA Health Services Research. No mention of COI.	N = 536 adult patients with DIS-III-R diagnosed major depressive disorder.	Mean age: 53 years; 522 males, 14 females	Clinical depression	Long form of the Center for Epidemiologic Studies Depression Scale (CES-D): 20-item questionnaire vs. Short form of the Center for Epidemiologic Studies Depression (CES-D): 10-item questionnaire vs. Beck Depression Inventory (BDI): 21- item scale vs. Short form of Beck Depression Inventory (BDI):13-item scale vs. Medical Outcomes Study (MOS): 8-item scale vs. Symptom Driven Diagnostic System for Primary Care (SDDS-PC): 5-item scale	Throughout the comparison of the instruments with the various cutoff points, there was a range of specificity (51%-72%) and sensitivity (89%-96%). Areas under the receiver operating characteristics (ROC) were similar in all (0.82-0.89). The two-item instrument had a specificity of 57% and sensitivity of 96%.	"The two-question case-finding instrument is a useful measure for detecting depression in primary care. It has similar test characteristics to other case-finding instruments and is less time-consuming."	Data suggest a two-question tool for screening depression has a sensitivity of 96% with a specificity of 57%.

							All participants completed both tests, all tests administered once.			
Kung 2013 (score=4.5)	Patient Health Questionnaire, Beck Depression Inventory (BDI)	Screening Tools	No COI or sponsorship.	N = 625 primary care patients	No mention of mean age or gender distribution	Mood disorders	Patient Health Questionnaire (PHQ-9) vs. Beck Depression Inventory-II (BDI-II). All participants completed both measurements	Strong overall correlation (r=0.77) between outpatients and inpatients. Stronger effect for outpatient group (r=0.81) compared to inpatient group(r=0.67)	"PHQ-9 and BDI-II scores, as continuous but not categorical variables, in a mood disorders subspeciality setting are closely correlated and essentially interchangeable. There are practical applications to our findings, as the PHQ-9 is shorter and free."	Data suggest both PHQ-9 and BDI-2 are closely correlated but the PHQ-9 is shorter.
Bech 2014 (score=4.5)	Hamilton Depression Rating Scale (HAMD)	Screening Tools	COI, one or more of the authors have received or will receive benefits for personal or professional use. No	N = 765 patients with MDD (diagnostic criteria not mentioned) and no missing	Mean age: 42.6 years; 283 males, 482 females	Major Depressive Disorder	Hamilton Depression Rating Scale (HAM-D) 6 subscale of HAM-D17 comprised of 1 (depressed mood), 2 (feelings of guilt), 7 (work activities, 8 (psychomotor retardation), 10	The null hypothesis of ordered location of the items, unidemensionality, was rejected for MADRS-5 (p=0.0021) and MADRS-6 (p=0.0016), but not for HAM-D6 (p=0.001). Cronbach's alpha coefficient was 0.91 for MADRS-6, 0.87 for MADRS-5, and 0.81 for HAM-D6.the Cronbach alpha	"[T]he HAM-D6 fulfils the Rasch criteria of unidemensionality as well as invariance across time or centres in the GENDEP study. By contrast, the MADRS5 was not accepted. On this basis we recommend the use of the HAM-D6 as	Data suggest HAM-D6 not MADRS5 is a valid tool to measure chance in antidepressant clinical trials.

			mention of sponsorship	values on the rating scale items (HAM-D17 & MADRS-10) at baseline, from previous study known as GENDEP analysis (Bech 2013)			(psychic anxiety), and 13 (general somatic symptoms) vs. The MADRS-5 subscale of the MADRS-10 covered apparent sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. All participants were analyzed by both subscales	coefficient for the HAM-D17 and MADRS-10 were above 0.82 and 0.88, respectively. The coefficient of homogeneity for the HAM-D17 is 0.27, 0.41 for the HAM-D6, 0.51 for the MADRS-5, and the MADRS-10 is 0.46.	outcome scale in trials of antidepressants."	
Zimmerman 2012 (score=4.5)	Clinically Useful Depression Outcome Scale (CUDOS)	Screening Tools	No sponsorship or COI.	N = 53 outpatient psychiatric patients who had ongoing treatment for depression	Mean age: 45.1 years; 13 males, 40 females	Major depressive disorder	Clinically Useful Depression Outcome Scale (CUDOS): Paper administration, completed once after an appointment with a psychiatrist vs. Clinically Useful Depression Outcome Scale-Web (CUDOS-W): Internet or	CUDOS and CUDOS-W were completed within a mean of 1.2 days of each other (SD=0.9). A high correlation in answers was seen between the two set of tests ($p<.001$). Mean scores were approximately the same for web and paper administration; item-scale correlations for web vs paper versions	"The results of this first study of the use of a Web-based system of monitoring outcome in routine clinical practice supported the reliability and validity of Internet administration of a depression scale, and patients clearly preferred Internet	Data suggest web-based CUDOS appears valid and reliable for assessment of depression.

				based on the DSM-IV scale			web administration, completed once 48 hours before an appointment with a psychiatrist. All participants completed both measurements.	were high (web=0.74 median, paper=0.76 median), each item in CUDOS and CUDOS-W had a substantial correlation (median=0.86). Patients preferred to complete the test via Internet administration (100%, (p<.001)).	administration to completion of a paper-and-pencil questionnaire in the office."	
Wong 2011 (score=4.5)	Center for Epidemiological Studies Depression Scale (CES-D), Beck Depression Inventory (BDI)	Screening Tools	No sponsorship or COI.	N = 366 Chinese participants with chronic pain	Mean age: 41.04 years; no mention of gender.	Depression	The Revised Clinical Interview Schedule (CIS-R) vs. the Beck Depression Inventory Standard and Short Forms (BDI/BDI-SF) vs. the Centre for Epidemiological Studies-Depression scale (CES-D). All participants completed the questionnaires	Results of receiver operating characteristic (ROC) curve analyses showed that all the three measures performed well at predicting depression with e area under the curve (AUC) ≥0.89 and high sensitivity and specificity.	"Our findings suggest that the three depression measures assessed have good predictive validity in the Chinese chronic pain context, and they could be used as screening or diagnostic measures of depression in Chinese chronic pain patients."	Data suggest BDI, CIS-R and CES-D have good predictive validity in screening depression in Chinese people but depression prevalence greatly varied according to location (i.e., pain clinic much higher than orthopedic clinic).
Beck 1997 (score=4.5)	Beck Depression	Screening Tools	No mention of	N = 50 patients hospita	Mean age: 39.72 years;	Major Depressive Disorders	Depressive symptoms assessed with Beck Depression	The correlation between BDI-PC and HDS scores was 0.62 (p<0.001). The	"A BDI-PC cut-off score of 4 and above was found to correctly classify	Data suggest the BDI-PC showed moderate

	Inventory (BDI)		sponsorship or COI.	lized for general medical problems and referred to the psychiatric service	20 male, 30 female		Inventory for Primary Care (BDI-PC) (n=50) vs. Depressive symptoms assessed with HDS scale (n=50) vs. Depression assessed by Mood Module (MM) section of PRIME-MED during clinical interview (n=50) All participants were assessed by all 3 measures	correlation between BDI-PC and MDD diagnosis was 0.66. ($p<0.001$). The correlation between HDS and MDD diagnosis was 0.37 ($p<0.01$). The mean BDI-PC score of the 33 inpatients with MDD (7.85) was 4.6 times higher than the mean PDI-PC score of the 17 patients without MDD (1.70) ($p<0.001$).	patients as being diagnosed with or without MDDD 82% of the time."	correlation to HDS (r=0.62) and has good internal consistency ($\alpha = 0.86$).
Viinamaki 2004 (score=4.5)	Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD)	Screening Tools	No mention of sponsorship. One or more of the authors has received or will receive benefits for personal or	N = 125 outpatients with suspected, but not diagnosed, depressive disorder	Mean age: 44 years; 44 male, 81 female	Major Depression	Assessed by Global Assessment of Functioning Scale (GAF) (n=125) vs. Assessed by Hamilton Rating Scale for Depression (HAMD) (n=125) vs. Diagnosed by Structured Clinical Interview for DSM-III-R by	For BDI-21: A cut-off score of 8/9 had 0.963 sensitivity, 0.375 specificity, and 0.338 Youden's index. A cut-off score of 10/11 had 0.917 sensitivity, 0.438 specificity, and 0.355 Youden's index. A cut-off score of 12/13 had 0.872 sensitivity, 0.625 specificity, and 0.497 Youden's index. A cut-off of 14/15 had 0.835 sensitivity, 0.813 specificity, and 0.648	"[W]ith a cut-off point of 14/15 the BDI-21 can be used to indicate the presence of a major depressive episode regardless of the phase of the major depressive disorder."	Data suggest the same BDI-21 Item cut-off point is appropriate for major depression screening among outpatients in any phase of the disease.

			professional use.				experienced interviewer (n=125) vs. Assessed with the 21-question Beck Depression Inventory (BDI-21) (n=125). All participants were assessed by each method at both baseline and 24-month follow-up.	Youden's index. As the cut-off score increased, sensitivity decreased and specificity increased. Youden's index was highest at 14/15.		
Doraiswamy 2010 (score=4.5)	Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)	Screening Tools	Sponsored by National Institute of Mental Health (NIMH), USA. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 229 participants who met the DSM-IV criteria for major depressive episode (MDE).	Mean age: 73 years; 89 males, 140 females	Depression	Montgomery-Asberg Depression Rating Scale (MADRS) vs. the Quick Inventory of Depressive Symptomatology –Clinician rated (QIDS-C16) vs. the Quick Inventory of Depressive Symptomatology -Self-report (QIDS-SR16). All participants completed the questionnaires.	With nearly equal Cronbach alpha reliability (0.85–0.89), all three scales were unidimensional.	"All three tests are valid for detecting geriatric major depression with the QIDS-C16 being slightly better. Self-rated QIDSSR16 is recommended as a screening tool as it is least expensive and least time consuming."	Data suggest QIDS-C16, MADRS and QIDS-SR16 perform similarly for screening of geriatric depression but the QIDS-SR16 is less costly and less time consuming.

Schaefer 1985 (score=4.5)	Zung Depression Scale, Beck Depression Inventory (BDI)	Screening Tools	No mention of sponsorship or COI.	N = 200 patients in a psychiatric ward (n=101) and chemical dependency ward (n=99).	Mean age: 38.2 years; 200 males, 0 females.	Depression	Beck Depression Inventory vs. Zung Self-Rating Depression Scale vs. Minnesota Multiphasic Personality Inventory Depression. All participants received the three measurements.	The Zung scale showed the highest validity ($p<0.05$) and the MMPI Depression scale had the lowest ($p<0.05$). The BDI has a bigger correlation than MMPI with the criteria ($p=0.0032$). There was no significant difference between means in the psychiatric-sample subjects ($p>0.015$).	"The results favor the Zung over the MMPI-D scale and, to a lesser degree, the BDI as a measure of depressive symptomatology in men."	Data suggest Zung better than Beck which is better than MMPI via validity coefficients and clinical ratings of depression. MMPI is the older version of the MMPI-2.
Blumenthal, 1975 (score=4.5)	Zung Depression Scale	Screening Tools	Sponsored by National Institute of Mental Health. No mention of COI.	N = 320 participants that are married. 160 couples included.	Ages not provided; 160 males, 160 females.	Depressive symptomatology	The relationship that work, social relationships and marriage has with depressive symptoms using Zung Self-Rating Depression Scale. All participants completed the self-rating depression scale.	13% of respondents had similar scores to those obtained from patients with diagnosed depressions. 27% similar to people with other psychiatric problems.	"The data presented in this report suggest that depressive symptomatology, as measured by the Zung SDS, in a general population, is associated with a reduced capacity for enjoyment and participation in major role functions."	Data suggest depression is correlated with major life functions of social life, job satisfaction and marital function as measured by the Zung SDS in a general population.
Schaefer 1985 (score=4.0)	MMPI Depression Scale, Beck Depression	Screening Tools	Sponsored by the Veterans Administration Medical	N = 101 inpatient psychiatric	Mean age: 38.2 years; 200	Depression	Beck Depression Inventory vs Zung Self-Rating Depression Scale vs Minnesota Multiphasic	Zung showed best T-test correlations ($p=0.15$) compared to MMPI-D ($p=0.50$) and to BDI ($p=0.54$). Estimated alpha	"The results favor the Zung over the MMPI-D scale and, to a lesser degree, the BDI as a measure of	Data suggest Zung validated DSM-III depression criteria better

	Inventory Scale, Zung Self-Rating Depression Scale		Research Service. No mention of COI.	ward patients and 99 chemical dependency ward patients	males, 0 females		Personality Inventory was taken by all participants	coefficients were 0.94 (psychiatric ward patients) and 0.88 (chemical ward patients) for BDI, 0.9 (psych patients) and 0.86 (chemical ward) for Zung, and 0.81 (psych patients) and 0.72 (chemical ward) for MMPI-D.	depressive symptomatology in men. Additional research on the scales' validities in women would be useful."	than Beck and both were better than MMPI. MMPI is the older version of MMPI-2. This is a screening tool not a psychological test
Romera 2008 (score=4.0)	Zung Depression Scale	Screening Tools	No mention of sponsorship. COI, Irene Romera, Helena Delgado-Cohen and Inmaculada Gilaberte are full-time employees of Lilly S.A.	N = 1138 patients diagnosed with MDD according to the DSM-IV guidelines.	Mean age: 55 years; 282 males, 856 females.	Depressive symptoms	Factor structure and composition of Zung Self-Rating Depression Scale to find different symptomatic dimensions of depression. All participants completed the self-rating depression scale.	Females had higher Factor 3 scores ($p<0.001$). Participants 65 years and older had higher scores in both factor 1 and factor 4 ($p<0.001$, $p=0.0002$). Participants living in rural or semi-rural areas had higher factor 1 score ($p=0.0005$).	"Our findings suggest that depressive symptoms in patients with MDD in the PC setting cluster into four dimensions: core depressive, cognitive, anxiety and somatic, by means of a factor analysis of the ZSDS."	Data suggest MDD is composed of four dimensions: core depressive, cognitive, anxiety and somatic per Zung SDS analysis.
Trivedi 2004	Quick Inventory of	Screening Tools	Sponsored by 11 sponsors.	N = 946 out-	Mean age: 41.4	Major depressive disorder	The Inventory of Depressive Symptomatology,	Cronbach's alpha (internal consistencies) had a range of 0.81-	"The QIDS-SR16 and QIDS-C16, as well as the longer	Data suggest high internal consistency

(score=4.0)	Depressive Symptomatology Self Report (QIDS-SR)		No mention of COI.	patients with Major Depressive Disorder (MDD) (n=544) and Bipolar Disorder (BD) (n=402) with the DSM-IV criteria	years; 234 males, 712 females		Clinician Rating (IDS-C16) vs. The Inventory of Depressive Symptomatology, Self-Report (IDS-SR16) vs the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C16) vs the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16). All participants were analyzed with all four tests.	.094 for all four scales. The highest item-total correlations on all four scales were sad mood, involvement, energy, concentration, and self-outlook. QIDS-SR16 and IDS-SR30 total scores were highly correlated among patients with MDD at exit (c=0.83), as well QIDS-C16 and IDS-C30 total scores were also highly correlated among patients with MDD (c=0.82) and patients with BD (c=0.81).	30-item versions, have highly acceptable psychometric properties and are treatment sensitive measures of symptom severity in depression."	between all four scales and are sensitive to depression symptom severity.
Bernstein 2007 (score=4.0)	Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)	Screening Tools	Sponsored by 21 sponsors. No mention of COI.	N = 441 subjects with nonpsychotic Major Depressive Disorder according to	Mean age: 42.5 years; no mention of gender	Depression	Quick Inventory of Depressive Symptomatology –Clinician rated (QIDS-C16) vs. the Quick Inventory of Depressive Symptomatology -Self-report (QIDS-SR16). All subjects	In QIDS-SR16 and QIDS-C16, nine symptom domains related well to depression. Item Response Theory (IRT) for "a" in QIDS-C16 for sad mood was 2.29 and thoughts of death or suicide was 1.35. IRT for "a" QIDS-SR16 for sad mood was 2.44 and thoughts of	"In this less educated, socially disadvantaged sample, differences between the QIDS-C16 and QIDS-SR16 were minor. The QIDS-SR16 is a satisfactory substitute for the more time-consuming QIDS-C16 in a broad	Data suggest comparable performance between the QIDS-SR16 with small differences making the QQIDS-SR16 less time consuming.

				DSM-IV-TR criteria.			completed both questionnaires.	death or suicide was 1.18.	range of adult, nonpsychotic, depressed outpatients."	
Bernstein 2009 (score=4.0)	Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR), Psychological Interview, Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by National Institute of Mental Health (NIMH). No mention of COI.	N = 175 subjects with a DSM-IV-R diagnosis for depression	Mean age: 44.1 years; 73 males, 103 females.	Depression	16- item self-report version of the Quick Inventory of Depressive Symptomatology (QIDS-SR16) vs. 17- item Carroll Depression Rating Scale (CDRS-SR17) vs self-report modification of the Hamilton Rating Scale for Depression) vs. the thirteen depression items from the Symptom Check List-90 (SCL-D13) vs. The Mini version of the Structured Clinical Interview for DSM-IV (MiniSCID). All subjects completed the questionnaires.	SCL-D13 was the most reliable (a=0.91) and was the most sensitive to differences in depression for all but the most depressed patients. For the most depressed patients, the most sensitive was the CDRS-SR17. QIDS-SR16 was the most similar to MiniSCID in diagnoses.	"All three measures performed satisfactorily, but there are clearly defined advantages to using the QIDS-SR16, as, by its very design, it assesses the core symptoms of depression and does not require a clinician."	Data suggest fair performance of all 3 screenings but an advantage of the QIDS-SR is that it does not need clinical administration.

							MiniSCID was used as a "gold standard" for depression.			
Brown 2008 (score=4.0)	Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR), Hamilton Depression Rating Scale (HAMD)	Screening Tools	Sponsored by National Institutes of Health. COI: Brown received an investigator initiated research grant from Forest Laboratories and Rush is a paid consultant and speaker to them.	N = 90 subjects with Major depressive disorder (MDD) according to DSM-IV-TR.	Mean age: 41.6 years; 30 males, 60 females	Depression, Major Depressive Disorder	Quick Inventory of Depressive Symptomatology –Self-report (QIDS-SR16) vs. the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR30) vs. the 17-item clinician-rated Hamilton Rating Scale for Depression (HRSD17). All subjects completed all questionnaires.	Cronbach a values are .87 for the QIDS-SR16, .95 for the IDS-SR30, and .87 for the HRSD17 for internal consistency at exit. QIDS-SR16 and HRSD17 total scores were highly correlated (r = 0.85).QIDS-SR16 and IDS-SR30 total scores were also highly correlated (r = 0.97). All QIDS-SR16 item total score correlations were significant (P < .001). The QIDS-SR16, IDS-SR30, and HRSD17 had comparable sensitivity to symptom change, indicating high concurrent validity for all 3 scales.	"The QIDS-SR16 showed good reliability and impressive construct validity. Strong psychometric properties of this brief self-report format and its sensitivity to treatment change suggest that the QIDS-SR16 is a valuable clinical tool."	Data suggest QIDS-SR was reliable with excellent construct validity.
Bech 2013 (score=4.0)	Hamilton Depression Rating Scale (HAMD)	Screening Tools	No mention of sponsorship. No COI.	N = 60 patients with depressive illness accordi	Mean age: 47 years; 14 males, 46 females	Major Depressive Disorder	Hamilton Depression Rating Scale (HAM-D) 17 vs. Composite International Diagnostic	Principal Component Analysis (PCA) was used to test the items on the HAM-D17. Items in the scale were found to have a range of scores from -0.10 to 0.58 for	"For the HAM_D17, our results indicate that profile scores are needed because the total score of all 17 items the HAM-	Data suggest accurate PCA interpretation should occur prior to exploratory factor analysis

				ng to DSM-III-R			Interview (CIDI), version 1.0. All participants received both measurements	the first principal component and 0.00 to0.55 for the second component. Indicating that the items of the scale are weighted differently. (P-values not given.)	D17 does not give sufficient information."	as the sum of all HAM-D17 scores does not provide sufficient depression symptom information.
Keilp 2012 (score=4.0)	Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)	Screening Tools	Sponsored by "Governmental agencies and private foundations." No COI.	N = 400 medication-free individuals meeting the DSM-IV criteria for Major Depressive Disorder	Mean age: 37.8 years; 162 male, 238 female	Major Depressive Disorder, suicidal ideation	Assessed with the Hamilton Depression Rating Scale (n=396) vs Assessed with Beck Depression Inventory (BDI) (n=366) vs Assessed with the Scale for Suicide Ideation (SSI) (n=400)	There was a "robust" correlation between total SSI score and the single suicide item on the HDRS and BDI scales (p values not given). BDI factor scores for Subjective Depression and Self-Blame were most strongly associated with Suicidal Ideation (p values not given). HDRS scores for Psychic Depression and Loss of Motivation were most strongly associated with Suicidal Ideation (p values not given).	"Depression severity is moderately associated with suicidal ideation, and accounted for primarily by core mood disturbance symptoms and self-punitive thinking. These associations may explain why suicide risk might remain high during treatment eve through somatic and vegetative symptoms improve."	Data suggest there is only modest correlation between measurements of suicidal ideation and depression severity.
Zimmerman 2012 (score=4.0)	Hamilton Depression Rating Scale (HAMD), Clinicall	Screening Tools	No mention of sponsorship. No COI.	N = 274 patients with Major Depressive	Mean age: 49.0 years; 87 males,	Major Depressive Disorder	Hamilton Depression Rating Scale (HAM-D) 17 vs. DSM-IV Global Assessment of Functioning	Participants scoring a 0-2 on the HAM-D were more likely than those scoring 3-7 to score below 20 on the CUDOS (98.2% versus 66.3%; p<0.001) and	"[W]e propose distinguishing between patients who are highly likely to be in remission (0-2 on the HAMD) from	Data suggest a lower cutoff value should be used in the HAM-D17 to accurately screen for

	y Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-self report (QIDS-SR)			Disorder, according to the DSM-IV and/or a clinical interview	187 females		(GAF) scale vs. Clinically Useful Depression Outcome Scale (CUDOS) vs. Quick Inventory of Depressive Symptoms (QIDS) vs. Clinically Useful Anxiety Outcome Scale (CUXOS) vs. Patient Global Index of Severity of Depression (PGI) vs. Psychosocial functioning and quality of life subscales of the Diagnostic Inventory of Depression (DID). All participants completed all measurements	CUXOS (96.4% versus 53.5%; p<0.001) and were more frequently in the remission range on the QIDS (73.2% versus 34.9%; p<0.001). Participants scoring a 0-2 on the HAM-D were more likely than those scoring 3-5 to score below 20 on CUDOS (98.2% versus 81.1%; p<0.005) and CUXOS (96.4% versus 60.4%; p<0.001) and were more often in the remission range on the QIDS (73.2% versus 47.2%; p<0.01).	patients who are possibly in remission (score 3-7)."	depression remission.
Kounali 2016 (score=4.0)	Beck Depression Inventory (BDI), Patient Health Question	Screening Tools	Sponsored by the National Institute for Health Research. No	N = 32 articles with depressive participants, studies	No mention of mean age or sex.	Depression	Beck Depression Inventory (BDI I/II) (n=25) vs. Patient Health Questionnaire (PHQ9) (n=9) vs. Hamilton Rating for Depression 17	Coefficient variation of 13% (95% credible interval: 6%, 25%) for the between-instrument ratios of standardized treatment effects. The most responsive test was the PHQ9 while	"Information on relative responsiveness of several test instruments can be pooled across networks of trials reporting at least	Meta-analysis of various depression screening instruments suggest PHQ-9 is most

	naire, Hamilton Depression Rating Scale (HAMD)		mention of COI.	in the Cochrane Depression Anxiety and Neurosis (CCDAN) Review Group's register			items (n=35) vs. Hamilton Rating for Depression 24 items: (n=2) vs. Montgomery-Asberg Depression Rating (MADRS) (n=21) vs. EuroQoL (EQ-5D) (n=4) vs. SF36 mental component summary (SF36 MCS) (n=9) vs. Physical component summary (SF36 PCS) (n=6)	the least was BDI. EQ-5D and SF36 had poor responsiveness.	two outcomes, allowing comparison and ranking of test instruments that may never have been compared directly"	responsive and BDI is least
Stulz 2010 (score=4.0)	Beck Depression Inventory (BDI)	Screening Tools	Sponsored by a grant from the Swiss National Science Foundation. No mention of COI.	N = 270 subjects with MDD according to the DSM-IV	Mean age: 38.5 years; 92 males, 178 females	Depression	Beck Anxiety Inventory (BAI) vs. Beck Depression Inventory (BDI)-II vs. Structured Clinical Interview for DSM-IV Axis I disorders (SCID I) vs. Structured Clinical Interview for DSM-IV Axis II disorders (SCID II). All subjects	BAI Purified (BAI-P) and BDI Purified (BDI-P)'s correlation of the sum scores (r=0.17) was significantly lower ($p<0.001$) than the Beck inventories (r=0.43)	"In conclusion, our findings indicate that the purification of two widely used self reports to assess depression (the BDI-II) and anxiety (the BAI) does only marginally increase the ability to differentiate depressive and anxiety disorders using these self reports."	Data suggest purification of the BDI-II and the BAI slightly increases the ability to discriminate between depression and anxiety via these self-report tools

							completed all measurements at baseline.			
Rouch-Leroyer 2000 (score=4.0)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	No mention of sponsorship or COI.	N = 3,777 subjects who were 65 or older and met the DSM-III-R criteria	Mean age: 75.0 years; 1,122 males, 1,670 females	Depressive symptomology	The Center for Epidemiologic Studies Depression Scale (CES-D) 20-item scale: vs the CES-D 5-item scale. All participants took the CES-D 20 item and 5 item scale	CES-D score of 17 for men and 23 for women had a sensitivity of 0.76 and a specificity of 0.71. There was a high sensitivity (>87.5%) and a good specificity (>57%) for the five item version	"In conclusion, the 5-Item CES-D is a simple, rapid and reliable tool which could be useful for screening depressive symptoms in epidemiological studies of the elderly."	Data suggest use of shortened CES-D in screening for depression in the elderly as it is rapid and appears quite reliable.
Lewinsohn 1997 (score=4.0)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	Sponsored by grants from National Institute of Mental Health. No mention of COI.	N = 1,005 subjects with a depressive disorder according to DSM-III-R	Mean age: 63.9 years; 419 males, 586 females	Clinical depression	Center for Epidemiologic Studies Depression Scale (CES-D) 20 item vs CES-D 5 item. All participants completed the CES-D screenings.	There was moderate internal consistency (a=.60) and test-retest reliability (r=.45) for the 5 item CES-D Scale. Specificity and sensitivity was 80, and PPV was 26 (95% CI=.51-.69) for the cutoff point of 4.	"These results indicate that there was no significant degradation in the ability of the CESD to screen for depression among community-residing elderly adults."	Data suggest CES-D can be used as a depression screening tool.
Levine 2013 (score=4.0)	Center for Epidemiological Studies Depressi	Screening Tools	No mention of sponsorship or COI.	N = 12,686 subjects from the National	Mean age: 18.4 years; 6,403 males,	Depression, Major depressive disorder	Center for Epidemiologic Studies Depression Scale (CES-D) 20 item: Completed in 1992 (n=8,858)	CES-D-SF had a cut off score of greater than or equal to 8 with a specificity of 0.97 (95 % CI 0.96, 0.97) and modest sensitivity 0.69 (95 %	"The seven-item CES-D-SF has acceptable psychometric properties, is associated with exposures	Data suggest the CES-D-SF, a 7-item shorter form of the CES-D, is associated with an

	on Scale (CES-D)			Longitudinal Survey of Youth 1979 survey. No diagnostic criteria mentioned.	6,283 females.		vs 7-item CES-D-SF: completed in 1994 (n=8,500) . All subjects were interviewed annually from 1979 to 1994 and then bi-annually until 2010.	CI 0.67, 0.71) with the CES-D cutoff score of 16.	documented to be associated with an increased likelihood of depression, and may be used to screen for suspected major depressive disorder in US community studies."	increased probability of depression, and therefore is an acceptable screen.
Dorfman 1995 (score=4.0)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	Sponsored by health Care Financing Administration cooperative agreement . COI, one or more authors are professors or associate professors .	N = 1,911 subjects who are depressed according to the DSM-III-R criteria	Mean age was not mentioned; 567 males, 406 females	Major depression	Mental Health Inventory (MHI-5): a shortened version of MHI developed by the Rand Corporation vs the Center for Epidemiologic Studies Depression Scale (CES-D). The two tests were given over the phone (n=973). Subjects with a score greater than 16 for CES-D or below 17 for MHI-5 was clinically evaluated at a clinic/social work	22.3% was clinically confirmed with major depression. 29.5% felt pervasive depressed mood (p<.001). In 35.6% of the subjects who was diagnosed by the CES-D or MHI-5 scores, clinical evaluation revealed no depression but may be false positives.	"Overall findings indicated that a telephone screening instrument incorporating the Rand Mental Health Inventory and the Center for Epidemiological Studies Depression Scale was an efficient tool for assessing a population with a higher rate of major depression."	Data suggest a telephone screening tool combining both the CES-D and Rand depression scale was appropriate in screening a population of older individuals considered to be well.

							station to determine the participants met the DSM-III-R criteria (n=220).			
Cosco 2017 (score=4.0)	Center for Epidemiological Studies Depression Scale (CES-D)	Screening Tools	No mention of sponsorship or COI.	N = 1,233 subjects. No diagnostic criteria mentioned.	Mean age: 54.5 years; 534 males, 699 females	Depression	Model 1: one factor model vs Model 2: two factor model with general depression and positive affect (PA) vs Model 3A: three factor model with PA, Interpersonal (IP) and a combined depressive affect and Somatic/Vegetative factors (SV) factor vs Model 3B: Three factor model with IP, SV, a combined depressive affect and PA factor vs Model 4: Radloff's four factor model. Models were derived from the Center for Epidemiological Studies-	Cronbach's alpha was 0.90. With the four factors in model 4, depressed affect had a 0.79 PA ($p<.001$) and an IP of 0.69 ($p<.001$). Four factor model had the highest values for Tucker Lewis Index and Comparative Fit Index and the lowest of Root Mean Square Error of Approximation and Standardized Root Mean Square.	"High internal consistency was demonstrated alongside a replication of the original 4-factor structure. Continued use of the CES-D in noninstitutionalized populations is warranted."	Data suggest the original 4-factor model of the CES-D had the best fit (internal consistency, and confirmatory factor analysis) for screening depression in middle-aged adults.

							Depression (CES-D). All participants were analyzed using these models			
Lowe 2004 (score=4.0)	Patient Health Questionnaire	Screening Tools	Sponsored by the Max-Kade-Foundation, New York, the John A. Hartford Foundation, the California Health Care Foundation, the Hogg-Foundation, and the Robert Wood Johnson Foundation. No mention of COI.	N = 434 participants recruited from the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial	Mean age: 70.9 years; 160 males, 274 females	Major depression, partial remission, full remission	Structured clinical interview for DSM-IV (SCID) vs. Hopkins Symptom Checklist Depression Scale (SCL-20) vs. Medical Outcomes Study 12-item Short-Form Health Survey (SF-12, Version 1) vs. Patient Health Questionnaire (PHQ-9)	PHQ-9 effect size for responsiveness significantly greater than SCL-20 at 3 months (-1.3 vs. -0.9) but not significantly great at 6 months (-1.3 vs. -1.2)	"Well-validated as a diagnostic measure, the PHQ-9 has now proven to be a responsive and reliable measure of depression treatment outcomes."	Data suggest the PHQ-9 is reliable and valid for measuring depression and treatment outcomes but because it is brief, it has added appeal.
Spangenberg 2015	Patient Health Questionnaire	Screening Tools	Sponsored by the University of	N = 193 participants	Mean age not mentioned, age	Major depression, dysthymic	All participants filled out both the patient health questionnaire	PHQ-9 P&P optimal cutoff ≥ 8, sensitivity (SEN) = 85.7, specificity (SPEC) =	"In summary, our findings suggest that no severe effect of mode of	Data suggest comparable efficacy between paper

(score=4.0)			Leipzig. No COI.	recruited from 9 public practices	range from 60-90; 79 males, 114 females	disorder, minor depression, depressive disorder	(PHQ-9) vs. Aachen Depression Item Bank (ADIB) in both tablet and pen-and-paper formats. Participants randomized to order of administration: tablet (TAB) first then pen-and-paper (P&P) (n=95) vs. pen-and-paper then tablet (n=98)	83.2. PHQ-9 TAB optimal cutoff ≥ 5, SEN = 85.7, SPEC = 69.7. ADIB P&P optimal cutoff ≥ -.923, SEN = 83.3, SPEC = 85.9. ADIB TAB optimal cutoff ≥ -1.054, SEN = 85.7, SPEC = 85.6. Mode of administration did not impact detection rates in either instruments	administration on self-report assessments of depression should be expected."	and pencil administration and tablet administration for self-report of depression assessments.
Thapar 2014 (score=4.0)	Patient Health Questionnaire	Screening Tools	No COI. Sponsored by the Sir Jules Thorn Charitable Trust, The National Institute for Social Care and Health Research Academic Health Science Collaboration, and	N = 337 participants from families with a history of depression	Mean age: 42 years; 22 males, 315 females	Recurrent depression	9-item Patient Health Questionnaire (PHQ-9) vs. 7-item Hospital Anxiety and Depression Scale depression subscale (HADS-D) vs. 21-item Beck Depression Inventory (BDI) vs. 4-item Patient Health Questionnaire (PHQ-4) vs. 2-item Patient Health	Area under the curve (AUC) and positive predictive value (PPV) at optimal cut-off values for three longer questionnaires comparable (AUC = 0.86–0.90, PPV = 49.4–58.4%). AUC for PHQ-9 significantly greater than for PHQ-2	"A novel four-item PHQ-based questionnaire measure of depression performs equivalently to three longer depression questionnaires in identifying depression relapse in patients with recurrent MDD."	Data suggest a 4-item PHQ-questionnaire to measure depression is comparable in performance to 3 longer questionnaires for depression relapse identification.

			The Waterloo Foundation.				Questionnaire (PHQ-2). All participants completed all measurements			
Walter 2003 (score=4.0)	Psychological Interview, Beck Depression Inventory (BDI)	Screening Tools	No mention of sponsorship or COI.	N = 650 primary care patients that participated in a depression overview information session	Mean age: 54.7 years; 217 males, 433 females	Depression	D-ARK: Depression Arkansas Scale consisting of 11 items corresponding to DSM-IV criteria for major depressive disorder (n=650) vs BDI-2: Beck Depression Inventory 2 Scale consisting of 21 items that identify intensity of depression in clinical and non-clinical patients (n=457) vs GDS: Geriatric Depression Scale consisting of 30-item scale designed to assess depression in older patients (n=193) vs SF-12: Short-form 12 scale	Reliability of the D-ARK scale was 0.84 compared to 0.86 for BDI-2 scale. Severity scale showed internal reliability (α=0.81-0.86) correlation with BDI-2 (r=0.78-0.83) and GDS (r=0.75).	"This study supports and enlarges on previous work in finding the D-ARK to be a reliable and valid instrument for assessing depression in several clinical settings. In light of its brief length, availability in the public domain, multiple outputs, and the availability of equivalent cutpoints from standard depression scales with the current study, practitioners may find the D-ARK a useful tool for many clinical and organizational purposes."	Data suggest the D-ARK is valid and reliable for screening for MDD.

							consisting of 12 item scale that deciphers chronic medical health and mental health problems (n=487)			
Zimmerman 1987 (score=4.0)	Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 164 relatives of normal control probands with the Diagnostic Interview Schedule (DIS)	Mean age: 39.5±16.0 years; 87 males, 98 females	Major Depressive Disorder (MDD)	IDDL: received inventory to diagnose depression lifetime version that consists of 22 groups of 5 statements vs DIS: received diagnostic interview schedule that generates diagnosis with and without reference to exclusion criteria for depression and major depressive disorder. All participants received both measurements	Agreement between DIS and IDDL was 91% (κ=0.60). Sensitivity of IDDL was 74% and its specificity was 93%.	"In conclusion, the present results suggest that it is possible to assess a lifetime history of MDD with a self-report scale. The IDDL is a psychometrically sound instrument which showed good concordance with a structured psychiatric interview."	Data suggest it is possible to assess lifetime history of MDD with a self-reported scale (IDDL).
Terluin 2002 (score=4.0)	Psychological Interview	Screening Tools	Sponsored by Solvay Pharma, Weesp,	N = 52 patients with major	Mean age: 40.4 years;	Major Depressive Disorder (MDD)	SDS: received Zung Self-rating Depression Scale vs HADS:	Diagnosis of depression assessed by general practitioners compared to results of self-report	"The validity of the diagnosis of major depression assessed by the GPs, as	Data suggest caution should be applied when

			and the Netherlands. No mention of COI.	depression (DSM-IV)	25 males, 27 females		received Hospital Anxiety and Depression Scale vs 4DSQ: received the four dimensional symptom questionnaire that measures distress, depression, anxiety and somatization. All participants received both measurements	depression questionnaires was r=0.35-0.61 (p<0.05). Reproducibility of diagnosis of depression was good (kappa=0.63).	compared to results of the self-report depression questionnaires, was satisfactory."	assessing the potential presence of depression in general practice when using SDI.
Zimmerman 1987, B (score=4.0)	Psychological Interview	Screening Tools	No mention of sponsorship or COI.	N = 398 relatives of psychiatric patients and normal controls	Mean age: 41.0±16.3 years; 181 males, 217 females	Major depressive disorder (MDD)	DIS: received diagnostic interview schedule that generates diagnosis with and without reference to exclusion criteria for depression and major depressive disorder vs IDD: received inventory to diagnose depression consisting of 22 groups of 5	Sensitivity of IDD was 54.5% and specificity was 98.5%. Overall agreement between IDD and DIS was 97.2%.	"The point prevalence of MDD was nearly identical according to the IDD (3.0%) and the DIS (2.8%). Moreover, we found good concordance between the two methods of diagnosing MDD."	Data suggest good concordance between the IDD and DIS.

							statements used to diagnose major depressive disorder. All participants received both measurements			
Bech 2015 (score=3.5)	Psychological Interview, Hamilton Rating Scale									Data suggest the subscales of depression, anxiety, and apathy contained in the CID appears appropriate for use in general practice.1
Kadouri 2007 (score=3.5)	Psychological Interview									Data suggest the iCGI can be improved.
Boisvert 2003 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest the CES-D scale can screen for depressive symptoms in military men and women.

1 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Chen 2006 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest factor validity for the CES-D10 using the three-factor model as it distinguished between depressed affect somatic symptoms and positive affect.
Li 2009 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest the CES-D may be useful as a first live screening tool to be followed up with a diagnostic tool
Williams 2007 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest the four-factor CES-D is appropriate for African American women but does vary with age.2
Zhang 2011	Center for Epidemio									Data suggest a four-factor model of the

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(score=3.5)	logical Studies Depression Scale (CES-D)									CES-D provides better fit for the 4 domains of somatic complaints depressed affect, positive affect and interpersonal problems.
Thomas 2004 (score= 3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data support 3 factor versus 4 factor structure in screening low income women for depression
Arean 1997 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest CES-D performs relatively well as a depression screening tool in older persons but item function reliability is decreased if age and ethnicity is not accounted for.

Beeher 1998 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest CES-D is an appropriate tool for screening depression in newly diagnosed cancer patients.3
Chung 2015 (score=3.5)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest similar performance for screening depression in CESD-20, PHQ-9, and PROMIS-D-8, in MS and spinal cord injury patients.
Campbell 2010 (score=3.5)	Beck Depression Inventory (BDI), Zung Depression Inventory									Data suggest BDI-II demonstrates better psychometric properties than the Zung.

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Steer 1997 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest BDI-II has good internal consistency for depression screening in psychiatric outpatients.
Faravelli 1986 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest all of the scales show significantly different factorial structures which equate to different concepts of depression which form the basis of these scales.
Kneipp 2010 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest the BDI-II and PHQ-9 perform comparably among low income women.4
Vanheule 2008	Beck Depressi									Data suggest Beck's model

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(score=3.5)	on Inventory (BDI)									was not a good fit for all criteria, thus, a model with unidimensional subscales that assesses somatic, affective and cognitive dimension was best.
Palmer 2014 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest the 3 factor model of the BDI-II provides the best fit.
Dahlstrom 1990 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest the BDI should be administered in a random order to adequately capture a higher number of depression scores.
Burkhart 1984 (score=3.5)	Beck Depression Inventory (BDI)									Data suggest projected protocols may serve as practical alternative to

										the current BDI which enhance the predictive validity and correlate more closely to the Hamilton Rating Scale.5
Piersma 1994 (score=3.5)	Brief Symptom Inventory									Data suggest both males and females reported statistically significant decreases on all BSI scales and global indices from admission to discharge.
Meijer 2011 (score=3.5)	Brief Symptom Inventory									Data suggest depression and anxiety are most closely related to psychological distress not somatization.
Williams 1988	Hamilton Depression Rating									Data suggest the use of a structured

5 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score=3.5)	Scale (HAMD)									interview guide for the HDRS improves individual item reliability.
Caldierarro 2015 (score=3.0)	Hamilton Depression Rating Scale (HAMD)									Data suggest melancholic depression is a more severe subtype of major depression per the CORE measure of psychomotor disturbance.6
Luckebaugh 2015 (score=3.0)	Hamilton Depression Rating Scale (HAMD)									Data suggest the full HDRS-17 has too many items but to identify rapid antidepressant effects, more than 2 items but less than 17 are required.
Foley 2002	Center for									Data suggest the CSE-D

6 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score=3.0)	Epidemiological Studies Depression Scale (CES-D)									captures differences in depressive symptoms across different ethnic populations.
Love 2006 (score=3.0)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest the 4 factor CES-D model for depression may not be an appropriate model for older urban black men.
Chaplesk i 1997 (score=3.0)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest 12 item Liang version of CES-D may be best suited for American Indians.7
Al-Modallal 2010 (score=3.0)	Center for Epidemiological Studies Depressi									Data suggest CES-D (both 20 item and 16 item) appear valid for screening

7 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

	on Scale (CES-D)									depressive symptoms in Jordanian women.
Carlson 2011 (score=3.0)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest reversed items are generally less reliable than non-reversed items.
Gomez 2015 (score=3.0)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest support for bi-factor model of CES-D without using positive affect (PA) items.
Fong 2016 (score=3.0)	Center for Epidemiological Studies Depression Scale (CES-D)									Data suggest bi-factor model of CES-D may be best for screening. depressive symptoms.
O'Hara 1998 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the BDI-II appears to be comparable to the original BDI. It may

										be possible to improve it if additional data such as population-specific cutoff scores to estimate depression severity.8
Beck 1984 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the 1961 and 1978 versions of the BDI are highly internally comparable.
Beck 1996 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the BDI-IA and BDI-II both have comparable levels of high internal consistency, with both containing 21 symptoms that all correlate with self-reported depression.

8 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Viljoen 2003 (score=3.0)	Beck Depression Inventory (BDI)									Preliminary evidence suggest it may be possible to divide the BDI-II into a two-factor analysis of cognitive and somatic subscales.9
Tsujii 2014 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest there are differences between self and observer rated depression severities which are associated with suicide risk in MDD even when evaluated as mild.
Steer 1998 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the diagnostic composition and different severities of anxiety and

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										depression likely influence self-reported anxiety and depression.
Campbell 1984 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the BDI is useful due to internal consistency but the three BDI items of mood, sense of failure and satisfaction appear to account for most of the variance.
Quilty 2010 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest different populations may exhibit different factor structure of the BDI-II.10
King 1982 (score=3.0)	Beck Depression									Data suggest no difference in BDI scores for subclinical

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	Inventory (BDI)									depression whether in public or private. Also, there were no significant gender response differences observed.
Ward 2006 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the general factor model gives an acceptable explanation of item covariance.
Ahava 1998 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest over 8 weeks, there was an observed 40% decline in BDI scores likely due to measurement error not any real change in depression.
Ball 2003 (score=3.0)	Beck Depression Inventory (BDI)									Data suggest the BDI-II mean score and the mean number of

										symptoms endorsed by the outpatients with MDD were significantly higher than those for outpatients with a Dysthymic Disorder (ps<.001).11
Knight 1997 (score=3.0)	Center of Epidemiological Studies Depression Scale (CES-D)									Data suggest the CES-D is impacted by health problems as reflected in the measurement of the subscales measuring somatic depression items.
Hertzog 1990 (score=3.0)	Center of Epidemiological Studies Depressi									Data support use of CES-D for a depression screening tool

11 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

	on Scale (CES-D)									in older individuals.
Guo 2017 (score=3.0)	Patient Health Questionnaire									Data suggest PHQ-9 is a valid and robust outcome measure.
Turvey 2012 (score=2.5)	Patient Health Questionnaire									Data suggest only moderate correlation between the IVR and the pencil and paper PHQ-9 but IVR is not as sensitive to higher levels of depressive symptom severity.12
Yang 2007 (score=2.5)	Center of Epidemiological Studies Depression Scale (CES-D)									Data suggest 3 items in the CES-D show significant evidence of response bias.
Grzywacz 2010	Center of Epidemiological									Data support use of the short CES-D

12 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score=2.5)	Studies Depression Scale (CES-D)									in the screening of mental health conditions (inclusive of depression) in Latino farm workers.
Posner 2001 (score=2.5)	Center of Epidemiological Studies Depression Scale (CES-D)									Data suggest the 4 factor model proposed by Radloff did not fit well in Latino men but when age and acculturation were adjusted for, it was appropriate for Latino women.
Rapson 2016 (score=2.5)	Center of Epidemiological Studies Depression Scale (CES-D)									Data suggest gender and sexual orientation affects depression experiences as reflected in the CES-D.13

13 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Psychometric Testing

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Mogge 2008 (score=8.0)	Personality Assessment Inventory, Zung Depression Scale, Beck Depression Inventory	Screening Tools and Psychometric Testing	No mention of COI or sponsorship	N = 96 participants who were referred due to psychiatric concerns	Mean age: 47.52 years; 48 males, 48 females	Depression	Assessment Depression Inventory Depression Scale (Dep) vs. Beck Depression Inventory – II (BDI II) vs. Zung Self-rating Depression Scale (ZSDS) vs. Personality Assessment Inventory (PAI). All participants took all assessments	ADI Dep scale correlated with the PAI Dep scale, BDI – II, and ZSDS significantly ($p < 0.01$).	"Results of this study suggest that the ADI, as a measure of depression, may have utilitarian value in an outpatient setting."	Data suggest high correlation between ADI and ZSDS, BDI II and PAI depression scales.
Piersma 1991 (score=7.5)	Millon Clinical Multiaxial Inventory-II (MCMI-II)	Screening Tools and Psychometric Testing	No mention of sponsorship or COI.	N = 109 inpatients with a diagnosis of a primary Axis I diagnosis of a depressive disorder according to DSM-III-R	Mean age: 38.68 years; 36 males, 73 females.	Major Depression	Patients were diagnosed using the DSM-III-R. Shortly after admission, patients completed the MCMI-II, a 175-item inventory with 25 scales, in group sessions.	The D scale had a higher sensitivity (86%) than the CC scale (61%) for predicting major depression. The CC scale had a greater specificity (52%) than the D scale (32%). the diagnostic power of the D scale was 73%, greater than the CC scale of 59%.	"The results from this study support previous findings with the MCMI-I ... in that the D and CC scales function similarly, and the CC scale does not actually assist in discriminating major depression from other depressive disorders."	Data suggest that the CC score of the MCMI-II had improved sensitivity but the D scores had improved specificity and was a better predictor of depression. This is an older version of the MCMI-IV.
Steffan 2003 (score=7.5)	Minnesota Multiphasic Personality Inventory-2 (MMPI-2)	Screening Tools and Psychometri	No mention of sponsorship or COI.	N = 101 students from Study 1, N = 218 students	Study 1: Mean age: 19.4 years; 38 males, 63 females	Depression	MMPI-2: Minnesota multiphasic personality inventory vs Self-Rating Depression Scale (SRDS) vs F, F – K,	In study 1, simulators scored higher on Md scale ($M=24.78\pm5.42$) than depressed participants ($M=10.06\pm4.55$, $p<.05$, $d=1.36$). In study 2,	"The results indicate that the Md scale possesses promising value in detecting malingered symptoms of depression."	Data suggest Md Scale appears predictive for differentiating between simulators

		c Testing		from Study 2	Study 2: Mean age: 20.3 years; 110 males, 108 females		Fb, Fp, and Ds-2 Indices	simulators scored higher on Md scale (M=23.6±5.48) than depressed participants (M=12.26±5.71, p<.05).		(malingering depressive) and true depressives.
Ritsher 2001 (score=7.0)	Minnesota Multiphasic Personality Inventory, Hamilton Depression Rating Scale (HRDS)	Screening Tools and Psychometric Testing	Sponsored by International Research and Exchanges Boards, U.S. Department of State, the Academy for Educational Development, National Security Education Program, the Open Society Institute, the National Institute of Mental Health, and the Department of Veterans Affairs Health Services Research and Development Service and Mental Health	N = 180 adult participants diagnosed with depression according to the ICD-10 (50%), Moscow-ICD-9 (72%) and Snezhnevsky (63%).	No mention of mean age, 46% under 26 years old; 94 males, 86 females	Depression	Hamilton Rating Scale for Depression (HRSD): 26 item questionnaire vs Minnesota Multiphasic Personality Inventory (MMPI) vs the Rorschach-Comprehensive System vs ICD-10	MMPI scales appeared to have greater validity compared to Rorschach hit rates between 44-48%. DEPI scale prediction of depression was OR=0.50 (95% CI 0.22-1.2, p=0.11), compared to OR=0.71 (95% CI 0.32-1.6, p=0.40) in ICD-10, and OR=1.6 (95% CI 0.64-4.2, p=0.30) in HRSD	"In this Russian clinical sample, the MMPI functioned more accurately than the Rorschach in detecting depression, regardless of how it was defined."	In this sample of Russian patients, MMPI was the better indicator of depression as Rorschach components were poorly associated with more established measures of depression. The MMPI is the older version of the MMPI-2.

			Strategic Healthcare Group. No mention of COI.							
Mogge 2006 (score=6.5)	Personality Assessment Inventory	Screening Tools and Psychometric Testing	No mention of COI or sponsorship.	N = 89 participants who took the Assessment of Depression Inventory (ADI) and Personality Assessment Inventory (PAI) as part of treatment evaluation	Mean age: 34.74 years; 88 males, 1 female	Depression, Purposeful distortion	Assessment of Depression Inventory (ADI) Depression Scale (Dep) vs. Assessment of Depression Inventory for Feigning (Fg) vs. Personality Assessment Inventory (PAI) Depression Scale (DEP) vs. PAI Subdivision for cognitive (PAI DEPC) vs. PAI Subdivision for affective (PAI DEPA) vs. PAI Subdivision for physical (DEPP). All participants completed all assessments	Intercorrelations between the ADI Dep scale, PAI DEP scale, DEPC, DEPA, and DEPP scales were significant in every comparison (all $p < 0.01$).	"This study supports the effectiveness of the ADI Dep scale as a measure of depression."	27% of study sample had affective disorder and remainder of population was mixed. Data suggest ADI is appropriate and effective for measuring depression.
Rogers 1996 (score=6.5)	Personality Assessment Inventory	Screening Tools and Psychometric Testing	Sponsored by Research Opportunities Grant, University of North Texas. No mention of COI.	N = 467 undergraduate students taking a psychology class (n=166), graduate students in clinical or counseli	Mean age: 31.22 years; 196 males, 271 females	Depression, Generalized Anxiety, Schizophrenia, Feigning of disorders	Undergraduate and graduate students were randomized to either a normal condition, feigning depression, generalized anxiety, or schizophrenia. Students and the clinical comparison group took the personality assessment inventory (PAI) and feigners	Statistical difference between groups on the inconsistency scale, infrequency scale, negative impression scale and positive impression scale ($p < 0.05$). Result of two-stage discriminant analysis showed highly significant discriminant function with Wilks' lambda = 0.3368 ($p < 0.001$) and canonical correlation = 0.81. Calibration hit rate = 92.2%	"Therefore, we performed a two-stage discriminant analysis that yielded a moderately high hit rate (> 80%) that was maintained in the cross-validation sample, irrespective of the feigned disorder or the sophistication of the simulators."	Data suggest PAI appears to be a valid instrument in detection of "feigned" mental disorders.

				ng psychology (n=80), or those with schizophrenia (n=45), major depression (n=136), or generalized anxiety (n=40) – no diagnostic criteria given			were compared to those with clinical diagnoses			
Bagby 2005 (score=6.0)	MMPI-2	Diagnostic	No mention of sponsorship or COI.	N=23 patient protocols of Minnesota Multiphasic Personality Inventory-2	Mean age: 39.91±7.30 years; 10 males, 13 females	Major Depression	F Scale: measures infrequency vs F_B: measures F Back vs F_P: measures F-psychopathology vs Md Scale	Md scale showed greatest predictive capacity compared to F scales. F_B and F/F_P combination scale showed greater predictive capacity compared to Md scale, but not significantly. Overall manova effect was Λ=0.6, F(8, 196)=2.16, p<.001.	"In sum, although the Md scale is able to detect accurately feigned depression on the MMPI–2 (predictive validity), it does not confer a distinct advantage (incremental validity) over the existing standard validity scales—F, FB, and FP."	Relatively small sample. Data suggest no significant advantage in using the Md scale of the MMPI-2 over the standard F, F_B, and FP scales although the Md scale can detect feigned depression.
Klonsky 2000 (score=6.0)	Minnesota Multiphasic Personality Inventory (MMPI)	Screening Tools and Psychometri	No mention of sponsorship or COI.	N=51 participants with dysthymia or major	Mean age: 30±9 years; no mention of specific number of	Dysthymia or Major Depressive Disorder	MMPI-2: Minnesota Multiphasic Personality Inventory vs DSM-IV: Diagnostic Statistical	For Scale 1, measures for dysthymia were sensitivity 67%, specificity 70%, positive predictive value (PPV) 61%, and negative predictive value (NPV) 75%	"In summary, a comparison of the MMPI-2 scale scores of outpatients with dysthymia and major depression revealed that	Small sample size. Data suggest individuals with dysthymia are similar to those with major

		c Testing		depressive disorder (DSM-IV)	sex (majority female)		Manual Fourth Edition Scale	for dysthymia; measure for major depressive disorder were sensitivity 70%, specificity 67%, PPV 75%, and NPV 61%. For Scale 2, measures for dysthymia were sensitivity 71%, specificity 63%, PPV 58%, and NPV 76% for dysthymia; measure for major depressive disorder were sensitivity 63%, specificity 63%, PPV 76%, and NPV 58%. For Scale 3, measures for dysthymia were sensitivity 57%, specificity 57%, PPV 48%, and NPV 73% for dysthymia; measure for major depressive disorder were sensitivity 57%, specificity 57%, PPV 73%, and NPV 48%.	the two groups are remarkably similar, with the exceptions that the major depressive sample generated unique elevations on Scales 1 and 3, and generated higher Scale 2 and mean of eight clinical scale T scores."	depression but large differences occur on scales 1 and 3 exist between the two groups.
Sellbom 2012 (score=5.5)	Minnesota Multiphasic Personality Inventory (MMPI)	Screening Tools and Psychometric Testing	Sponsored by Ontario Mental Health Foundation Senior Fellowship. No COI.	N = 544 patients with bipolar disorder, major depressive disorder, and/or schizophrenia	Mean age:38.6 years; 275 males, 269 females	Bipolar disorder, Major Depressive Disorder, and Schizophrenia	MMPI-2: Minnesota multiphasic personality inventory (High Order Scales such as EID, THD, BXD scales) vs MMPI-2-RF: Minnesota Multiphasic Personality Inventory-2-Restructured Form (RC-Restructured Clinical Scales)	Patients with major depression scored higher (M=74.01) on EID scale compared to bipolar (M=68.24) or schizophrenic patients (M=61.22) ($p<.001$), and scored lower than both groups in the THD scale ($p<.001$) and the BXD scale ($p<.02$). Patients with major depression were not easily differentiated among the RC scales.	"The higher order scales (H-O)—the Emotional/Internalizing Dysfunction (EID) and Thought Dysfunction (THD) scales were most useful in differentiating between patient groups. For differentiating bipolar disorder patients from the other diagnostic groups, the Activation (ACT) Specific Problem scale was most useful. Although not all hypothesized scale differences emerged; overall, the pattern of results provides support for the diagnostic	Data suggest MMPI-2-RF scores appear predictive in identifications of clinically diagnosed mental disorders. Specifically, the higher order (HO) scales appear useful in the detection of internalizing, externalizing and thought dysfunction which correlate to depression.

									construct validity of the MMPI-2-RF scales."	
Craigie 2007 (score=5.0)	MCMI-III	Diagnostic	No mention of sponsorship or COI.	N=115 outpatients with a primary diagnosis of depression	Mean age: 38.6 years; 33 males, 82 females	Depression	MINI: MINI International Neuropsychiatric Interview vs MMCI-III: Million Clinical Multiaxial Inventory-III that assesses Axis I and II psychopathology vs BDI-II: Beck Depression Inventory-II measures severity of depression symptoms vs CCL: the Cognitions Checklist assesses frequency of dysfunctional cognitions vs Q-LES-Q: the Quality of Life Enjoyment and Satisfaction Questionnaire measures degree of enjoyment and satisfaction of daily living	Clinical significant improvement was achieved in 31.6% of sample with a score >10 in BDI-II. No improvement was observed in 58.6% of no personality disorder group compared to 26.5% with simple personality disorder, and 32.4% in complex personality disorder group ($p>0.05$).	"In conclusion, the results of the current study indicate that depressed patients with a more complex MCMI-III personality profile, experience greater severity of pretreatment depression related symptoms, compared to those with a simple or nonremarkable profile."	Data suggest patients with a more complex MCMI-III profile likely experience more pre-treatment depressive symptoms and these patients may benefit from time-limited CBT. The MCMI-III is an older version of the MCMI-IV.
Bagby 2000 (score=5.0)	MMPI-2	Diagnostic	Sponsored by a grant from Social Sciences and Humanities Research Council of Canada. No mention of COI.	N=23 participants	Mean age: 37.2±11.03 years; 10 males, 13 females	Major Depression	Ds: Dissimulation scale vs F-K: F-K Dissimulation Index vs DS: the Deceptive-Subtle scale vs FBS: Fake Bad Scale vs Ob: the Sum of Obvious scale	Sensitivity was 83% for F scale, 91% for F_B, 91% for the combination of F+F_B, 87% for Ds, 74% for FBS, and 83% for Ob. Specificity was 85% for F scale, 85% for F_B, 73% for FBS, and 81% for Ob.	"These findings suggest that even experts are unable to feign major depression successfully on the MMPI-2, and that the F_B scale might be the most effective indicator for detecting feigned depression."	Data suggest trained experts who routinely assess depression are unlikely to adequately feign major depression using MMPI-2 with the F_B scale being most useful in detecting feigned depression.

Basso 2013 (score=5.0)	MMPI-2	Diagnostic	No mention of COI or sponsorship.	N = 101 participants with primary diagnosis of MDD (meeting DSM-IV criteria), 32 participants with psychotic features, and 17 controls	Mean age: 34.23 years; 43 males, 107 females	Symptoms of major depressive disorder	Brief batter of neuropsychological tests: California Verbal Learning Test, F-A-S test of verbal fluency, Trail Making Tests A and B, Digit Span subtest from the Wechsler Adult Intelligence Scale-III, and Grooved Pegboard Test vs. The Minnesota Multiphasic Personality Inventory (2) (MMPI-2). All participants took all measurements	Principal component analysis of MMPI-2 pointed towards symptom dimensions of negative affect, agitation, lassitude and malaise. Symptoms of depression were correlated with various neuropsychological tests (negative effect for verbal fluency, trail making tests A and B, CVLT, grooved pegboard and impairment index – all $p < 0.05$; agitation hostility for trial making test B, digit span backward, grooved pegboard test and impairment index – all $p < 0.05$)	"Although presence of a depression diagnosis is associated with various forms of psychiatric morbidity, these data imply that discrete dimensions of depressive symptoms may possess specific neural substrates. Collectively, these data support emerging models that better characterize major depression according to these dimensional models rather than a categorical taxonomy."	Data suggest depression does not present in a uniform manner as patients exhibit a wide array of varying symptoms such as negative effect, agitation and malaise.
Talarowska 2011 (score=4.5)	MMPI-2	Diagnostic	No mention of COI or sponsorship.	N = 50 subjects meeting ICD-10 criteria for major depression disorder, single or multiple episode(s)	Mean age: 44.12 years; 20 males, 30 females	Severity of depression symptoms	The Minnesota Multiphasic Personality Inventory (2) (MMPI-2) neurotic triad: Hs = hypochondria, D = Depression, Hy = hysteria) vs. Hamilton Depression Rating Scale (HDRS). All participants took all measurements	Higher scores in Hs ($p = 0.007$), D ($p = 0.021$), and Hy scales ($p = 0.001$) were associated with higher degree of depression via HDRS scores	"The higher the degree of hypochondria and hysteria symptoms, measured by the MMPI-2 test at the onset of therapy in patients with depressive disorders, the higher is the severity of depression found after 8 weeks of therapy with SSRI agents, measured by the HDRS scale."	Data suggest a high correlation between the degree of hypochondriac and hysteria symptoms in depression, to the severity of depressive symptoms 8 weeks post SSRI treatment.
Nelson 1991 (score=4.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N=87 outpatients with major depression or dysthymia	Mean age: 36.76±12.16 years; 42 males, 45 females	Major Depression	BDI: Beck Depression Inventory vs MMPI vs SCL-90-R: Symptom Check List-90-Revised measures recent symptom patterns of psychiatric and medical patients	MMPI showed a hit rate of 77% compared to BDI and diagnostic outcomes. Sensitivity was 78% for MMPI compared to 67% in BDI. Specificity was 75% for MMPI.	"In general, results from the present study support the utility of the MMPI as an index of depression in adult outpatients."	Data suggest MMPI is a valid tool in assessment of depressed outpatients. The MMPI is an older version of the MMPI-2.

Nyquist 2018 (score=4.5)	MMPI-2	Screening Tools and Psychometric Testing	No sponsorship or COI.	N=321 students from a public university who volunteered for psychology course	Mean age: 18.9±1.54 years; 83 males, 238 females	Depression	MMPI-2-CA: Minnesota Multiphasic Personality Inventory-2-Computerized "Adaptive" Version vs MMPI-2: the conventional modality Test, retest design.	Time was saved using the MMPI-2-CA compared to MMPI-2, $t(113)=73.24$, $p<.001$. Mean difference in effect size was $d=9.63$. Mean administration time was 21.0 minutes in MMPI-2 compared to 15.1 minutes in the MMPI-2-CA.	"The criterion correlations suggested minimal differences in discriminant and convergent validity across administration modes, suggesting limited to no impact of administering targeted MMPI-2 scales in terms of construct validity."	Data suggest MMPI-2 depression module saves time compared to the conventional computerized (CC) model and 42.6% fewer items are administered with small losses of construct validity between the two models.
Bosch 2014 (score=4.5)	Minnesota Multiphase Personality Inventory (MMPI) - 2	Screening Tools and Psychometric Testing	No mention of sponsorship or COI.	N=86 outpatients at a psychiatric hospital	Mean age: 41.79±12.33 years; 27 males, 59 females	Depression	MMPI-2: Minnesota multiphasic personality inventory vs RC-Scale: measures emotions and behavior vs MWT-B: measures verbal intelligence vs BDI-II: Beck depression inventory. All participants received each test.	Depression patients showed higher UT-scores>65 on 9 of clinical scales and 4 of the RC scales. Schizophrenia reached UT-score >65 only on clinical scale 2-D, but in none of the RC scales.	"To conclude, the main finding of our study is that, with regard to psychopathology and personality self-report, it is hard to differentiate long-term patients with schizophrenia from healthy controls, considering their flat profiles and low individual UT-scores."	Data suggest it is challenging to differentiate between schizophrenic patients from healthy controls but the MMPI-2 is better at distinguishing long-term (chronic depression) from healthy controls.
Rogers 1993 (score=4.5)	Personality Assessment Inventory	Screening Tools and Psychometric Testing	No mention of sponsorship or COI.	N = 149 students who were either undergraduate students taking a psychology course or graduate	Mean age: 26.6 years; 48 males, 101 females.	Schizophrenia, depression, and generalized anxiety disorder	The naïve group consisted of undergraduates. Some were told to fake one of the disorders (n=76) and some were given standard Personality Assessment Inventory (PAI) instructions to be controls (n=25) vs the sophisticated	90.8% of the naïve group and 87.9% of the sophisticated group were successful is faking a disorder. The negative impression scale (NIM) is not effective with generalized anxiety (38.7%), slightly effective with feigned depression (55.9%), and effective with feigned schizophrenia (90.9%).	"We found that the NIM cutting score (>8) was highly effective with feigned schizophrenia, marginally effective with feigned depression, and ineffective with feigned generalized anxiety disorder."	Data suggest whether sophisticated or naïve subjects are used, the PAI appears to effectively discriminate between real and feigned personality measures.

				students in clinical and counseling psychology.			group consisted of graduate students. Some were told to fake one of the disorders and were given one week to prepare (n=33) and some were given standard PAI instructions (n=15)			
Schaefer 1985 (score=4.0)	MMPI Depression Scale, Beck Depression Inventory Scale, Zung Self-Rating Depression Scale	Screening Tools and Psychometric Testing	Sponsored by the Veterans Administration Medical Research Service. No mention of COI.	N = 101 inpatient psychiatric ward patients and 99 chemical dependency ward patients	Mean age: 38.2 years; 200 males, 0 females	Depression	Beck Depression Inventory vs Zung Self-Rating Depression Scale vs Minnesota Multiphasic Personality Inventory was taken by all participants	Zung showed best T-test correlations (p=0.15) compared to MMPI-D (p=0.50) and to BDI (p=0.54). Estimated alpha coefficients were 0.94 (psychiatric ward patients) and 0.88 (chemical ward patients) for BDI, 0.9 (psych patients) and 0.86 (chemical ward) for Zung, and 0.81 (psych patients) and 0.72 (chemical ward) for MMPI-D.	"The results favor the Zung over the MMPI-D scale and, to a lesser degree, the BDI as a measure of depressive symptomatology in men. Additional research on the scales' validities in women would be useful."	Data suggest Zung validated DSM-III depression criteria better than Beck and both were better than MMPI. This is a screening tool not a psychological test
Norman 1985 (score=3.5)	Minnesota Multiphase Personality Inventory (MMPI)									Small sample. Data suggests use of MPI in conjunction with DST when assessing personality dysfunction in depressed individuals. The MMPI is the older version of the MMPI-2.[14]

[14] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Streit 2013 (score=3.5)	Minnesota Multiphase Personality Inventory (MMPI)	Diagnostic								Data suggest scale 2 of the MMPI and the WCS of depression have different correlates when only one of these scales is used, therefor clinicians may need to use both scales. The MMPI is an older version of the MMPI-2.
Bence 1995 (score=3.5)	Minnesota Multiphase Personality Inventory (MMPI)									Data suggest clinical judgement is necessary to adequately interpret the scales and subscales of the MMPI-2 when assessing depression.
Wetzler 1994 (score=3.5)	Minnesota Multiphase Personality Inventory (MMPI)									Variable numbers of individuals taking any test making interpretation of interrelationship between the MMPI and either the Millon or Millon-II impossible. The MMPI is the older version of the MMPI-2 and the Millon and Millon-II are

										older versions of the MCMI-IV.[15]
Lubin 1995 (score=3.5)	Minnesota Multiphase Personality Inventory (MMPI)									Data suggest the ST-DACL lists provide comparable scores to the CESD, BDI, or MMPI to measure presence and severity of depression. The MMPI is the older version of MMPI-2.
Boone 1998 (score=3.5)	Personality Assessment Inventory									Mixed population of mental health disorders (40% affective disorder, which included major depression, mild depression and bipolar depression). Data suggest an extremely low or extremely high score on Negative Impression Management (NIM) needs further evaluation for presence or absence of malingering. However, most of

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										the PAI measures were reliable.[16]
Piersma 1989 (score=3.5)	MCMI-II									Mixed study population (different mental health disorders). Data suggest correlation between MCMI-II and MCMI-I scores with some differences requiring further studies to validate results. The MCMI-I and –II are older versions of the MCMI-IV.
Piersma 1989 (score=N/A)	MCMI-II	Post-Hoc analysis of Piersma Jan 1989								Data suggest test-retest reliability best for personality scales but correlation between MCMI-I and MCMI-II good. The MCMI-I and –II are older versions of the MCMI-IV.
Nelson 1996 (score=2.5)	MMPI-2									Data suggest the D-O subscale of the MMPI-2 is useful for assessing depression but not the D-S subscale in

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										psychiatric outpatients.
Overholser 1990 (score=2.5)	MCMI									Possible selection bias as only a fraction of the entire sample was retested for pattern stability of the MCMI scales. The MCMI is an older version of the MCMI-IV.[17]

[17] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Pharmacogenomics Testing

Diagnostic Studies										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Yeh 2015 (score=4.0)	Pharmacogenomics Testing	Diagnostic	No COI. Sponsored by National Science Council, Tri-Service General Hospital and Medical Affairs Bureau, Ministry of National Defense.	N = 243 Han Chinese patients with major depressive disorder (MDD) meeting DSM-IV-TR criteria	Mean age: 39.0 years; 107 males, 136 females	Major depressive disorder	21-item Hamilton Depression Rating Scale (HDRS) vs. Tridimensional Personality Questionnaire (TPQ). All participants underwent both measurements. All participants were measured for SLC6A2 gene polymorphisms to compare against screening measurements	Participants completing the 8-week Venlafaxine treatment showed significant remission associated with SLC6A2 promoter SNP (rs28386840), and intronic SNPs (rs1532701, rs40434, rs13333066, and rs187714) ($p<0.007$).	"Our study provides initial evidence of SLC6A2 gene polymorphisms predicting the likelihood of remission after venlafaxine treatment."	Data suggest the SLC6A2 gene may be associated with treatment remission in Venlafaxine treated MDD patients.

Randomized Controlled Trials										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bradley 2018 (score=6.0)	Pharmacogenomics Testing	RCT	Sponsored by AltheaDx. AltheaDx employs multiple authors.	N = 685 participant meeting DSM-5 criteria for depression and/or anxiety	Mean age: 47.56 years; 187 males, 498 females	Guided pharmacology treatment by NeuroIDgenetix test (n=352) vs. Standard Care (n=333)	Follow-up at weeks 4, 8, and 12	Remission rate at 12 weeks among those with severe depression: control group = 35%, NeuroIDgenetix group = 13% (OR = 3.54, p = 0.02). Remission rate at 12 weeks among those with severe	"From these results, we conclude that pharmacogenetic-guided medication selection significantly improves outcomes of patients diagnosed with	Data suggest pharmacogenetic-guided treatment significantly improves antidepressant efficacy resulting in improved outcomes.

								or moderate depression: control group = 41%, NeuroIDgenetix group = 49% (OR = 2.03, p = 0.01)	depression or anxiety, in a variety of healthcare settings."	
Singh 2015 (score=5.5)	Pharmacogenomics Testing	RCT	No mention of COI or sponsorship.	N = 148 participants with a principle diagnosis of major depression disorder meeting DSM-5 criteria	Mean age: 44.25 years; 60 males, 88 females	Pharmacokinetic pathway polygene pharmacogenetic interpretive report (CNSDose®) to guide treatment (n=74) vs. Unguided treatment (n=74). Both groups received 12 weeks of clinical care by psychiatrist	Follow-up at weeks 4, 8, and 12	Those with treatment guided by CNSDose® had 2.52 times the chance of remission (z = 4.66, p < 0.0001)	"These data suggest that a pharmacogenetic dosing report (CNSDose®) improves antidepressant efficacy. The effect size was sufficient that translation to clinical care may arise if results are independently replicated."	Data suggest adherence to pharmacogenetic dosing significantly increases antidepressant efficacy (>2.5 fold better), than not using pharmacogenetic dosing.
Breitenstein 2016 (score=5.0)	Pharmacogenomics Testing	RCT	COI, one or more of the authors have received or will receive benefits for personal or professional use. Sponsored by HMNC GmbH, the German Federal Ministry of Education and Research and the Max Planck Society.	N = 73 inpatients at the Max Planck institute of Psychiatry (MPI-P) received antidepressant treatment for MDD meeting DSM-IV criteria and 128 control	Mean age: 46.9 years; 106 males, 95 females	Received daily standard dose of P-glycoprotein (P-gp) substrate antidepressants for 4 weeks – dosage depended on antidepressant, could receive one	No follow-up	Significant genotype x plasma antidepressant concentration interaction occurred – minor allele carriers of rs2032583 [F(1,65) = 7.221, p = 0.009] and minor allele carriers of rs2235015 [F(1,65) = 4.939, p = 0.030] had	"The treatment of MDD can be optimized by ABCB1 genotyping combined with monitoring of plasma drug concentrations: For minor allele carriers of rs2032583 and rs2235015, plasma antidepressant	Treatment as usual bias. Data suggest if an individual carrier rs203s583 and rs2235015 an antidepressant with P-gp substrate properties should be given.

				sample that was retrospectively matched		of 4 SSRIs, 1 SNRI, or 4 TCAs (n=40) vs. Received daily high dose of P-gp substrate antidepressants for 4 weeks, dosage was double the amount of standard dosage (n=33) vs. Control group (n=128)		greater symptom reduction at endpoint	levels should not exceed the recommended range in order to obtain optimal treatment outcome."	
McGrath 2013 (score=4.5)	Pharmacogenomics Testing	RCT	Sponsored by National Institutes of Health grants. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 82 participants with a primary diagnosis of Major Depressive Disorder meeting DSM-IV-TR criteria	Mean age and gender distribution was not provided for the entire sample	12 weeks of escitalopram oxalate (daily 10-20 mg) (n=40) vs. 12 weeks of Cognitive Behavioral Therapy, 16 1-hour sessions, twice weekly for 4 weeks, then weekly for 8 weeks (n=41)	No follow-up	Significant correlation between baseline insula activity and ratio of change in Hamilton Depression Rating Scale (HDRS) for escitalopram and CBT groups (p=0.001). Positive correlation for CBT group (p=0.001) with opposite but less significant correlation for escitalopram group (p=0.09).	"If verified with prospective testing, the insula metabolism-based treatment-specific biomarker defined in this study provides the first objective marker, to our knowledge, to guide initial treatment selection for depression."	Data suggest there may be a treatment specific biomarker which guides treatment selection in MDD.

Perez 2017 (score=4.5)	Pharmacogenomics Testing	RCT	Sponsored by the Spanish Centre for Industrial Technological Development. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 316 participants with principal diagnosis of Major Depressive Disorder meeting DSM-IV-TR criteria, with clinician-rated scores in Clinical Global Impression-Severity (CGI-S) scale >= 4 at both screening and randomization visits	Mean age: 51.2 years; 115 males, 201 females.	PGx-guided: psychiatrists were given patients' pharmacogenomics test report, treatment and antidepressant choice and dosage guided by results (n=155) vs. Control: No pharmacogenomics test results given, received treatment as usual (n=161)	Follow-up at 4, 6, 8, and 12 weeks	PGx-guided group self-reported higher rates of improved condition at week 12 (p=0.0476). Difference in sustained response within 12 weeks not observed (38.6% versus 34.4%, p=0.4735, OR=1.19)	"PGx-guided treatment resulted in significant improvement of MDD patient's response at 12 weeks, dependent on the number of previously failed medication trials, but not on sustained response during the study period. Burden of side effects was also significantly reduced."	Treatment as usual-care bias. Data suggests PGx guided treatment resulted in significant improved response at 12 weeks.
Winner 2013 (score=4.5)	Pharmacogenomics Testing	RCT	No mention of sponsorship. COI, all authors employed by AssureRx Health, Inc.	N = 51 outpatients recruited from Pine Rest Christian Mental Health Services with a diagnosis of Major Depressive Disorder (MDD) or Depressive Disorder not otherwise	Mean age: 49.2 years; 10 males, 41 females	Treatment as usual (n = 25) vs. GeneSight – psychiatrists given a pharmacokinetic and pharmacodynamics gene testing results to help guide antidepressant choice and dosage (n = 26)	Follow-up at baseline, 4, 6, and 10 weeks	GeneSight treatment showed higher reductions in depressive symptoms compared to TAU group (p=0.28), measured via Hamilton Rating Scale for Depression (HAMD-17) at week 10	"Pharmacogenomic-guided treatment with GeneSight doubles the likelihood of response in all patients with treatment resistant depression and identifies 30% of patients with severe gene-drug interactions who have the greatest improvement in depressive	TAU bias. Small sample size. Data suggest symptom improvement is more than twice as likely with gene-sight directed therapy.

				specified (DDNOS) with Hamilton Rating Scale for Depression score ≥ 14					symptoms when switched to genetically suitable medication regimens."	
Hall-Flavin 2012 (score=3.5)										Data suggest use of a pharmacogenomic algorithm improved clinical outcomes with depression but effects not apparent until after 2 weeks.[18]
Hall-Flavin 2013 (score=3.0)										Open label study. Data suggest significant improved outcomes with the use of a multigenetic pharmacogenomic testing platform (GeneSight) for treatment of MDD.
Maciukiewicz 2015 (score=3.0)										Data suggest Il-6 variants play a role in duloxetine and

[18] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										placebo response.[19]
Steimer 2005 (score=3.0)										Data suggest a combination of normal CYP2C19 and slightly slower (diminished) CYP2D6 lead to high concentration of intermediate metabolite (NT) leading to adverse effects.
Espadaler 2017 (score=3.0)										Retrospective analysis. Data suggest patients who followed the treatment guidance via pharmacogenetic testing were 4 times more likely to have an improved treatment response than those who did not.
Paddock 2007 (score=2.5)										Data suggest that the glutamate system plays a key role in modulating response to SSRIs.

[19] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Education

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Katon 1999 (score=6.0)	Education	RCT	Sponsored by grant from National Institute of Mental Health, Rockville, Md. No mention of COI.	N = 228 patients with 4 or more major depressive symptoms for DSM-III-R criteria	Mean age: 47.0 years; 58 males, 170 females	Intervention Group: received antidepressant medication (8-9 weeks prior to 1st intervention) and 2 sessions with psychiatrist for 4 weeks (1-50 minute initial session, 1-25 minute follow up session) (n=114) vs Control Group: received usual care treatment for depression including antidepressant medication, visits with physicians (n=114)	1, 3, 6 months	Intervention group showed greater decrease in severity of depressive symptoms compared to controls (3, 6 months follow up p=0.001, p=0.08). Intervention group was more likely to receive medication compared to controls (68.8% vs 43.8%, respectively; p<0.001).	"A multifaceted care program targeted for primary care patients whose depressive symptoms persisted for 6 to 8 weeks after initiation of usual care treatment was found to improve outcomes relative to usual care. This suggests that targeting collaborative care in a stepped-care fashion may be a viable option for efficient use of specialty services in primary care setting."	Usual care bias. Data suggest the stepped collaborative care group significantly improved antidepressant medication adherence as well as depression compared to usual care group. Multiple co-interventions.
Jacob 2002 (score=6.0)	Education	RCT	Sponsored by The Wellcome Trust. No mention of COI.	N = 70 patients diagnosed with mental disorder measured by General Health	Mean age: 47.9 years; 0 males, 70 females	Experimental Group: received educational leaflet based on issues about common mental	2 months	Of the education group 42.9% recovered with a score of 2 or less on the GHQ compared to 20% in control group (OR=2.99, 95%	"Patients with common mental disorders, especially those with milder forms of the condition, who received the	Data suggest interventional group of mildly depressed patients had a higher recovery rate.

				Questionnaire		disorders (n=35) vs Control Group: did not receive education leaflet (n=35)		CI 1.03-8.7, p<0.05). For patients that received intervention, there was an association with recovery (OR=3.4, 95% CI 1.01-11.5) and with patients that had lower initial GHQ scores (OR=7.1, 95% CI 1.05-30.2).	educational material had a higher recovery rate than patients who do not receive such education."	
Morokuma 2013 (score = 5.5)	Education	RCT	Sponsored by a grant from the Kochi Mental Health and Welfare Association to Kochi in 2008-09. No mention of COI.	N = 34 patients diagnosed with MDD according to DSM-IV.	Mean age: 42.83 ± 10.82 years; 14 males, 18 females.	Psychoeducation group: went through 6 sessions held weekly for 90 minutes (n= 18) vs Control group: received outpatient treatment given by psychiatrist once every other week for 15 min.	9 month	Time to relapse was significantly longer in the Intervention group than in control group (Log-rank chi-squared = 6.48, df = 1, p= 0.011). Median time to relapse was 274 day for the intervention group and 221 for control group. The crude risk ratio of relapse by 9 months was 0.12 (95% CI; 0.02-0.87, p = 0.015)	"Despite these weaknesses, our method of group psychoeducation, which is simple and easily introduced, can benefit many patients with MDDs."	Small sample size, most patients with mild depression. TAU bias. Data suggest at 9 months, the HRSD-17 reflected decreased scores in the intervention group.
Buntrock 2016 (score=5.0)	Problem Solving Therapy/Education	RCT	Sponsored by the European Union and the BARMER CEK. COI: One or more of the authors have received or will receive benefits	N = 406 patients with major depressive episode, bipolar disorder, psychotic disorder or	Mean age: 45.04±11.89 years; 106 males, 300 females	Intervention Group: received guided-web based psychoeducation, behavior therapy, and problem	6, 12 months	Incidence of MDD was 32% in the intervention group (95% CI 25-39%) compared to 47% (95% CI 40-55%) in the control group (p=0.002). Depression	"Among patients with subthreshold depression, the use of a web-based guided self-help intervention compared with enhanced usual	Data suggest at the 12 month assessment the web based self-help intervention decreased the incidence of MDD in

			for personal or professional use.	not having a history of MDD in the past 6 months (DSM-IV)		solving therapy consisting of 6 30-minute sessions (n=202) vs Control Group: received enhanced usual care consisting of psychoeducation offering more information than just from the primary care physician (n=204)		symptom severity had a HR=0.59 (95% CI 0.42-0.82, p=.002).	care reduced the incidence of MDD over 12 months."	individuals with subthreshold depression.
Stangier 2013 (score=5.0)	Education/ CBT	RCT	Sponsored by German Research Funding. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 180 participants with recurrent nonpsychotic major depressive disorder diagnosed by DSM-IV Criteria	Mean age: 48.6±11.6 years; 50 males, 130 females	Cognitive Behavior Therapy (CBT): received 50-minute maintenance CBT session weekly until final phase with monthly sessions (n=90) vs Manualized Psychoeducation: received 20-minute sessions of psychoeducation tailored to each participant (n=90)	2, 8 months, 1 year	Recurrence of major depressive episode was 607 days for CBT group compared to 531 days in psychoeducation group. Relapse rate was 51% for CBT group compared to 60% in psychoeducation group at 1 year. The hazard ratio comparing CBT to psychoeducation was 0.622 (95% CI=0.356-0.850).	"The results indicate that maintenance CBT has significant effects on the prevention of relapse or recurrence only in patients with a high risk of depression recurrence. For patients with a moderate risk of recurrence, nonspecific effects and structured patient education may be equally effective."	Data suggest CBT maintenance prevents relapse in high-risk depression recurrence individuals.

Conradi 2007 (score=5.0)	Education/ CBT	RCT	Sponsored by grants from the Dutch Organization for Scientific Research (NOW), the Medical Sciences Program and Chronic Diseases Program, Research Foundations of the Health Insurance Company 'Het Groene Land', the Regional Health Insurance Company (RZG), National Fund Mental Health (NFGV), and the University Hospital Groningen to J. Ormel and H. Kluiter. No conflict of interest.	N = 267 patients with major depressive episodes diagnosed by Composite International Diagnostic Interview (CIDI)	Mean age: 42.8±11.3 years; 93 males, 174 females	PEP: received psycho-educational prevention program (PEP) consisting of educational books, videos, and 3 sessions with a psychiatrist (n=112) CBT-enhanced PEP: received PEP and 10-12 individual 45-minute sessions of cognitive behavioral therapy (CBT) (n=44) vs Psychiatrist-enhanced PEP: received PEP as well as 1-hour session with 2 psychiatrists, antidepressant medication (n=39) vs UC: received usual care of brief supportive counseling, anti-depressant prescription and eventual psychological referral (n=72)	3, 6, 36 months	Enhanced PEP and Enhanced-CBT PEP groups showed better improvement compared to UC group in BDI score (enhanced PEP BDI=2.07, 95% CI 1.13-3.0; CBT-enhance BID=1.62, 95% CI 0.7-2.55) and compared to PEP group (enhanced PEP BDI=2.37, 95% CI 1.35-3.39; CBT-enhance BID=1.93, 95% CI 0.92-2.94). Of all the patients, 64% showed recurrence of depressive episode and a mean BDI score of 9.6.	"The PEP program had no extra benefit compared to UC and may even worsen outcome in severely depressed patients. Enhancing treatment of depression in primary care with psychiatric consultation or brief CBT seems to improve the long-term outcome, but findings need replication as the interventions were combined with the ineffective PEP program."	Usual care bias. At 3 years, data suggest lack of efficacy for PEP, but brief CBT or psychiatric consultation appear to improve long-term outcome. Multiple co-interventions.

Katzelnick 2000 (score=4.5)	Education	RCT	Sponsored by grant from Pfizer Pharmaceuticals Inc., New York, NY. No mention of COI.	N = 407 patients with current major depression or in partial remission for major depression diagnosed by DSM-IV criteria	Mean age: 45.5 years; 92 males, 315 females	DMP Group: received depression management program (DMP) consisting of physician education, patient education, antidepressant treatment, and treatment coordination (n=218) vs UC Group: received usual care consisting of self-referral to any specialty services normally available to health plan members, no additional monitoring, case management, or psychiatric liaison services (n=189)	6 weeks, 3, 6, 12 months	Improvement in Ham-D scores were greater in DMP group compared to UC group at 6 weeks (-3.3 vs -2.0, p=0.04), 3 months (-5.6 vs -3.9, p=0.02), 6 months (-7.3 vs -4.0, p<0.001), and 12 months (-9.2 vs -5.6, p<0.001). The UC group showed 23.2% of patients increased Ham-D scores compared to 12.8% of DMP patients (p=0.01).	"In depressed high utilizers not already in active treatment, a systematic primary care–based treatment program can substantially increase adequate antidepressant treatment, decrease depression severity, and improve general health status compared with usual care."	Usual care bias. Data suggest systematic primary care treatment may decrease depression severity and general health by increasing utilization of appropriate antidepressant medication treatment. Multiple co-interventions.
Imamura 2016 (score=4.5)	Education	RCT	No mention of sponsorship or COI.	N = 1236 Japanese workers considered high risk (consulted specialist for mental	Mean age: 39.5 years; 870 males, 366 females	Intervention Group: were invited to visit educational website about stress management and depression	1, 4 months	A significant effect was only observed for high-risk subgroup on depressive symptoms at 1 month (t=-2.35, p=0.02, d=-0.57).	"A web-based psychoeducation approach may not be effective enough in improving depressive symptoms in a	Data suggest significant improvement in depressive symptoms only in high-risk group at one

				health problem), moderate-risk (had high levels of depression), and low-risk (did not have depression)		(n=618) vs Control Group: were asked to complete baseline and follow-up surveys (n=618)			general population of workers, while it may be effective for workers who had recently sought help for mental health."	month, which is post-hoc.
Chiesa 2015 (score=4.5)	Education/ Mindfulness	RCT	No sponsorship or COI	N = 43 patients with diagnosis of major depression via DSM-IV-TR diagnosis criteria.	Mean age: 50.9 years; 12 males, 31 females.	Patients received eight sessions of either mindfulness-based cognitive therapy (MBCT) according to manualized procedures (N = 20) vs: psycho-education (N = 20) carried out by a clinical psychologist and structured to be similar to MBCT.	Follow-up at baseline 4th, 8th, 17th, and 26th week.	Significant improvement of depressive symptoms as measured by Hamilton Rating Scale for Depression (HAM-D) for MBCT group compared with psycho-education group in both short term and long term periods (short term: p=0.002);(long term: p=0.002).	"[T]he results of the present study suggest the superiority of MBCT over psycho-education for patients with MD who did not achieve remission following antidepressant treatment."	Small sample. Data suggest MBT group showed long-term improvement in anxiety & mindfulness.
Aagaard 2017 (score=4.5)	Education	RCT	No sponsorship or COI	N = 80 patients with recurrent depression reassessed via ICD diagnosis criteria.	Mean age: 48 years; 46 males, 34 females.	Psycho-educative program group: patients received eight 2-hour sessions of a psycho-educative program with 2-year follow-up (n=42) vs.	Follow-up 6, 12, 18, and 24 months.	Significant reduction of the consumption of psychiatric services (p=1.2e-8) and depressive symptoms (p=3.9e-8) as measured by Beck's depression inventory (BDI)	"The primary hypothesis could not be confirmed. Our results, including the positive effects we have discovered, motivate for new well-designed studies	Treatment as usual bias. Data suggest at 2 years, both groups had similar decreases in the consumption of psychiatric services as

						Control group: patients received standard care (n=38).		for both case and control patients.	concerning effects of supplementary psycho-educative treatment to patients with recurrent depression including larger sample size, a longer psychoeducation al program with more sessions, a longer observation time, and additional outcome measurements including duration to relapse."	well as reduction in BDI scores.
Almeida 2012 (score=4.5)	Education	RCT	Sponsored by National Health and Medical Research Council of Australia (NHMRC) and Beyondblue Australia. No COI.	N = 21,762 patients with self-reported symptoms of depression via PHQ-9 and DSI-SS criteria.	Mean age: 71.8 years; 8,959 males, 12,803 females.	Education intervention group: patients received printed educational material, practice audits, and newsletters (n=11,402) vs. Control group: patients received audits and newsletters but did not receive printed educational material (n=10,360).	Follow-up at baseline, 12, and 24 months.	Intervention group did not show significant improvement on depression outcomes at 12 months (adjusted OR = 0.90; 95% CI, 0.79-1.03) but did see improvement on self-harm behavioral outcomes at 24 months (adjusted OR = 0.80; 95% CI, 0.66-0.96).	"The results of this trial show that an educational intervention targeting general practitioners reduced the prevalence of a composite measure of clinically significant depression or self-harm behavior. The effect of the intervention was modest (3% to 17% reduction in	Open label. Cluster-randomized. Data suggest targeted education reduced the 2-year prevalence of depression and self-harm behavior by 10%. However, this did not affect recovery but did prevent the onset of new cases. Trial of randomized

									the odds of having these symptoms at 24 months)."	practitioners not patients.
McCusker 2016 (score=4.5)	Education	RCT	Sponsored by Fonds de la Recherche Québec – Santé. No mention of COI.	N = 165 patients with depressive symptoms via PHQ-9 ≥ 5 criteria.	Mean age: 57.2 years; 29 males, 136 females.	Intervention group: patients received telephone-based self-care interventions for depression including a toolkit of self-care tools and supportive telephone calls (n = 87) vs. Control group: patients received toolkit with no supportive telephone calls (n = 78).	Follow-up at both 3 and 6 months.	Patients within the intervention group had greater rates of satisfaction with self-care interventions for depression compared to control group as measured by PHQ-9 outcomes (p=.013 at baseline to 6 months).	"The study results inform the use of depression SCIs among middle-aged and older primary care patients with chronic physical conditions. Trained lay coaching can increase the use of more complex CBT-based tools used in this SCI. Greater engagement in the use of some of the tools (notably, writing in the paper tools) was associated with greater patient satisfaction, but not with improved depression outcomes. Sex differences in patterns of tool use may be helpful in targeting specific tools by sex."	Data suggest adherence to CBT may be improved via telephone coaching but may not result in improved outcomes.
Cook 2012 (score=4.0)	Education	RCT	Sponsored by National Institute on	N = 519 participants diagnosed	Mean age: 45.8±9.9 years; 177	WRAP Group: received wellness	2, 8 months	WRAP group showed larger reduction in BSI	"Our findings build on prior evidence	Study population mixed for

			Disability and Rehabilitation Research, U.S. Department of Education, and by the Center for Mental Health Services, Substance Abuse and Mental Health Services Administration. No COI.	with severe mental disorder under DSM-IV Criteria	males, 342 females	recovery action planning (WRAP) intervention of 5 sessions involving an educational component and peer support (n=251) vs Control: received care as usual (medication management and individual therapy) (n=268)		depression (58.6 to 50.7) and anxiety scores (56.9 to 49.2) from baseline to 8 month follow-up compared to control group (BSI 57.5 to 52.4; Anxiety 56.5 to 50.5).	of the positive impact of WRAP on recovery from serious mental illness (6–9) and go further in demonstrating the longitudinal effectiveness of this intervention when subjected to rigorous testing. Results of the analysis show that participation in WRAP reduced symptoms of depression and anxiety and enhanced perceived recovery."	various mental health diagnoses. Waitlist control bias. Data suggest WRAP group reported a greater reduction of anxiety and depression via BDI over time. Multiple co-interventions.
Yeung 2017 (Score=4.0)	Tai Chi/Education	RCT	Study sponsored by the national center for complimentary and integrative health. No COI.	N = 67 Chinese adults (18-70 yrs.) who were diagnosed with MDD via DSM-IV and Hamilton Rating Depression Scale (HAMD) score 14-28.	Mean age: 54±13; 19 males, 48 females.	Tai Chi (n = 23) – one-hour class held twice a week for 12 weeks of yang-style tai chi vs. Education (n = 22) – received mental health coaching for 1 hour each week for 12 weeks vs. Waitlist – (n = 22) were waitlisted and	Follow-up at baseline and weeks 6, 12, 18, and 24.	Response rate, tai chi vs education vs waitlist, at 12 weeks: 56% vs 21% vs 25%. Remission rate, tai chi vs education vs waitlist, at 12 weeks: 50%, 21%, 10%. Tai Chi vs Waitlist, positive remission OR (95% CI), week 24: 2.20 (1.11-5.64) ($p<0.05$) Tai Chi vs Waitlist, positive	"A 12 week tai chi intervention is safe and feasible and shows promise in improving depression outcomes in Chinese Americans with MDD."	Waitlist control bias. Contact time bias. Data suggest superiority to education controls.

						acted as controls		response OR (95% CI), week 24: 2.51 (1.11-5.70) (p<0.05)		
Wells 2004 (score=4.0)	Education/ Disease Management Program	RCT	No mention of sponsorship or COI.	N = 991 participants with current depressive symptoms via WHO's CIDI screening criteria.	Mean age: 43.6 years; 285 males, 706 females.	Intervention groups: patients randomized to 2 quality improvement (QI) intervention groups where they received either medication management support (QI-meds) (n = 322) or cognitive behavioral therapy (QI-therapy) (n = 357) vs. Control group: patients received usual care (n = 312).	Follow-up every 6 months for 24 months with final follow-up at 57 months.	Patients randomized to quality improvement interventions showed lowering of the rate of probable depressive order when compared with patients receiving usual care (p=.04).	"Programs for QI for depressed primary care patients implemented by managed care practices can improve health outcomes 5 years after implementation and reduce health outcome disparities by markedly improving health outcomes and unmet need for appropriate care among Latinos and African Americans relative to whites; thus, equity was improved in the long run."	Usual care bias. Data suggest at 5 years, results show managed care practice implemented QI programs may improve health outcomes. Multiple co-interventions.
Seeherunwong 2016 (score=4.0)	Education	RCT	Sponsored by Thai Nursing Council. No mention of COI.	N = 56 participants with diagnosis of MDD via DSM-IV TR criteria.	Mean age: 45 years; 9 males, 47 females.	Experimental group: patients received four sessions of treatment with educational, motivational, and cognitive components each lasting 30-60 minutes	Follow-up every one or two weeks for four follow-ups.	Participants in the experimental group had improvements on drug adherence behavior for depressive symptoms at follow-up (p=.004).	"The participants in the experimental group had more correct drug adherence behaviors in terms of the dosage and timing when compared to	Data suggest experimental group showed statistically significant drug adherence than the control group. Multiple co-interventions.

						(n = 30) vs. Control group: patients received normal care (n = 26).			those in the control group with statistical significance."	
Meyer 2009 (score=4.0)	Education	RCT	No sponsorship. COI. Mario Weiss is CEO of GAIA AG, which develops products related to the research described in this paper. Björn Meyer employed by the GAIA AG at the time of the study.	N = 396 participants recruited via German internet depression forums.	Mean age: 34.9 years; 95 males, 301 females.	Intervention group: patients received web-based interventions for 9-weeks along with usual treatment (n = 320) vs. Control group: patients received usual treatment (n = 76).	Follow-up at baseline, 9, 18, and 27 weeks.	Participants receiving web-based intervention had significantly lower depression severity levels as measured via BDI for first follow-ups (p=.002) with diminishing results afterwards.	"The present study showed that an integrative online treatment program—Deprexis—was effective in improving symptoms of depression among many of its users. On average, program users experienced lasting symptom reductions and improvements in functioning, whereas those who did not use the program remained at their original level of distress and dysfunction."	Waitlist and treatment as usual biases. Multiple co-interventions. Data suggest an integrative online program may be beneficial in treatment of depression.
Wetherell 2017 (score=3.5)										Antidepressant type and utilization different between groups. Data suggest best improvement in mindfulness group in terms

										of depression, excessive worry and perhaps some memory function.[20]
Wang 2017 (score=3.5)										Pilot study. Waitlist control bias. Data suggest a mutual recovery program "may" benefit the mental health of elderly depressed individuals.
Kumar 2015 (score=3.5)										Usual care bias. Data suggest the combination of structured psycho-education and appropriate medications is effective for faster reduction of depressive symptoms, reduced severity and improved wellbeing and quality of life.

[20] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Clarke 2002 (score=3.5)										Usual care bias. Data suggest lack of efficacy.[21]
Shimazu 2011 (score =3.5)										Data suggest family psychoeducation groups had extended periods of no relapse and at 9 months, the relapse rate was 8% compared to 50 % for controls.
Christensen 2004 (score=3.0)										Data suggest comparable efficacy in both interventions.
Lobello 2010 (score=3.0)										Open label study. Data suggest participation in Dialogues plan did not improved venlafaxine or patient treatment satisfaction.
Mackinnon 2008 (score=2.5)										Data suggest both interventional

[21] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										groups saw benefits.
Sherrill 1997 (score=2.5)										Data suggest positive feedback from study participants but clear benefits on depression are unclear.[22]

[22] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Martiny 2012 (score=7.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Eli Lilly, Danish Agency for Science, Technology and Innovation, The Region 3 Foundation, the Olga Bryde Nielsen Foundation, Frederiksborg General Hospital, AstraZeneca. COI: Dr. Martiny has served as s speaker for pharmaceutical companies and Dr. Bech received funding and was a speaker or member of advisory boards for pharmaceutical companies.	N = 75 adults with a DSM-IV major depressive disorder	Mean age: 47.7 years; 31 males, 44 females	Wake Therapy: received instruction to stay up entire night and not sleep until following day at 8 pm, then allowed to walk freely and avoid darkness (maintained light intensity of ambient level) and received 30 minutes of light therapy at 4 am on wake therapy nights to alleviate tiredness and daily morning light therapy (5500 K temperature and 10000 lux white light at 40cm distance from screen for 30 min) (n=38) vs Exercise Therapy: received individualized daily 30-min exercise	2-9 weeks	Response was observed in 71.4% of wake therapy group compared to 47.3% of exercise group (OR=2.8, 95% CI 1.1-7.3, p=0.04). Remission rates were 45.6% for wake therapy group compared to 23.1% of exercise group (OR=2.8, 95% CI 1.1-7.3, p=0.04).	"Patients treated with wake therapy in combination with bright light therapy and sleep time stabilization had an augmented and sustained antidepressant response and remission compared to patients treated with exercise, who also had a clinically relevant antidepressant response."	Data suggest combination wake and light therapy and sleep time stabilization experienced augmented and sustained antidepressant benefits compared to exercise alone.

Mather 2002 (score=7.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the Biomedical and Therapeutics Committee of the Chief Scientist's Office, Department of Health. Author McMurdo is co-director of DD Developments, a University of Dundee company providing exercise classes for older people with profits to support research into aging.	N = 86 patients with symptoms of depression, an absence of cognitive impairment (Mini-Mental Sate Examination score > 26), a diagnosis of mood disorder via clinical interview with ICD-10 criteria, and Geriatric Depression Scale score > 10	Mean age: 65.0 years; 27 males, 59 females	Exercise Group: received exercise classes for 45 min sessions twice per week for 10 weeks of weight-bearing exercise with 5-10 min warm-up and cool-down (n=43) vs Control Group: received twice weekly health education talks for a period of 10 weeks including physical and mental health education (n=43)	10, 34 weeks	Reduction in HRSD score was observed in 55% of exercise group compared to 33% of control group (OR=2.51, 95% CI 1.00-6.38, p=0.05).	"Because exercise was associated with a modest improvement in depressive symptoms at 10 weeks, older people with poorly responsive depressive disorder should be encouraged to attend group exercise activities."	Data suggest exercise improved depressive symptoms in older adults over health education.
Brenes 2007 (score=6.5)	Exercise (Aerobic, Strengthening, Flexibility)/ Sertraline	RCT	Sponsored by grant form Wake Forest University School of Medicine Women's Health Center of Excellence for Research, Leadership, and Education, The Claude D. Pepper Older Adults Independence Center and the Wake Forest University General	N=37 adults with minor depression (DSM-IV criteria)	Mean age: 74.5 years; 14 males, 23 females	Medication Group: received open-label sertraline 25 mg/day for week 1 and 50 mg/day for week 2 (increasing 25 mg dose increments for a max of 150 mg) (n=11) vs Exercise Group: completed a 3 days a week for 16 weeks exercise program of aerobic and resistance exercise training (60-min	2, 6, 10, 14 weeks, and 4 months	Depression HRSD scale was reduced in exercise and sertraline group compared to an increase in usual care condition (p=0.005). All groups showed an improvement	"Individuals in the exercise condition showed greater improvements in physical functioning than individuals in the usual care condition. Both sertraline and exercise show promise as treatments for	Pilot study with usual care bias. Data suggest both exercise and sertraline benefit late life depression but exercise also improves the individual's physical function.

			Clinical Research Center, and National Institute of Mental Health Grant. No mention of COI.			sessions) (n=14) vs Usual Care Group: received a phone call by research staff at weeks 2, 6, 10, 14 weeks by research staff about patient's general health status (n=12)		in SF-36 scale while the improvement in exercise and sertraline group showed greater improvement compared to the usual care group (p=0.11).	late-life minor depression. However, exercise has the added benefit of improving physical functioning as well."	
Blumenthal 2007 (score=6.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the National Center for Research Resources, Clinical Research Centers Program. COI, one or more of the authors received or will receive benefits for personal or professional use.	N = 202 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 52 years; 49 males, 153 females	Supervised aerobic exercise – three 45-minute exercise sessions (n=51) vs. Home-based aerobic exercise – met with exercise physiologist for instruction, then completed exercises at home, recorded with exercise log (n=53) vs. Sertraline – 50-200 mg/day, given up to 4 dosages of zolpidem if experiencing insomnia (n=49) vs. Placebo – dosing equal to sertraline group (n=49). All treatments administered for 4 months	Follow-up at weeks 2, 4, 8, 12, and 16	All treatment groups had higher depression remission rates compared to placebo (p = 0.057) but there was no statistical difference between these three groups	"The efficacy of exercise in patients seems generally comparable with patients receiving antidepressant medication and both tend to be better than the placebo in patients with MDD. Placebo response rates were high, suggesting that a considerable portion of the therapeutic response is determined by patient expectations, ongoing symptom monitoring, attention, and other	Potential dissimilar contact time between exercise groups (home vs supervised). Data suggest similar efficacy between exercise groups and antidepressants, both of which are better than placebo.

									nonspecific factors."	
Danielsson 2014 (score=6.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI. Sponsored by Närhälsan Research and Development Primary Health Care and Swedish Research Council.	N = 62 participants meeting DSM-IV criteria for major depression	Mean age: 45.44 years; 14 males, 48 females	Exercise – exercise in a gym with gym equipment (stationary bike, cross-trainer, rowing machine, treadmill, etc.), individual sessions biweekly for two weeks, then group sessions biweekly for 8 weeks, all sessions lasting 60 minutes (n=22) vs. Basic Body Awareness Therapy (BBAT) – sessions with a physical therapist, individual sessions biweekly for two weeks, then group sessions biweekly for 8 weeks, all sessions lasting 60 (n=20) vs. Advice group – met with physical therapist on advice for physical activity, able to contact physical therapist for study duration (n=20)	Follow-up at 10 weeks	Mean change in Montgomery Asberg Rating Scale (MADRS): exercise = -10.3, BBAT = -5.8, advice = -4.6. Significant difference in this measure between all groups (p=0.038). Exercise significantly greater than advice group (p=0.048)	"Exercise in a physical therapy sitting seems to have effect on depression severity and fitness, in major depression. Our findings suggest that physical therapy can be a viable clinical strategy to inspire and guide persons with major depression to exercise. More research is needed to clarify the effects of basic body awareness therapy."	Data suggest supervised exercise group exhibited improved depression scores (MADRS) and CV fitness better than either the BBAT or advice groups.
Krogh 2012 (score=6.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Trygfonden, Nordea-Danmark fonden, Helsefonden, and Åse and Ejnar Daneilsen's fond. COI, one or more of the authors have received or will receive benefits for	N = 155 participants meeting DSM-IV criteria for major depression	Mean age: 41.6 years; 38 males, 77 females	Aerobic exercise – 45 minute sessions, 3 times per week for 3 months (n=56) vs. Stretching exercise – 45 minute sessions, 3 times per week for 3 months (n=59)	Follow-up at 3 months	Mean difference in Hamilton Depression Rating Scale scores between groups at post intervention = -0.78 (p = 0.52)	"The results of this trial does not support any antidepressant effect of referring patients with major depression to a three months	Recruitment lower than anticipated (115 vs 212). Lack of efficacy as data suggest that aerobic exercise not better than

			personal or professional use.						aerobic exercise program."	stretching exercise and at 3 months there was no associated antidepressant effect from the aerobic exercise group.
Singh 2005 (score=6.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of sponsorship or COI.	N=60 adults with major or minor depression (DSM-IV criteria)	Mean age: 69.3 years; 27 males, 33 females	High Group: received high intensity progressive resistance training (PRT) of large muscle groups (3 days/week for 8 weeks) (n=20) vs Low Group: received low intensity resistance using same regimen as high group, but at 20% of 1RM (60 minute sessions) (n=20) vs GP Care: received usual care from general practitioner (n=20)	8 weeks	Improvement in GDS scale and HRSD scale were larger in exercise group compared to control ($p<0.006$, $p=0.14$; respectively).	"High intensity resistance training is superior to low intensity resistance training or usual care by a GP in older community-dwelling adults with clinical depression."	Data suggest high PRT better than low PRT when treating depressive symptoms as a 50% reduction in HRS-D scores achieved in 61% of the high PRT group and 29% of the low PRT group compared to 21% in usual care group.
Chalder 2012 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI. Sponsored by the Department of Health as part of the National Institute for Health Research Health Technology Assessment program.	N = 361 participants with a current diagnosis of ICD-10 depressive episode	Mean age: 39.86 years; 122 males, 239 females	Intervention – offered three face-to-face sessions with a trained physical activity facilitator over 8 months, also able to have 10 telephone calls as well, plus usual care (n=182) vs. Control – usual care (n=179)	Follow-up at months 4, 8, and 12	Beck Depression Inventory II mean score: adjusted difference between groups = -0.54 ($p = 0.68$). No significant differences in mood improvement at any time	"The addition of a facilitated physical activity intervention to usual care did not improve depression outcome or reduce use of antidepressants compared with usual care alone."	TREAD Study. Usual care bias. Data suggest lack of efficacy as trial did not show that the addition of facilitated exercise activity was better than either antidepressant

								point between groups		use or usual care.
Imayama 2011 (score=5.5)	Weight Loss Program/ Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by The National Cancer Institute (NCI). No COI.	N = 439 overweight or obese postmenopausal women, no depression diagnosis	Mean age: 57.9 years; 0 males, 439 females	Exercise: received daily 45 min moderate-to-vigorous aerobic exercise 5 days a week (n=117) vs Diet: received a reduced calorie weight loss intervention 1200-2000 kcal/day with sessions with dietician weekly(n=118) vs Diet+Exercise: received both reduced calorie weight loss and exercise interventions (n=117) vs Control: did not receive intervention during trial, but were offered 4 group diet and exercise session after 12 months (n=87)	12 months	Body weight decreased by 7.2 kg in the diet group ($p<0.01$), 2.0 kg in exercise group ($p=0.03$), 8.9 kg in the diet and exercise group ($p<0.01$) compared to controls. Diet and exercise group reduced depression ($p=0.03$) compared to control group and increased social support ($p=0.05$).	"Our findings suggest that the combination of dietary weight loss and exercise may have a larger beneficial effect on HRQOL compared with dietary weight loss or exercise alone. Weight loss and improvements in aerobic fitness and psychosocial factors (depression, stress, and social support) were predictors of increased HRQOL, suggesting that these factors could mediate the intervention effects on HRQOL."	Data suggest combination diet and exercise has positive effects on psychological health and HRQOL.
Krogh 2009 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by "Assurance and Pension". No COI.	N=165 patients with unipolar depression (DSM-IV criteria)	Mean age: 38.9±9.46 years; 43 males, 122 females	Strength Group: received strength training involving circuit training (n=55) vs Aerobic Group: received aerobic exercise program using machines (n=55) vs	4, 12 months	Mean HAM-D_{17} scores were -1.3 (-3.7-1.2, $p=0.3$) and 0.4 (-2.0-2.9, $p=0.3$) for the strength and aerobic groups	"[O]ur trial does not provide evidence for a biologically mediated effect of exercise on clinical depression in a	Pragmatic trial. Multiple co-interventions. Low compliance. Data do not show efficacy of exercise on

						Relaxation Group: received light balance exercise to avoid muscular contractions or stimulation of the cardiovascular system (n=55) All groups met 2 times per week for a total of 32 (1.5 hour) sessions		compared to relaxation group at 4 months. Mean HAM-D_{17} scores were -0.2 (-2.7-2.3, p=0.8) and 0.6 (-1.9-3.1, p=0.6) for the strength and aerobic groups compared to the relaxation groups.	pragmatic outpatient setting. Exercise recommendations suggest that the intervention should have been offered 3 times per week."	symptom severity in depressed patients per HAM-D17. However, work loss was reduced 12.1% in aerobic group and 2.7% in strengthening group compared with relaxation.
Murri 2015 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/ Sertraline	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU) grant. No COI.	N=121 patients with major depression on Hamilton Rating Scale for Depression (HRSD) score ≥ 18	Mean age: 75.2 years; 35 males, 86 females	Sertraline Only: received 50 mg sertraline (n=42) vs Sertraline+Non-progressive Exercise (S+PAE): received 50 mg sertraline and 3 session per week for 24 weeks of exercise sessions(n=37) vs Sertraline+Progressive Aerobic Exercise (S+NPE): received 50 mg sertraline and exercise involving improved cardiopulmonary condition (n=42)	4, 8, 12, 24 weeks	Remission rates at 4 weeks were 36% for S+PAE group, 40% for S+NPE group, and 7% for sertraline only group (p=0.001). Remission rates at 8 weeks were 60% in S+PAE group, 49% in S+NPE group, and 40% for sertraline only group (p=0.22). Remission rates at 12 weeks were 83% for S+PAE group, 54% for	"Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression."	Data suggest exercise as adjunct therapy for depression in late life individuals.

								S+NPE group, and 45% for sertraline only group (p=0.001). HRSD scores decreases more in the exercise groups compared to the sertraline only group.		
Penninx 2002 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary Analysis of FAST Study (Ettinger et al 1997)	Sponsored by Claude D. Pepper Older Americans Independence Center of Wake Forest University, National Institute on Aging, General Clinical Research Center Grant. No mention of COI.	N=439 persons with knee osteoarthritis, depressive symptoms measured by the Center for Epidemiological Studies—Depression Scale (CES-D)	Mean age: 68.7 years; 131 males, 307 females	Aerobic Group: received 3 months of facility-based walking program (10 min warm up and cool down with 40 min sessions of 50-70% heart rate reserve) and 15 month home-based walking program, also received 3-4 week phone calls (n=149) vs Resistance Group: received 3 month facility-based program (3 1-hour sessions per week) and 15-month home-based program of repetitions of upper and lower body exercises with weights (n=146) vs Control Group: received monthly education sessions by nurse on arthritis management, at 4-6 months were called bimonthly, and 7-18 months called monthly to maintain health updates and provide support (n=144)	3, 9, 18 months	Aerobic exercise group reported 23% lower depression scores over time compared to controls with an increase of 2% depression score (p<.001). Resistance exercise group showed a reduction in depression score of 6% compared to controls (p=.27).	"Aerobic and resistance exercise significantly reduced disability and pain and increased walking speed both, and to an equal extent, in persons with high depressive symptomatology and persons with low depressive symptomatology."	Data suggest both aerobic exercise and resistance exercises can reduce pain and disability but aerobic exercise significantly reduced symptoms of depression over time. Assessments occurred at 3, 9, and 18 months post interventions. In addition, both high depressive individuals as well as low saw benefits but low group was most compliant. Aerobic exercise

										decreased pain and disability and increased walking speed.
Trivedi 2011 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by NIMH, NARSAD Independent Investigator Award, and the National Cancer Institute. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N=122 participants with major depressive disorder (MDD) for DSM-IV criteria	Mean age: 47.1 years; 22 males, 100 females	16-KKW Exercise Group: received 16 kcal per kg of total weekly energy expenditure (4 mph walking for 210 minutes per week) (n=61) vs 4-KKW Exercise Group: received 4 kcal per kg of total weekly energy expenditure (3 mph for 75 minutes per week) (n=61)	12 weeks	Remission rates were identical for both exercise groups of 29.5% (p<.0001). Adjusted remission rates were 28.3% for 16-KKW group compared to 15.5% in 4-KKW group. Family history of mental illness showed higher remission rates in males compared to females (high dose: M 85.4% vs F 39%; low dose M 0.1% vs F 5.6%; p<.0001).	"There was a trend for higher remission rates in the higher-dose exercise group (p<0.06), with a clinically meaningful NNT of 7.8 in favor of the high exercise dose. Significant differences between groups were found when the moderating effects of gender and family history of mental illness were taken into account and suggest that higher-dose exercise may be better for all men and for women without a family history of mental illness."	Compliance better in 4 KKW group vs 16 KKW group. Data suggest a trend towards higher remission rates in higher-dose exercise group. Data also suggest those without family history of depression or mental illness may be more likely to achieve remission via higher doses of exercise.
Greer 2015 (score=N/A)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary Analysis of TREAD	Sponsored by NARSAD and NIMH. COI: One or more of the authors have received or will receive benefits for	N=39 participants with a primary diagnosis of MDD	Mean age: 46.7±9.6 years; 5 males, 34 females	16-KKW Exercise Group: received 16 kcal per kg of total weekly energy expenditure (4 mph walking for 210 minutes per week)	4 months	Depressive symptoms decreased in both group (13.5 pts in low dose vs 17.3	"This study suggests a dose–response effect of exercise in specific executive	Data suggest a dose-response exercise effect for specific executive function as

		Study Trivedi 2011	personal or professional use.	(DSM-IV criteria)		(n=19) vs 4-KKW Exercise Group: received 4 kcal per kg of total weekly energy expenditure (3 mph for 75 minutes per week) (n=20)		pts in high dose). Improvements in spatial working memory observed for high dose group compared to decreasing in low dose group.	function and working memory tasks among depressed persons with a partial response to SSRI and cognitive complaints, with some cognitive functions improving regardless of exercise dose."	well as working memory tasks in MDD patients. Data suggest improvement in cognitive function following exercise of at least 30 minutes of aerobic activity 5 times per week. Cognition assessed via the Inventory for Depressive Symptomology item "Concentration and Decision Making."
Blumenthal 1999 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/ Sertraline	RCT	Sponsored by the National Institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 156 people with major depressive disorder via DMS-IV criteria, assessed by the Diagnostic Interview Schedule and the Hamilton Rating Scale for	Mean age: 57 years; 43 males, 113 females	Sertraline initiated with 50 mg and titrated until well tolerated group (n = 48) vs three supervised exercise sessions per week group (n = 53) vs both sertraline and exercise as above group (n = 55)	Follow up at 1, 2, 3, 4, 6, 8, and 12 weeks.	Growth curve analysis of HAM-D showed the rate of treatment response differed across the treatment groups (P=0.02). 60.4% of the exercise group, 68.8% of the medication group and 65.5% of the combination	"An exercise training program may be considered an alternative to antidepressants for treatment of depression in older persons. Although antidepressants may facilitate a more rapid initial therapeutic response than exercise, after	Data suggest comparable response between all 3 groups and antidepressant appeared to result in a faster response but at the end of the 16-week intervention, exercise and antidepressant were equally effective for

				Depression (HAM-D)				group no longer met DSM-IV criteria for MDD post treatment (No statistical difference found)	16 weeks of treatment exercise was equally effective in reducing depression among patients with MDD.	treating MDD symptoms.
Babyak 2000 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/ Sertraline	Secondary Analysis of Blumenthal 1999	Sponsored by the National institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 133 volunteers who met DSM-IV criteria for MDD and scored at least 13 on the HRSD at study entry.	Mean age 50 and mix of both males and females.	Group that did three supervised exercise sessions per week for 16 weeks at 70%-85% heart rate reserves with a 10 min warm up, 30 minutes at proper intensity and 5 min cool down (n = 44; Exercise) vs group that received sertraline initiated at 50 mg and titrated until well-tolerated up to 200 mg (n = 42; Medication) vs group that did both the exercise and medication interventions (n = 47; Combination)	Follow up at 2, 6, 10, 14, and 16 weeks in original study. Follow up at 4 and 10 months for secondary study.	At 10 months 30% of the exercise group were still considered depressed based on DSM-IV diagnosis or an HRSD score greater than 7 vs 52% in the medication group and 55% in the combination group (p=0.028). Looking at the 83 patients assessed as being in remission at 4 months, at 10 months participants in the exercise group had an odds ratio of 6.10 (p=0.01) of being partially or fully recovered compared to	"Among individuals with MDD, exercise therapy is feasible and is associated with significant therapeutic benefit, especially if exercise is continued over time."	Data suggest exercise was associated with lower relapse rates than those associated with the medication group.

								the other two groups.		
Huang 2015 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/ Cognitive Behavioral Therapy	RCT	Sponsored by the Chang Gung University. No COI.	N = 57 patients with Geriatric Depression Scale-15 scores ≥ 5	Mean age: 76.53 years; 27 males, 30 females	Three times per week 50 min physical fitness exercise sessions group (n = 19) vs weekly 60-80 min cognitive behavioral therapy sessions group (n = 18) vs usual care group (n = 20)	Follow up at 1 week (T1), 3 months (T2), 6 months (T3), and 9 months (T4) after baseline.	CBT group GDS-15 score at baseline was 7.78 vs 4.28 at T2 (P=0.009). Exercise group GDS-15 score at baseline was 8.63 vs 4.63 at T2 (P=0.003). Exercise groups quality of life SF-36 score was 60.61 at baseline vs 76.12 at T2 (P<0.001).	"Immediately after a 12-week intervention, there were significant decreases in depressive symptoms and more perceived social support amongst those in the CBT group. When considering the effectiveness in the decrease of depressive symptoms longer term, the increase in the 6-min walk distance and raising the patients' quality of life, physical fitness exercise program may be a better intervention for elderly adults with depressive symptoms."	Usual care bias. Data suggest both exercise and CBT decreased depressive symptoms but the exercise group had decreased symptoms for a longer period with improved fitness and quality of life.
Schuch 2014 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Fundo de Incentivo a Pesquisa e Eventos do Hospital de Clinicas de Porto Alegre, Coordenaçao de aperfeiçoamento	N = 50 patients with major depression evaluated through the Mini	Mean age: 40.3 years; 13 males, 37 females	Exercise dose of 16.5 kcal/kg of weight/week of aerobic exercise spread out to three weekly sessions group (n = 25) vs usual	Follow up at baseline, two weeks and discharge.	Remission rate at discharge was 48% in the exercise group vs 32% in the control though the difference	"Add-on exercise is an efficacious treatment for severely depressed inpatients,	Data suggest exercise improved depressive symptoms and quality of life.

			de pessoal de nível superior and Conselho nacional de desenvolvimento científico e tecnologico. No conflict of interest.	internationa l Neuropsyc hiatric interview according to the DSM-IV criteria with a score of 25 or more on the Hamilton scale for depression.		treatment control group (n = 25)		was not statistically significant. Psychological quality of life scores for the exercise group were 30.09 at baseline, 55.75 on week two and 60.16 on discharge vs 25.87 at baseline, 42.78 on week two, and 41.06 on discharge for the control (Group x time interaction P=0.023)	improving their depressive symptoms and QoL. Initial acceptance of exercise remains a challenge."	
Martiny 2013 (score=5.0)	Light Therapy	RCT	Sponsored by Eli Lilly, The Danish Agency for Science, Technology and Innovation, The Danish Medical Research Council, the Olga Bryde Nielsen Foundation, and the Frederiksborg General Hospital Research Grant. One or more of the authors have received or will receive benefits for personal or professional use.	N = 75 patients currently experiencin g a major depressive episode and with a HAM-D17 score of 13 or greater	Mean age: 47.5 years; 31 males, 44 females	Group 1: received wake therapy, daily morning light therapy (10,000 lux daily for 30 min), and duloxetine (medication) 60mg daily for 9 weeks (n=37) vs. Group 2: participated in an individual exercise program of at least 30 minutes daily and duloxetine 60mg daily for 9 weeks (n=38)	No mention of follow-up past the duration of 9-week study.	Primary outcome was remission rates at day 5, based on Hamilton Depression Scores. Mean HAM-D score for group 1 was 4.1, compared with 8.7 for group 2 after 5 days of treatment (p=0.004).	"The intervention induced an acute antidepressant response without relapse between wake nights but with a diminishing effect after intervention. Development is still needed to secure maintenance of response."	Data suggest wake therapy group better than exercise group for response rates although compliance is difficult to assess thoroughly. Response rates diminished at day 8.
Knubben 2007 (score=5.0)	Exercise (Aerobic, Strengtheni	RCT	No mention of sponsorship. No COI.	N = 38 patients with a major	Mean age: 49.47 years; 17	Endurance exercise of walking on a treadmill every day alternating 3 minute intervals of	Follow up at baseline and 10 days.	BRMS scores for the endurance group were	"We conclude that an endurance training	Data suggest patients with MD may benefit from a

	ng, Flexibility)			depression episode according to the DMS-IV and score of >12 on the Bech-Rafaelsen Melancholy Scale (BRMS)	males, 21 females	intensity corresponding to a lactate concentration of 3 mmol/l in capillary blood and a heart rate of 80% max and half speed for a total of 30 minutes for 10 days (n = 20) vs placebo group of light stretching and relaxation exercises for 30 minutes every day (n = 18)		17.6 and 11.2 at day 10 with a difference of -6.45 vs 18.7 at baseline and 15.5 at day 10 for the placebo with a difference of -3.2 (P=0.01 comparing differences).	programme substantially Improves symptoms in selected patients with moderate to severe depression. Endurance training can thus be a helpful complementary treatment for patients with severe affective disorders in the first 3 weeks of pharmacotherapy."	short-term endurance-training program by improving mood. Small sample with short intervention time.
Ho 2014 (score=5.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the Physiotherapy Department and the Department of Psychiatry of Tai Po Hospital, Hospital Authority, Hong Kong.	N = 52 patients admitted to the Psychiatric Unit in Tai Po Hospital with a C-BDI score of 9 or above and meeting the ICD-10 criteria for MDD.	Mean age: 46.22 years; 17 males, 35 females	Aerobic exercise of 5 supervised exercise sessions per week for 3 weeks consisting of a 5 minute warm up, 30 minutes interval training and then 5 minutes cool down group (n = 26) vs maintain current physical activity level with a 10-minute stretching exercise on large muscle groups group (n = 26)	Follow up at baseline and 3 weeks.	Mean change in MADRS score for the exercise group from baseline to end of 3 weeks was 10.08 vs 4.69 for the control group (P<0.05).	"Aerobic exercise in addition to pharmacological intervention can have a synergistic effect in reducing depressive symptoms and increasing flexibility among Chinese population with mild to moderate depression. Early introduction of exercise training in in-patient phase can help	Lack of long term follow-up. Data suggest aerobic exercise in addition to medication may have a synergistic effect for decreasing symptoms of depression and improving flexibility.

									to bridge the gap of therapeutic latency of antidepressants during its nonresponse period."	
Pfaff 2013 (score=5.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Healthway (the Western Australian Health Promotion Foundation). No COI.	N = 200 deemed suffering from clinical depressive illness according to a standardizes mental health telephone assessment with a score of 10 or more on the Patient Health Questionnaire (PHQ-9)	Mean age: 61.0 years; 74 males, 126 females	Usual care group (n = 92) vs 12 week exercise program of either 5 days/week moderate intensity or 3 days/week vigorous exercise group (n = 102)	Follow up at baseline, 4, 8, 12, 26, and 52 weeks.	At 52 weeks, 66.7% of the usual care group had depression in remission vs 68.1% of the exercise group. However, the difference was not statistically significant.	"This home-based physical activity intervention failed to enhance fitness and did not ameliorate depressive symptoms in older adults, possibly due to a lack of ongoing supervision to ensure compliance and optimal engagement"	65+year olds enrolled. Usual care bias. Data suggest both groups improved regardless of intervention but exercise was not superior to usual care likely due to unsupervised compliance. Measures of fitness did not improve, suggesting lack of compliance.
Krogh 2014 (score=5.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of sponsorship. No COI.	N = 79 patients from the DEMO-II trial which required a diagnosis of major depression (DSM-IV) based on the Danish version of	Mean age: 41.3 years; 26 males, 53 females	Aerobic training of stationary bikes at approximately 80% max heart rate for 45 min three times a week for three months (n = 41) vs control of stretching and low impact exercise for 45 minutes three times a week for three months (n = 38)	Follow up at baseline and at 3 months.	Total hippocampal volume pre intervention was 6.353 in the aerobic exercise group vs 6.421 in the control group while it was 6.325 post intervention in the aerobic	"Despite a significant increase in maximal oxygen uptake, a pragmatic exercise intervention did not increase hippocampal volume or resting levels of neurotrophines	Poor participation rate. Data suggest lack of efficacy. Exercise did not appear to increase hippocampal volume or resting levels of neurotrophines

				the Mini International Neuropsychiatric Interview. All participant scored above 12 on the HAM-D_{17}				group vs 6.38 post intervention in the control group (Between group p-value 0.54).	in out-patients with mild to moderate major depression."	in mild to moderate major depressed individuals.
Ström 2013 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Swedish council for working Life and social research, Swedish research council, and a professor's contract awarded to Gerhard Andersson. Gerhard Andersson is an academic editor for Peer J.	N = 48 participants mild to moderate depression diagnosed by DSM-IV axis 1 disorders	Mean age: 49.2 ± 10.7 years; 8 males, 40 females	Treatment Group: Received self-help program consisting of nine modules , once a week for nine weeks, and were also given a pedometer to track physical activity (given weekly feedback by therapist) (n=24) vs Control group (n=24)	6 months	Treatment group showed improvement of depressive symptoms of 70.8% compared to control group 37.5% ($p < 0.001$). There was a moderate effect size reported as (Cohen's d = 0.67; 95% CI 0.09- 1.25).	"In summary, the findings in this study indicate that internet-administered therapist guided physical activity can be an effective treatment for depressive symptoms for people with mild to moderate major depression, but there is no evidence of effectiveness in raising levels of physical activity or quality of life, nor reducing symptoms of anxiety."	Wait list control bias data suggest reduced depressive symptoms In internet delivered physical activity.
Belvederi, 2015 (score=4.5)	Exercise (Aerobic, Strengthening,	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU)	N = 121 primary care patients	Mean age: 75.2 ± 6.0 years;	Sertraline only (S): Prescribed drug 50 mg (2 week titration period, zolpidem 10mg/day and	None	45% of participants In Sertraline group, 73% of	"Physical exercise may be a safe and effective	Data suggest significant efficacy in the

	Flexibility)/ Sertraline		2010-12 grant, area 2 for clinical Governance. No mention COI	with major depression (score of 18 or higher on the 17-item HRSD) selected by physicians and conditions were compatible with regular exercise	35 males, 86 females	lorazepam 2mg/day was allowed for insomnia) (n=42) vs Sertraline plus non-progressive exercise (S+NPE): Prescribed 3 supervised group exercise sessions per week (60 min, 24 wks in groups of 3 to 6 participants) in addition to sertraline as in the sertraline group (n=37) vs Sertraline plus progressive aerobic exercise (S+PAE): Prescribed the same group exercise sessions, but training scheme was programmed to increase over the weeks (n=42)		participants in (S+NPE) group, and 81% (S+PAE) group achieved remission ($p < 0.001$; 95% CI 1.27 – 3.54)	augmentation to antidepressant therapy in late-life major depression."	physical exercise group.
Martinsen, 1989 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of sponsorship or COI	N = 98 inpatients that meet DSM-III-R criteria for major depression, dysthymic disorder or depressive disorder not otherwise specified (NOS).	Mean age: 41.04 ± 9.96 years; 30 males, 68 females.	Aerobic Group: performed intense aerobic exercise (70% of maximum aerobic capacity) (n = 51) vs Nonaerobic Group: Muscular strength, flexibility, coordination, and relaxation (n=48)	None	Depression scores on admission almost identical in both aerobic and nonaerobic groups ($p > 0.10$). Both groups had significant reduction in depression scores during the study ($p <0.001$)	"We found no differences between aerobic and nonaerobic forms of exercise in the treatment of clinical depression …"	Data suggest comparable efficacy between aerobic vs non-aerobic exercise groups but VO max higher in aerobic groups, otherwise the reduction in depression scores was significant and equal in both groups
Motl, 2005 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by National Institute on Aging (Grant 2R01 AG 12113). No mention of COI	N = 174 formerly sedentary (lack of exercise	Mean age: 65.5 years; 49 males,	Walking Group: 3 times a week for 6-months intensity started at 50-55% VO2 peak, increased to 65% VO2	12, 60 months	Depressive symptoms scores were decreased immediately	"In summary, we provide novel evidence that supports (a) the effectiveness	At 5 years post intervention data suggest exercise benefits

				during the last six months), no depression diagnosis	125 females.	peak. (n=85) vs Toning Group: low-intensity resistance exercises, 1 set of 8-12 per major muscle group. Walked 10-15 min and increased by 1 min per session until 40-45 min (n=89)		after the intervention (5.6 ± 0.4), followed by a sustained reduction for 12 (4.7 ± 0.4) and 60 months after intervention initiation (4.2 ± 0.6).	of an exercise training intervention for the sustained reduction of depressive symptoms among non-depressed older adults and (b) physical self-esteem as an important factor that underlies changes in depressive symptoms after an exercise training intervention among older adults."	sedentary older adults and its effects are sustained in reducing depressive symptoms and physical self-esteem. Depression scores immediately dropped and sustained for up to 5 years.
Patten 2017 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI. Sponsored by the National Center for Advancing Translational Sciences (NCATS, part of NIH), Mayo Clinic, and the Department of Psychiatry and Psychology.	N = 30 women with depression measured via Center for Epidemiological Studies Depression Scale score of at least 16	Mean age: 37.5 years; 0 males, 50 females	Both groups enrolled in 12-week programs with three 30-40 minute sessions each week with wellness coaches. Both groups given nicotine patches as well. Wellness coach focused on health education – covering various women's health and lifestyle issues (n=15) vs. Wellness coach focused on exercising, women met at YMCA and had 25-35 minutes of exercise (n=15)	Follow-up at 12 weeks	Patient Health Questionnaire (PHQ-9) scores at 12 weeks did not differ between groups (p = 0.90)	"Vigorous intensity supervised exercise is feasible and enhances short-term smoking cessation among depressed female smokers."	All female study. Data suggest vigorous intensity, supervised and sustained exercise assist smoking cessation in depressed women.
Euteneuer 2017 (score=4.0)	Exercise (Aerobic, Strengtheni	RCT	COI, one or more of the authors have received or will	N = 101 participants meeting	Age and gender informatio	Cognitive Behavioral Therapy (CBT) with exercise (CBT-E), 50	Follow-up at weeks 8 and 16	Depressive severity measured via	"Behavioral activation in conjunction with	Waitlist control bias. Data suggest CBT-E

	ng, Flexibility)		receive benefits for personal or professional use. PSOnsored by the German Research Foundation.	DSM-IV major depression criteria with 30 healthy controls	n only available for 98 participants. Mean age: 37.31 years; 50 males, 48 females	minute psychotherapy sessions weekly for 16 weeks, with creation of at least 40 minute exercise sessions per week (n=36) vs. CBT with pleasurable low-energy activities, 50 minute psychotherapy sessions weekly for 16 weeks, with creation of at least four 40 minute sessions of euthymic exercises that bring awareness to different senses (CBT-C) (n=35) vs. Waitlist control (n=30)		Beck Depression Inventory II – at week 8: CBT-E = 18.4, CBT-C = 19.1, WL = 29.5, at week 16: CBT-E = 14.6, CBT-C = 14.8, WL = 23.5 ($p < 0.001$). Scores not significantly different between CBT-E and CBT-C at week 8 ($p = 0.816$) and week 16 ($p = 0.889$)	exercise may have the potential to reverse, in part, immunological alterations in MD."	group associated with the greatest anti-inflammatory decreases compared to both CBT-C and WLC groups as measured by IL-10 at weeks 8 and 16 suggesting an association between elevated inflammatory markers and depression.
Salehi 2016 (score=4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI or sponsorship.	N = 60 participants meeting DSM-IV-TR criteria for major depressive disorder	Mean age: 31.0 years; 44 males, 16 females	Electroconvulsive therapy (ECT) – three sessions per week, for 4 weeks (n=20) vs. Aerobic exercise training (AET) – three weekly sessions, 40-45 minutes per session, for 4 weeks (n=20) vs. ECT and AET for four weeks (n=20)	Follow-up at 4 weeks	All groups produced significantly decreased Beck Depression Inventory (BDI) mean scores at 4 weeks ($p < 0.0001$). However, BDI scores did not differ between groups ($p > .05$)	"The pattern of results suggests that ECT, AET and particularly their combination are promising directions for the treatment of patients suffering from MDD, and that it remains unclear to what extent pBDNF is key and a reliable biomarker for MDD."	While all interventions led to improved symptoms, efficacy was best in combo AET and ECT and combo better than either AET or ECT alone.

Pentecost 2015 (score=4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI. Sponsored by National Prevention Research Institute phase 4 and its partners, National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula at the Royal Devon and Exeter NHS Foundation Trust.	N = 60 participants with depression diagnosed via Clinical Interview Schedule-Revised (CIS-R)	Mean age: 44.4 years; 31 males, 29 females	Psychological wellbeing practitioners (PWPs)-supported self-help program. Initial assessment with PWP lasting up to 35 minutes, with 12 support sessions (25-35 minutes each). Focus on behavioral activity (BA) alone (n=30) vs. Focus on BA with physical activity promotion (BAcPAc) (n=30)	Follow-up at 4 months	Clinical Interview Schedule-Revised scores at baseline and at 4 months: BA = 29.0, 16.7, BAcPAc = 27.2, 19.3 (no statistical test given to evaluate differences in groups)	"This study demonstrates the difficulties of embedding a pilot trial into existing current clinical practice, in this case IAPT services."	Pilot study. Data suggest addition of physical activity (PA) to behavioral activation (TAU), may potentially improve depressive symptoms but results are inconclusive due to multiple study challenges including recruitment and assessment.
Schuver 2016 (score=4.0)	Yoga/ Exercise (Aerobic, Strengthening, Flexibility)	RCT	No COI. No mention of sponsorship.	N = 40 participants with depression via the SCID-I (DSM-IV)	Mean age: 42.68 years; 0 males, 40 females	Yoga – 60-75 minutes per sessions twice a week for 12 weeks along with 15 minute mindfulness telephone sessions once a week for 1 month and then twice a week for 2 months (n=20) vs. Walking program – 65 minute walking sessions and eight telephone sessions with a counselor (n=20)	Follow-up at 12 and 16 weeks	No significant between group difference on depression scores at 12 weeks ($f(1,31)=0.61$, $p=0.44$, $d=0.25$) and 16 weeks ($f(1,31)=0.80$, $p=0.78$, $d=0.08$)	"These findings suggest that mindfulness-based yoga may provide tools to manage ruminative thoughts among women with elevated depressive symptoms."	Comparable efficacy. Data suggest mindfulness yoga may decrease ruminative thoughts in depressed women but both groups reported decreases in depressive symptoms.
Kerling, 2015 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No sponsorship. COI, Multiple researchers received speaker honoraria.	N = 42 inpatients with moderate to severe depression,	No mention of mean age; 26 males, 16 females	Exercise Group: three training protocols per week for 4 minutes at moderate intensity (n=22) vs Two Treatment group: took	None	ANCOVA models controlling for baseline levels of depression did not yield a	"Adjunctive exercise training in depressed inpatients improves physical fitness,	Standard care Bias. Data suggest exercise may be an adjustment

				diagnostic criteria being DSM-IV and confirmed with clinical interviews (SCID I/II)		part in daily activity program that consisted of supervised activation (walking, ball games and stretching exercises for 20 min) (n=20)		significant effect of exercise with respect to MADRS (F = 2.23; p = 0.14) or the BDI-2 (F = 0.69;p = 0.41)	mets factors, and psychological outcome."	therapy for depressed patients as It improves physical and psychological outcomes.
Doyne, 1987 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of sponsorship or COI.	N = 40 women recruited through mass media diagnosed with major to minor depressive disorder via the Research Diagnostic Criteria (Spitzer, Endicott and Robins)	Mean age: 28.52 ± 4.36 years; 0 males, 40 females	Aerobic Group: (walked or ran around a 1/8th-mile indoor track, at 7 min interval pulse was taker to maintain 80% work capacity (n = no mention) vs Nonaerobic Group: (used a universal exercise machine, 10 station program paced to allow the heart rate to below 50-60% work capacity). (n = no mention) vs Wait-list control group: (told that the exercise program delayed for 8 weeks). Then had a choice of program (n= no mention)	1, 7, and 12 months	BDI and HRSD using mixed MANOVA, results showed a significant time effect F(4,138) = 14.98, p < 0.01,(Condition X Time [pre, mid, post]), and Condition X Time interaction, F(8, 138) = 4.78, p < 0.05	"Findings from the current study indicate that AE is an effective intervention for symptoms of depression and cognitive control impairments in MDD. Considering the frequent report of cognitive impairments in MDD and the failure of these."	Data suggest both exercise groups improved depressive symptoms
Ossip-klein, 1989 (score = n/a)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary analysis of Doyne 1987	No mention of sponsorship or COI.	N = 40 women recruited through mass media diagnosed with major to minor depressive disorder via the Research	Mean age: 28.52 ± 4.36 years; 0 males, 40 females	Aerobic Group: (walked or ran around a 1/8th-mile indoor track, at 7 min interval pulse was taker to maintain 80% work capacity (n = no mention) vs Nonaerobic Group: (used a universal exercise machine, 10 station program paced to allow the heart rate to below	1, 7, and 12 months	A 3 x 4 (Condition x Time) mixed MANOVA showed significant effects for time, F 6,208 = 13.95, p < 0.0001, and for the Condition x Time	"These results suggest that both running and weight lifting exercise programs improve self-concept in clinically depressed women."	Wait list control bias Data suggest comparable efficacy in both exercise groups for improved self-concept

				Diagnostic Criteria (Spitzer, Endicott and Robins)		50-60% work capacity). (n = no mention) vs Wait-list control group: (told that the exercise program delayed for 8 weeks. Then had a choice of program (n= no mention)		interaction, F 12,208 = 3.77, p < 0.0001.		
Olson, 2017 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the Charles and Johanna Busch Memorial Fund at Rutgers, the State University of New Jersey. No COI.	N = 30 participants with current diagnosis of MDD (no mention of scale used to make diagnosis) with no current psychological or pharmacological treatments for depression beyond stable (>6 weeks at stable dose) antidepressant or mood stabilizer treatment.	Mean age: 21.1 ± 2.0 years; 6 males, 24 females	Aerobic Exercise group (AE): consisted of 45 min continuous steady-state exercise on a treadmill of a cycle ergometer at a moderate intensity, 40-65%. (n=15) vs Placebo Exercise Group (PE): consisted of 30-45 min of Light stretching targeting major muscle groups	None	An repeated measures ANOVA on BDI-II revealed a significant main effect of time, $F(1,28) = 22.21$, $p < 0.001$, $\eta_p^2 = 0.44$. Superseded by a significant Time X Condition interaction $F(1,28) = 4.54$, $p = 0.04$, $\eta_p^2 = 0.14$	"Findings from the current study indicate that AE is an effective intervention for symptoms of depression and cognitive control impairments in MDD. Considering the frequent report of cognitive impairments in MDD and the failure of these symptoms to subside despite antidepressant treatment, the use of exercise as a standalone or adjunctive treatment for MDD is recommended."	Small sample with short interventions duration time. Data suggest 8 weeks of AE resulted in a reduction of depressive symptoms and improved conflict monitoring in MDD patients. This suggests combination therapy of exercise with CBT and Pharmacological therapies.
Hoffman, 2008, (score = 4.0)	Exercise (Aerobic, Strengthening,	RCT	Sponsored by Grant MH 49679 from National Institutes of Health and Grant M01-RR-30 from the	N = 202 sedentary participants who met DSM-IV	Mean age: 51.7 ± 7.6 years; 49 male, 153 female	Supervised Aerobic Exercise: Exercise 3 a week for 16 weeks. Assigned training ranges between 70-85%	None	Participants in al treatment groups experienced decreased	"These findings suggest that exercise does not confer clinically	Data suggest exercise was no better than sertraline for memory or

	Flexibility)/ Sertraline		General Clinical Research Center Program. COI Dr. Doraiswamy received grants and honoraria from serval pharmaceutical companies. Dr. Blumenthal previously received an investigator-initiated research grant from Pfizer/Eisai for an unrelated study.	and Hamilton Depression Rating Scale (HAM-D) criteria for MDD		of HR (n=51) vs Home-Based Aerobic Exercise: participants received an initial exercise training session with an exercise physiologist, target HR between 70-85% HR (n=53) vs. Sertraline Group: received Zoloft (50 mg and titrated until 200mg), met with a staff (n=49) vs Placebo Pill group: met with a staff psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=49)		symptoms of depression measured by HAM-D, BDI.	meaningful improvements in neurocognitive function among clinically depressed adults. Exercise offered no clear benefit relative to placebo pill on any of the neuropsychological tests we used in this study."	verbal fluency but better than sertraline for executive function. However individuals in the exercise groups demonstrated higher aerobic capacities then the non-exercise groups
Hoffman, 2011 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)/ Sertraline	Secondary analysis	Sponsored by Grant MH 49679 (J.A.B>) from the National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center Program, National Institutes of Health, own stock NovaDel Pharma, and receives royalties from John Wiley and Sons. No Mention of COI.	N = 172 sedentary adults with MDD (scored 12 or more on Beck Depression Inventory-2) and were not receiving antidepressant medication of psychotherapy and physically inactive	Mean age: 51.79 ± 7.64 years; 46 male, 126 females	Supervised Aerobic Exercise group: participated 3 45 min exercise groups weekly. Each person was assigned individual target rate between 70-85% (n=43) vs Home-Based Aerobic Exercise: participated in initial training session with an exercise physiologist, as well as two follow up sessions after the first and second month (n=48) Sertraline Group: received Zoloft (50 mg and titrated until 200mg), met with a staff vs. psychiatrist at 2,4,8,12 and 16 weeks (n=41) vs Placebo Pill group: met with a staff	1 year	46% of MDD remission increase at post treatment for 66% of participants available at follow up	"The effects of aerobic exercise on MDD remission seem to be similar to sertraline after 4 months of treatment; exercise during the follow-up period seems to extend the short-term benefits of exercise and may augment the benefits of antidepressant use."	One-year follow-up of Hoffman 2008. Data suggest at one year there was a 50% chance of relapse to depressive symptoms in the exercise group but there were extended benefits of exercise, which perhaps may augment antidepressant use for 0-180 minutes of exercise per week.

						psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=40)				
García-Toro, 2012 (score=4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Instiuto de Salud Carlos III of the Spanish Ministry of Health Grant (FIS no P107 0544). No COI	N = 80 outpatients with a depressive episode (MDD, dysthymic disorder, or bipolar disorder via DMS-4) on anti-depressants	Mean age: 50.1 ± 11.45 years; 18 males, 62 females.	Active group: Recommend to 1) go to sleep after 11 pm, get up before 9 am. 2) Walk 1 hour a day. 3) get sun exposure for 2 h/d. 4) avoid sweets and eat fish 3 times a week and eat fruit, cereal, nuts and vegetables daily (n = 40) vs Control group: Recommended to 1) sleep the hours feel you need. 2) Physical activity to best meet needs. 3) If exposed to sunlight avoid for sunburn 4) Try to eat healthy and balanced diet. (n = 40)	None	Between group comparison of active group and control group: Beck score – 15.8 versus 21.7 (p = 0.03), Global Clinical Impression scale (GCI) score – 2.4 versus 3.5 (p = 0.00), HAM-D score – 10.7 versus 16.5 (p = 0.00)	"In conclusion, the benefits of lifestyle changes for patients suffering from Depression can be achieved by using a simple combination of hygienic-dietary recommendations on a written piece of paper."	Data suggest lifestyle changes inclusive of exercise, proper sleep, diet and exposure to sunlight may be adjunct therapy recommendation for depression with benefit non-heterogeneous population
Craft, 2007 (score=4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the National Institutes of Health: The Office of Women's health research (k-12-HD-4244) and the clinical Research feasibility funds (M01RR00533). No mention of COI	N = 32 women with diagnosed depressive symptoms by physician with Beck Depression Inventory, BDI)	Mean age: 40.4 ± 10.6 years; 0 males 32 females	Home-based group: exercised at home (Participated in in 1 clinic-based personalized instructional session at the medical center to acclimatize to walking on a treadmill. 4 wk. intervention). (n=16) vs clinic-based group: completed exercise twice a week at medical center and once at home. (Intensities were increased gradually, with the goal of walking 30-40 at 60-80% max	3 month	Total sample (N =32), 46.9% of participants (15 of 32) experienced a ≥50% reduction in depressive symptoms. 31.3% (10 of 32) achieved remission of their symptoms (BDI score <9)	"Both a home-based and more intensive structured (clinic-based) exercise intervention were associated with improvements in time spent in moderate and vigorous physical activity and a reduction in depressive symptoms at 3-month follow-up".	Data suggests improved physical activity and depressive symptoms with both exercise groups suggesting even a home based exercise program can improve depressive symptoms.

						heart rate. 4 wk. intervention) (n=16)				
Callaghan, 2011 (score=4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of Sponsorship. No COI.	N = 38 living with depression receiving and selected by their general practitioner, or local mental health services. No mention of diagnostic scale used to determine depression diagnosis	Mean age 53.7 ± 12.85 years: 0 males, 38 females	Intervention arm group: 12 sessions of treadmill aerobic exercise of preferred intensity in groups up to 5/3 times a week for 4 weeks (n=19) vs Active comparator arm Group: prescribed intensity (n=19)	None	The Mean BDI score from baseline to plenary session between the intervention group (-8.5 ± 9.8) and the active comparator arm (-0.9 ± 6.6) showed statistical significance P =0.006	"Preferred intensity exercise coupled with motivational education and support is likely to improve health and quality of life of women living with depression and improve their exercise adherence rates"	Data suggest exercise of preferred intensity improves participation, physiological, psychological and social outcomes
Helgadóttir, 2016 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the Lj Boethuus Foundation, the Vårdal Foundation (RS2009/27), the Brain Foundation Sweden (Hjärnfonden), and 6 Swedish counties and regions involved. No COI.	N = 620 with mild to moderate depression (Patient Health Questionnaire – 9 score ≥ 10	Mean age: 73.7 years; 0 men. 620 females	Treatment as usual group (TAU) (n=310) vs Light exercise group: (yoga or similar) (n=106) vs moderate exercise group: (aerobic conditioning) (n= 105) vs vigorous (aerobic conditioning) (n= 99)	3 month	Compared to the TAU, means MADRS scores in the Light group went down 4.1 points (p <0.001), the vigorous group reduced 3.1 points (p=0.002) and the moderate group reduced by 2.1 points (p = 0.032)	"In conclusion, the results indicate that exercise, whether performed at a light, moderate or vigorous intensity, can be at least equally effective in the treatment of mild to moderate depression compared to treatment as	Usual care bias, Data suggest compliance is all exercise groups was poor. All exercise groups were different and sometimes varied from prescribed type. Data suggest , whether light, moderate or intense is as

									usual by a physician."	effective as TAU
Gusi, 2008 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	No mention of sponsorship. No COI	N = 106 with moderate depression or from under the RDC or being overweight (score of 6-9 on the 15-item Geriatric Depression Scale)	Mean age: 72 ± 5 years; 0 males, 106 females	Exercise group: consisted 3, 50 min walks on a public park of forest track, led by exercise leader. exercise (n =55) vs Control group: received best care in general practice and given a recommendation to exercise (n =51)	6 month	Anxiety and depression measured by EQ-5D, STAI and Geriatric Depression Scale improved in exercise group and BMI decreased: (mean BMI change 1.2%; p = 0.003). 90% probability that the walking programme is the strategy.	"The current study presented a pragmatic and cost-effective strategy to enhance the level of physical activity in overweight or moderately depressed elderly women."	Usual care bias, data suggest increasing the level of physical activity In overweight elderly women is both a coat effective and efficacious strategy to treat depressive symptoms.
Doose, 2015 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the Robert enke foundation (Robert Enke Stiftung). No COI.	N = 46 with mild to severe depression (ICD-10 criteria)	Mean age 47.87 ± 10.47 years; 34 males, 29 females	Intervention Group: Participated in exercise supervised by a coach 3 times a week for 8 weeks, for 1 hour. (n=30) vs Control Group (n=16)	None	The intervention group score was reduced by 9.5 (CI[-11.38;-7.58], p < 0.0001 (HRSD-17)]	"This exercise intervention was a success considering its implementation and acceptance both by sports club staff and participants."	High dropout (24%) wait list control and treatment as usual biases. Data suggest an observed and clinically significant change in HRSD-17 scores and small changes in physical fitness I the exercise group completers. Participants self-selected exercise intensity, which has been

										shown to increase compliance (Callaghan et al. 2011).
Van Der Waerden, 2013 (score = 3.5)										Waitlist control bias. Data suggest either alone or In combination with psycho-education, exercise may benefit certain groups suffering from depressive symptoms or elevated stress.[23]
Veale, 1992 (score = 3.5)										Sparse methods usual care bias. Data suggest comparable efficacy between groups.
Rippoll, 2015 (score = 3.5)										Articles suggest general practitioners blinded to allocation but general practitioners opened envelopes to discuss

[23] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										intervention with individual patients, therefore, GP's unblended. Compliance not easily assessed. Firm conclusions regarding efficacy cannot be determined.
Bartholomew, 2005 (score = 3.0)										Sparse details on compliance single session intervention. Data suggest both exercise and quiet rest improved distress, confusion, fatigue, tension, and anger exercise. Significantly improved vigor and wellbeing scores.[24]
Kubesch, 2003 (score = 3.0)										Small sample. Data suggest 30 men of aerobic activity positively benefits executive function in

[24] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										depressed patients
Partonen, 1998 (score = 2.5)										Sparse methods. Data suggest supervised physical exercise in combination with bright light exposure is beneficial for mood and certain quality of life factors.
Klein 1985 (score=2.5)										High dropout rate. Data suggest running is appropriate in the treatment of depression and is durable.[25]

[25] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Yoga

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Streeter 2017 (score=5.5)	Yoga	RCT	Sponsored by the Boston University Clinical and Translational Science Institute, the CCS, the General Clinical Research Unit at Boston University Medical Center, and MBN. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 32 with a current diagnosis of major depressive disorder (Beck Depression-II (BDI-II) score ≥ 14	Data on age and sex only available for 30 participants. Mean age: 36.55 years; 5 males, 25 males	High-dose group (HDG) – Iyengar yoga for 90 minutes (60 minutes of yoga postures, 10 of relaxation, and 20 of coherent breathing), three classes and four 30-minute homework session per week for 12 weeks (n=16) vs. Low-dose group (LDG) – same type of yoga, two sessions and three 30-minute homework sessions per week for 12 weeks (n=16)	No follow-up post-intervention	BDI-II scores for HDG and LDG groups, respectively: baseline – 24.6 & 27.7, Week 4 – 14.1 & 14.8, Week 8 – 8.5 & 14.0, Week 12 – 6.0 & 10.1. Both groups reported decreased BDI-II scores (HDG – $p < 0.001$, LDF – $p < 0.001$). No significant difference at 12 weeks between groups ($t = -0.32$, $df = 28$, $p = 0.75$)	"During this 12-week intervention of yoga plus coherent breathing, depressive symptoms declined significantly in patients with MDD in both the HDG and LDG. Both groups showed comparable compliance and clinical improvements, with more subjects in the HDG exhibiting BDI-II scores ≤10 at week 12."	Small sample. Data suggest comparable efficacy between groups as depressive symptoms improved in both groups.
de Manincor 2016 (score=5.0)	Yoga	RCT	No COI or sponsorship.	N = 101 with a Depression Anxiety Stress Scale (DASS-21) depression score of 10-27 or anxiety score of 8-19	Mean age: 38.80 years; 20 males, 81 females	Yoga intervention – four 1-hour lessons over a six week period (n=47) vs. Waitlist control – informed that was a waitlist	Follow-up at 6 weeks	Statistically significant decrease in DASS-21 depression scores between yoga and waitlist groups (Mean difference: −4.30, $p = .01$)	"Yoga plus regular care was effective in reducing symptoms of depression compared with regular care alone. Further investigation is	Usual care bias. Waitlist control bias. Data suggest yoga group experienced improved depression scores.

						period of six weeks (n=54). All participants were asked to also continue all other treatments as usual			warranted regarding potential benefits in anxiety."	
Noradechanunta 2017 (score=5.0)	Yoga/Tai Chi	RCT	Sponsored by the Faculty of Health and Behavioural Sciences, University of Wollongong under the HDR Student Funding Scheme. The Faculty Student Funding Scheme funded author Noradechanunta.	N = 39 sedentary participants deemed healthy via Physical Activity Readiness Questionnaire	Mean age: 66.6 years; 10 males, 29 females	Thai Yoga (TY) – 90 minutes sessions (n=13) vs. Tai Chi – 80 minute sessions (TC) (n=13) – vs. Control (C) – received telephone-supervised exercise regimens (n=13). All treatments given over 12 weeks	Follow-up at 6, 12, and 24 weeks	Center for Epidemiological Studies of Depression (CES-D) scale scores at 24 weeks: TY – 4.6, TC – 4.8, C – 3.4. No difference between groups for decreasing CES-D scores ($F(6, 108) = 0.986$ ($p=0.438$))	"The findings suggest that older adults can make significant improvements in their health and well-being by engaging in low intensity Thai Yoga exercise."	Small sample. Data suggest no differences between groups.
Chu 2017 (score=5.0)	Yoga	RCT	No COI. Sponsored by the Taiwan National Science Laboratory, Department of Medical Research, Kaohsiung Medical University Hospital, and Kaohsiung	N = 26 women with mild to moderate depressive symptoms (score of 14–28 on Beck Depression Inventory-II [BDI-II])	Mean age: 32.73 years; 0 males, 26 females	Yoga – 60 minutes sessions twice per week for 12 weeks (n=13) vs. Control – No intervention given (n=13)	Follow-up at 12 weeks	BDI-II scores at baseline and 12 weeks for yoga and control groups, respectively: 29.77, 16.85 ($p<0.05$), 23.62, 21.15 ($p>0.05$)	"A 12-week yoga program was effective in increasing parasympathetic tone and reducing depressive symptoms and perceived stress in women with elevated depressive symptoms."	Small sample. Non-treatment control bias. Data suggest a 12-week program of 2 sessions per week at 60 minutes per session was effective for reducing perceived stress and depressive

			Medical University.							symptoms as well as increasing parasympathetic tone.
Schuver 2016 (score=4.0)	Yoga	RCT	No COI. No mention of sponsorship.	N = 40 participants with depression via the SCID-I (DSM-IV)	Mean age: 42.68 years; 0 males, 40 females	Yoga – 60-75 minutes per sessions twice a week for 12 weeks along with 15 minute mindfulness telephone sessions once a week for 1 month and then twice a week for 2 months (n=20) vs. Walking program – 65 minute walking sessions and eight telephone sessions with a counselor (n=20)	Follow-up at 12 and 16 weeks	No significant between group difference on depression scores at 12 weeks (f(1,31)=0.61, p=0.44, d=0.25) and 16 weeks (f(1,31)=0.80, p=0.78, d=0.08)	"These findings suggest that mindfulness-based yoga may provide tools to manage ruminative thoughts among women with elevated depressive symptoms."	Comparable efficacy. Data suggest mindfulness yoga may decrease ruminative thoughts in depressed women but both groups reported decreases in depressive symptoms.
Shahidi 2011 (score=3.5)										Data suggest laughter yoga may be as effective as group exercise for improving satisfaction of life and depression symptoms.[26]

[26] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Falsafi 2016 (score=3.5)										Figure 1 does not show completers. Data suggest improvement in both groups for anxiety, depressive symptoms, and stress. The mindfulness group reported increase self-compassion.
Sharma 2005 (score=3.5)										Data suggest sahaj yoga group improved symptoms of depression and achieved remission versus anti-depressant group.
Neff 2012 (score=3.0)										Score relates to second study described. Small sample size. Waitlist control bias. Data suggest improved self-compassion, well-being, and mindfulness in Mindful Self-Compassion

										program group.[27]
Jain 2007 (score=3.0)										Waitlist control bias. Data suggest both intervention groups resulted in improved mood and decreased stress. Mindfulness appears to decrease rumination.
Woolery 2004 (score=2.5)										Small sample size. Waitlist control bias. Short intervention time. Data suggest yoga group reported less depression and trait anxiety.
Bonura 2014 (score=2.5)										Waitlist control bias. Data suggest yoga group had reduced anger, anxiety, and depression from self-reported post-

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										intervention questionnaires.
Javnbakht 2009 (score=2.0)										Waitlist control bias. Data suggest a twice weekly.[28]

[28] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Tai Chi

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lavretsky 2011 (score=7.5)	Tai Chi /Escitalopram	RCT	Supported by the grants MH077650, MH86481, and AT003480 to Dr. Lavretsky and NIH grants T32-MH19925, HL079955, AG026364, CA10014152, CA116778, RR00827, and P30-AG028748. No mention of COI.	N = 112 older adults (60+ years old) with a current MDD episode, a 16 or higher on the Hamilton Depression Rating Scale (HAMD), and a 26 or higher on the Mini-Mental State Exam	Mean age: 40.6±7.3; 28 males, 45 females.	TCC (n = 36) 4 weeks of escitalopram drug dosing then participated 2 hours of Tai Chi a week for 10 weeks vs. HE (n = 37) 4 weeks of escitalopram drug dosing and weekly health education sessions for 10 weeks	Follow-up at baseline, 4, 6, and 14 weeks.	Final HAMD scores, TCC vs HE groups, percentage: 94% achieved HAMD score less than 10, 65% achieved remission (HAMD <6) vs. 77% HAMD of 10 or less and 51% achieving remission (HAMD <6) (x^2=3.68, p<0.06). Both groups demonstrated improvement in depression, but TCC group showed greater reductions (group*time interaction: $F_{[5, 285]}$=2.26; p<0.05).	"Complementary use of a mind–body exercise, such as TCC, may provide additional improvements of clinical outcomes in the pharmacologic treatment of geriatric depression."	Both groups experienced improvement in symptoms. Data suggest TCC and escitalopram group trended to show reduction in depressive symptoms with remission than the HE and escitalopram group.
Yeung 2012 (score=6.5)	Tai Chi	RCT	Sponsored by the CDC. No COI.	N = 39 Chinese adults (18-70 yrs.) with a DSM-IV diagnosis of MDD and baseline score of 12 or more on the Hamilton Depression	Mean age: 55.3±10.7; 9 males, 30 females.	Tai Chi (n = 26) – one hour class held twice a week for 12 weeks of yang-style tai chi vs. Waitlist (n = 13) – placed on a waitlist and did not receive any intervention.	Follow-up at baseline, 6 and 12 weeks.	Tai Chi vs. Wait list, HAMD response rate (decrease by 50%) and remission rate (HAMD <7), percentage: 24% and 19% vs 0% and 0% (p=0.15 and p=0.30).	"A 12-wk tai chi intervention may be effective in improving symptoms and inducing remission in Chinese Americans with MDD. Future studies with larger sample sizes will be	Small sample. Waitlist control bias. Data suggest a trend towards improvement in tai chi group.

				Rating Scale (HAMD).					needed to provide more definitive outcomes."	
Hsu 2015 (Score=5.5)	Tai Chi	RCT	No sponsorship. No COI.	N = 60 older Taiwanese adults (65+ yrs.) who had sufficient cognitive function (>24/30, mini mental state examination)	Mean age: 81.25±8.12; 22 males, 38 females.	Tai Chi (n = 30) – 40 minutes of seated Tai Chi classes three times a week for 26 weeks vs. Control (n = 30) – continued their usual care.	Follow-up at baseline, 13 and 26 weeks.	Geriatric Depression Scale-Short Form mean score (GDS-SF) at 26 weeks, Tai Chi vs control: 3.76±3.65 vs 7.76±5.15 (p=0.00). GDS-SF mean score change, baseline to 13 weeks, tai chi vs control: 0.53±4.09 vs 2.40±4.73 (p=0.10). GDS-SF mean score change, 13 weeks to 26 weeks, tai chi vs control: -0.63±4.08 vs 3.50±6.44 (p=0.00).	"Improving the QOL of older people living in a LTC setting should be an important goal of health promotion programs. One such health promotion intervention program, which can be used, is seated Tai Chi exercise."	Usual care bias. Data suggest Tai Chi group had improved quality of life and depression scores.
Noradechanunta 2017 (score=5.0)	Yoga/Tai Chi	RCT	Sponsored by the Faculty of Health and Behavioural Sciences, University of Wollongong under the HDR Student Funding Scheme. The Faculty Student Funding Scheme funded author	N = 39 sedentary participants deemed healthy via Physical Activity Readiness Questionnaire	Mean age: 66.6 years; 10 males, 29 females	Thai Yoga (TY) – 90 minutes sessions (n=13) vs. Tai Chi – 80 minute sessions (TC) (n=13) – vs. Control (C) – received telephone-supervised exercise regimens	Follow-up at 6, 12, and 24 weeks	Center for Epidemiological Studies of Depression (CES-D) scale scores at 24 weeks: TY – 4.6, TC – 4.8, C – 3.4. No difference between groups for decreasing CES-D scores ($F(6, 108) = 0.986$ ($p=0.438$))	"The findings suggest that older adults can make significant improvements in their health and well-being by engaging in low intensity Thai Yoga exercise."	Small sample. Data suggest no differences between groups.

			Noradechanunta.			(n=13). All treatments given over 12 weeks				
Yeung 2017 (Score=4.0)	Tai Chi	RCT	Study sponsored by the national center for complimentary and integrative health. No COI.	N = 67 Chinese adults (18-70 yrs.) who were diagnosed with MDD via DSM-IV and Hamilton Rating Depression Scale (HAMD) score 14-28.	Mean age: 54±13; 19 males, 48 females.	Tai Chi (n = 23) – one-hour class held twice a week for 12 weeks of yang-style tai chi vs. Education (n = 22) – received mental health coaching for 1 hour each week for 12 weeks vs. Waitlist – (n = 22) were waitlisted and acted as controls	Follow-up at baseline and weeks 6, 12, 18, and 24.	Response rate, tai chi vs education vs waitlist, at 12 weeks: 56% vs 21% vs 25%. Remission rate, tai chi vs education vs waitlist, at 12 weeks: 50%, 21%, 10%. Tai Chi vs Waitlist, positive remission OR (95% CI), week 24: 2.20 (1.11-5.64) ($p<0.05$) Tai Chi vs Waitlist, positive response OR (95% CI), week 24: 2.51 (1.11-5.70) ($p<0.05$)	"A 12 week tai chi intervention is safe and feasible and shows promise in improving depression outcomes in Chinese Americans with MDD."	Waitlist control bias. Contact time bias. Data suggest superiority to education controls.

Evidence for the Use of Qi Gong

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Chan 2013 (score=4.0)	Qi Gong	RCT	No mention of sponsorship. No COI.	N = 154 adults with chronic fatigue syndrome (CFS) screen using CDC diagnosis criteria	Mean age: 42.4±6.5; 32 males, 105 females.	Qi Gong (n = 72) participated in 10 sessions (2x/week) with an instructor followed by self-practice at home for 12 weeks vs. Control (n = 65) did not participate in any Qi Gong	Follow-up at baseline and four months.	Hospital anxiety and depression scale (HADS) mean score change, baseline to post intervention, Qi Gong vs Control: -1.3±2.7 vs 0.4±3.7 (time X group $F_{[1, 135]}$ 9.918 (p=0.002)). Total fatigue mean score change (Chalder Fatigue Scale), baseline vs post intervention, Qi Gong vs Control: -13.1±11.7 vs -6.6±8.3 (Time x group $F_{[1, 135]}$ 13.888 (p=0.000)).	"In conclusion, the results of this study show that Qigong exercise may be effective in reducing fatigue symptoms and alleviating depressive symptoms for patients with CFS-like illness and that the improvement of fatigue symptoms may predict the alleviation of depressive symptoms after Qigong intervention."	Waitlist control bias. Data suggest fatigue and depression scores improved in the Qi Gong group but had little effect on improving anxiety.
Tsang 2006 (score=3.5)										Data suggest at 8 weeks, Qi gong group had improved mood, self-efficacy, self-concept and wellbeing but at 16 weeks the benefits were improved efficacy and well-being.[29]

[29] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Weight Loss

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Imayama 2011 (score=5.5)	Weight Loss Program	RCT	Sponsored by The National Cancer Institute (NCI). No COI.	N = 439 overweight or obese postmenopausal women, no depression diagnosis	Mean age: 57.9 years; 0 males, 439 females	Exercise: received daily 45 min moderate-to-vigorous aerobic exercise 5 days a week (n=117) vs Diet: received a reduced calorie weight loss intervention 1200-2000 kcal/day with sessions with dietician weekly (n=118) vs Diet+Exercise: received both reduced calorie weight loss and exercise interventions (n=117) vs Control: did not receive intervention during trial, but were offered 4 group diet and exercise session after 12 months (n=87)	12 months	Body weight decreased by 7.2 kg in the diet group ($p<0.01$), 2.0 kg in exercise group ($p=0.03$), 8.9 kg in the diet and exercise group ($p<0.01$) compared to controls. Diet and exercise group reduced depression ($p=0.03$) compared to control group and increased social support ($p=0.05$).	"Our findings suggest that the combination of dietary weight loss and exercise may have a larger beneficial effect on HRQOL compared with dietary weight loss or exercise alone. Weight loss and improvements in aerobic fitness and psychosocial factors (depression, stress, and social support) were predictors of increased HRQOL, suggesting that these factors could mediate the intervention effects on HRQOL."	Data suggest combination diet and exercise has positive effects on psychological health and HRQOL.

Busch 2013 (score=4.5)	Weight Loss Program	RCT	Sponsored by S. Pagoto. No COI.	N = 161 patients that met DSM-IV criteria for major depressive disorder (MDD)	Mean age: 46.0±10.95 years; 0 males, 161 females	BA Group: received 10 weekly individual sessions focused on behavioral depression treatment including behavioral weight loss sessions and counseling (n=67) vs LI Group: received 16 group weight loss sessions and 10 individual sessions (intensive phase received counseling sessions and monthly maintenance phone calls with general health education) (n=76)	6, 12 months	Improvement in depression observed in 73.1% of BA group compared to 53.9% in LI group at 6 months. Patients that showed depression improvement also lost more weight than participants with those who did not for both groups; however BA group showed more weight loss (p=0.02).	"In summary, we found that the majority of women in our sample experienced reliable improvement in depression during the trial, regardless of whether they received depression treatment in addition to behavioral weight loss treatment."	Data suggest most women in this trial achieved improvement of their depression whether or not they received specific depression treatment in addition to weight loss treatment fewer than 2% of all participants experienced worsening depressive symptoms suggesting improvement in depression is associated with weight loss.
Pagoto 2013 (score=N/A)	Weight Loss Program	Secondary Analysis of Pagoto 2013	Sponsored by grant to Dr. Pagoto from the National Institute of Mental Health and partial support was provided by	N = 161 obese women with major depressive disorder (DSM-IV criteria)	Mean age: 45.9±10.8 years; 0 males, 161 females	BA Group: received Brief Behavior Therapy for 10 weekly sessions involving activity monitoring,	6, 12 months	Differences in weight loss at 6 months between BA condition and LI condition were not significant (p=0.48) as well as at 12 months (p=0.63). At 6	"In summary, brief behavior therapy for depression effectively reduces depression symptoms when administered	Group differences in baseline BMI (BA=36, LI=34.2). Individuals who currently used tricyclics and mood

			National Heart Lung Blood Institute grant. No COI.			and (n=78) vs LI Group: received lifestyle intervention protocol delivered by a dietitian and exercise physiologist of exercise and diet goals (n=83)		months, BA group showed greater decline in BDI-2 scores compared to LI group (p=0.005) and the same for 12 months (p=0.0687). Patients that showed depression remission by 6 months lost more weight compared to those who did not show remission (p=0.001).	directly prior to a lifestyle intervention in depressed women. Lifestyle interventions also appear to have a significant impact on depressive symptoms, however people achieving full remission from depression tend to have weight loss outcomes equivalent to studies of non-depressed patients."	stabilizers excluded from the study. Data suggest the addition of behavioral therapy to a lifestyle intervention does not improve weight loss at 1 year. However, as depression symptoms decrease there is associated weight loss suggesting depression may impede weight loss. BA group on depressive scores more than the LI group.
Simon 2010 (score=4.5)	Weight Loss Program/Dieting	RCT	Sponsored by National Institutes of Health Grant. No mention of COI.	N = 203 patients with clinical depression and obesity (DSM-IV criteria)	Mean age: 50.1 years; 0 males, 203 females	Weight Loss Only Group: received daily intake goals of 1200-1500 kcal, restrict fat intake to 20%, and increase physical activity goals, structured meal plans, and weekly	6, 12, 24 months	Average weight decreased in 31% of patients that lost more than 5% of body weight (12% of patients lost more than 10%). Decrease in depression observed in 55 patients at 6 months, 34 patients at 12 months, and 27	"Among women with co-occurring obesity and depression, short-term improvement in depression is associated with weight loss. This association is clearest early in weight loss treatment."	Data support improvement in depression is associated with weight loss.

						sessions with nutritionist and weight loss counselors (n=102) vs Combined Group: received weight loss intervention program and 26 sessions over 1 year (120 min/session) and depression intervention of psychologist sessions (n=101)		patients at 24 months. An increase in depression observed in 22 patients at 24 months.		
Linde 2011 (score=N/A)	Weight Loss Program/Dieting	Secondary Analysis of Simon 2010.	Sponsored by National Institutes of Health Grant. No COI.	N = 203 patients with clinical depression and obesity (DSM-IV criteria)	Mean age: 52.2 years; 0 males, 203 females	Weight Loss Only Group: received daily intake goals of 1200-1500 kcal, restrict fat intake to 20%, and increase physical activity goals, structured meal plans, and weekly sessions with nutritionist and weight loss counselors (n=102) vs Combined Group: received	6, 12 months	Average weight loss at 6 months was 2.8 kg for weight loss only group compared to 1.8 kg in combined group (p=0.26). Average weight loss at 12 months was 3.1 kg for weight loss only group compared to 2.3 kg in combined group (p=0.55). SCL-20 decreased over time for both groups; however, no significant differences observed between groups.	"Depressed obese women lost weight and demonstrated improved mood in both treatment programs. Future weight loss trials are encouraged to enroll depressed women."	Poor participation rate at least three quarters of all study participants on anti-depressants, which was not replaced by either program. Data suggest both programs resulted in weight loss and improved mood.

						weight loss intervention program and 26 sessions over 1 year (120 min/session) and depression intervention of psychologist sessions (n=101)				
Ruusunen 2012 (score=4.0)	Weight Loss Program	RCT	Sponsored by the Finnish Graduate School of Psychiatry (AR), the Juho Vainio Foundation, Academy of Finland, and the Novo Nordisk Foundation and partly by the SalWe Research Program for Mind and Body. No COI.	N = 522 overweight participants at risk for depression	Mean age: 55.18 years; 172 males, 350 females	Intervention Group: given detailed advice involving healthy diet and exercise to achieve goals with 7 counseling sessions with nutritionist and 1 session every 3 months thereafter, exercise was individualized (n=69) vs Control Group: received general and verbal written information about diet and exercise (n=71)	36 month	Reduction of depressive symptoms was -2.0±6.16 points (p=0.248) in the intervention group compared to -3.5±5.63 points (p=0.031) in the control group (p=0.307). Antidepressant medication increased in the intervention group by 2.9% at 3-year follow-up.	"Participation in the lifestyle intervention study improved Beck Depression Inventory scores, with no specific group effect. Among the lifestyle changes, particularly successful reduction of body weight was associated with the greater reduction of depressive symptoms. Thus, regardless of the intensity of the treatment, the success in executing alterations in one's lifestyle and behavior is associated with beneficial	Data suggest as depressive symptoms decreased, there was an associated weight loss suggesting mood is correlated with success or lack thereof of lifestyle changes.

									changes in mood and psychological well-being."	
Naparstek 2017 (score=4.0)	Weight Loss Program	RCT	Sponsored by National Institutes of Health. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 136 overweight or obese patients at risk for depression	Mean age: 46.9±11.5 years; 23 males, 102 females	IBWL Group: received internet behavioral weight loss program plus the community initiative consisting of weight loss, calorie, and physical activity goals, 12 weekly multimedia lessons, self-monitoring platform (n=83) vs Control Group: received community initiative alone consisting of pedometer, access to an online platform to report physical activity, free community workshops on healthy eating and activity, and prizes for meeting goals (n=42)	3 months	IBWL patients lost more weight compared to control group (IBWL: 4.1±4.4%, Control: 1.6±4.4%, p=0.005), and showed greater improvements in depression symptoms (p=0.02). IBWL group showed larger decrease in patients that met elevated depression risk criteria (66.7%) compared to controls (30.0%, p=0.049).	"This study is the first to show that Internet-delivered obesity treatment improves depression risk and depressive symptoms in individuals with overweight or obesity."	Data suggest internet delivered treatment may improve depressive symptoms in overweight and for obese patients.

Crerand 2007 (score=3.5)										Data suggest the non-dieting program resulted in greater reductions in negative feelings regarding obesity in women who seek treatment versus dieting program. Both groups results in improved depressive symptoms self-esteem and body image.[30]
Klem 1997 (score=3.0)										Data suggest interventional group reported decreased depressive symptoms over time. Also, women in the interventional group reported greater activity levels and greater reductions in caloric intake. Weight loss correlated to baseline

30 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										weight (i.e., heavier women lost more weight than did normal weight women).
Stapleton 2013 (score=2.5)										Waitlist control bias. High attrition rate at 12 months. Study suggests depression has a major role in weight loss and weight loss maintenance, as there were significant decreased depression symptoms at 12 months.[31]

[31] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Dieting

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Simon 2010 (score=4.5)	Weight Loss Program/Dieting	RCT	Sponsored by National Institutes of Health Grant. No mention of COI.	N = 203 patients with clinical depression and obesity (DSM-IV criteria)	Mean age: 50.1 years; 0 males, 203 females	Weight Loss Only Group: received daily intake goals of 1200-1500 kcal, restrict fat intake to 20%, and increase physical activity goals, structured meal plans, and weekly sessions with nutritionist and weight loss counselors (n=102) vs Combined Group: received weight loss intervention program and 26 sessions over 1 year (120 min/session) and depression intervention of psychologist sessions (n=101)	6, 12, 24 months	Average weight decreased in 31% of patients that lost more than 5% of body weight (12% of patients lost more than 10%). Decrease in depression observed in 55 patients at 6 months, 34 patients at 12 months, and 27 patients at 24 months. An increase in depression observed in 22 patients at 24 months.	"Among women with co-occurring obesity and depression, short-term improvement in depression is associated with weight loss. This association is clearest early in weight loss treatment."	Data support improvement in depression is associated with weight loss.
Linde 2011 (score=N/A)	Weight Loss Program/Dieting	Secondary Analysis of Simon 2010.	Sponsored by National Institutes of Health Grant. No COI.	N = 203 patients with clinical depression and obesity (DSM-IV criteria)	Mean age: 52.2 years; 0 males, 203 females	Weight Loss Only Group: received daily intake goals of 1200-1500 kcal, restrict fat intake to 20%, and increase physical activity goals, structured	6, 12 months	Average weight loss at 6 months was 2.8 kg for weight loss only group compared to 1.8 kg in combined group (p=0.26). Average weight loss at 12 months was 3.1 kg	"Depressed obese women lost weight and demonstrated improved mood in both treatment programs. Future weight loss trials are encouraged to	Poor participation rate at least three quarters of all study participants on anti-depressants, which was not replaced by either program. Data suggest both programs resulted in weight loss and improved mood.

						meal plans, and weekly sessions with nutritionist and weight loss counselors (n=102) vs Combined Group: received weight loss intervention program and 26 sessions over 1 year (120 min/session) and depression intervention of psychologist sessions (n=101)		for weight loss only group compared to 2.3 kg in combined group (p=0.55). SCL-20 decreased over time for both groups; however, no significant differences observed between groups.	enroll depressed women."	
Hussin 2013 (score=3.5)										Data suggest improved anger tension and confusion but no significant improvement in depression in Fasting and Calorie Restriction (FCR) group.[32]
Badrasawi 2013 (score=2.0)										Crossover design. Small sample. Data suggest depression may be reduced and mood improved.

[32] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Cognitive Behavioral Therapies

Cognitive Behavioral Therapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Jakobsen 2014 (score= 6.5)	Cognitive Behavioral Therapy/ Psychotherapy	RCT	Sponsored by Health Science Fund, Region Zealand, Denmark. COI, the principal investigator developed a treatment manual and a consultant developed a mentalisation-based treatment manual.	N = 44 patients diagnosed with depression according to the DSM-IV-TR guidelines	Mean age: 39.4 years; 6 males, 38 females.	Group 1: third-wave cognitive therapy with one 45 min psychotherapy session and one 1.5-hour mindfulness-skills training group every week for 18 weeks (n=22) vs. Group 2: mentalisation based 45 min psychotherapy session and one 1.5-hour mentalisation-based group therapy session every week for 18 weeks (n=22)	18 weeks	After adjustment with baseline there was a significant difference in Hamilton Depression Rating Scale scores (p=0.039), Beck's Depression Inventory scores (p=0.46), and WHO 5 scores (p=0.46). There was no statistical difference between Global Severity Index scores (p=0.66).	"Third-wave cognitive therapy may be more effective than mentalisation-based therapy for depressive symptoms measured on the HDRS."	Small sample. Data suggest third-wave CBT may be better than MBT for treatment of depression.
Rohan, 2015	Light therapy/ CBT	RCT	Sponsored by the National	N = 177 volunteers with	Mean age: 45.6	Light Therapy: 10,000 lux of	Follow-up	Depression scores significantly	"In conclusion, these findings suggest that CBT-SAD and light	Data suggest comparable efficiency.

(score= 6.5)			Institute of Mental Health. No COI.	major recurrent depression with a seasonal pattern, passing the SIGH-SAD and DSM-IV-TR criteria for a Seasonal Affective Disorder (SAD) episode through the duration of the study.	years; 29 males, 148 females.	cool-white fluorescent light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive restructuring to improve coping with the change in weather, which in turn, alleviates depression. (n=88)	at 2 years.	improved with light therapy and CBT-SAD when measured with SIGH-SAD and BDI-II. The SIGH-SAD score at each time-point differed from others ($p<0.01$), the difference between scores at weeks 4/5 fell low ($p=0.07$). Similar patterns were observed through the HAM-D ($F=119.80$, $df=6, 920$, $p<0.001$).	therapy are comparably effective treatment modalities for targeting acute SAD. Accordingly, CBT-SAD should be disseminated into practice and considered as a viable alternative to light therapy in treatment decision making."	

Rohan, 2016 (score= n/a)	Light therapy/ CBT	2-year follow up of Rohan 2015	Supported by the National Institute of Mental Health. No COI.	N = 177 adults with major depression that were a part of a randomized trial of 6-weeks of CBT-SAD or light therapy.	Mean age: 45.6 years; 29 males, 148 females.	Light Therapy: 10,000 lux of cool-white fluorescent light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive restructuring to improve coping with the change in weather, which in turn,	No follow up.	There was no difference in outcomes during the first year of follow-up. During the second winter of follow-up, CBT-SAD was associated with less SIGH-SAD recurrences ($p<0.013$) and remissions than light therapy recurrences ($p<0.032$). BDI-II remission rates were significantly lower in the CBT-SAD group ($p<0.022$) than the light therapy group ($p<0.082$).	"In conclusion, our prior report found that CBT-SAD and light therapy are comparably effective treatment modalities for acute SAD (8), but these follow-up data show better outcomes for CBT-SAD than light therapy two winters later. Accordingly, CBT-SAD should be considered as an efficacious SAD treatment and disseminated into practice, particularly if the focus is on recurrence prevention."	During year one there were comparable findings but data suggest CBT superior to light therapy for treatment of SAD as CBT-SAD was associated with less severe symptoms and sustained fewer remissions.

						alleviates depression. (n=88)				
Meyerhoff, 2016 (score= n/a)	Light therapy for depression/CBT	Secondary Analysis of Rohan 2015	Supported by the National Institute of Mental Health. No mention of COI.	N = 177 adults with major depression that were a part of a randomized trial of 6-weeks of CBT-SAD or light therapy.	Mean age: 45.6 years; 29 males, 148 females.	Light Therapy: 10,000 lux of cool-white fluorescent light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive restructuring to improve coping with	No follow-up.	BDI-II depression severity improved as treatment progressed with time ($p<0.001$). Higher treatment expectations from patients resulted in a lower depression severity ($p<0.001$) and a lower treatment expectation resulted in a higher treatment severity.	"Treatment expectations changed across treatment, affected outcome, and should be assessed and monitored repeatedly throughout treatment. Findings suggest that treatment expectations at mid-treatment are a mechanism by which CBT-SAD reduces depression, which should be replicated in SAD samples and examined for generalizability to non-seasonal depression. These findings underscore the importance of further research examining treatment expectations in mediating CBT's effects in depression and other types of psychopathology."	Data suggest treatment expectations change as a function of treatment and time and those with higher expectation had lower depression severity.

						the change in weather, which in turn, alleviates depression. (n=88)				
Rohan, 2007 (score= 6.5)	Light therapy for depression/CBT	RCT	Supported by the National Institute of Mental Health and the Uniformed Services University of the Health Science (USUHS). No mention of COI.	N=61 adults with major depression, meeting the SIGH-SAD criteria for a current SAD episode.	Mean age: 45 years; 6 males, 55 females.	Light Therapy (LT): 10,000 lux, 90-minute a day, one am and one pm for week one; dosing tailored to each individual response to treatment for weeks 2-6. (n=16) vs Cognitive Behavioral Therapy (CBT): group therapy, 1.5 hours twice-weekly (n=15) vs CBT + LT: received both treatments simultaneously for 6 weeks. (n=15) vs Minimal contact/delayed treatment	Follow-up at a session during the summer; following June or July.	CBT + LT had a larger proportion of patients with significant change throughout the duration of the treatment when compared to MCDT on SIGH-SAD, HAMD-D, and BDI-II scales ($p<.001$, $p<.001$, $p<.001$). CBT and CBT + LT is deemed effective for SAD treatment on all three scales.	"These findings suggest that CBT, alone or as an adjunct to LT, holds promise as an efficacious treatment for acute SAD that could be added to the clinician's therapeutic repertoire and warrants further study. However, the data are too preliminary to support widespread dissemination of CBT for SAD at present on the basis of this first controlled trial."	Data suggest combination CBT plus LT had a significantly greater number of clinically significant changes versus MCDT.

						control (MCDT): monitored weekly by in-person SIGH-SAD's for 6 weeks, then treated by LT. (n=15)				
Paykel 1999 (score= 6.0)	Cognitive Behavioral Therapy	RCT	Sponsored by the Medical Research Council, London, England, and the Oxford and Anglia Region. No mention of COI.	N = 158 patients diagnosed with depression according to the DSM-III-R criteria	Mean age: 43.3 years; 80 males, 78 females.	Group 1: clinical management and drug continuation (n=78) vs. Group 2: clinical management, drug continuation and 16 cognitive therapy sessions in 20 weeks with an additional 2 sessions 6-14 weeks later (n=80)	1 year.	There was no significant difference in the intention to treat analysis (p=0.03) and protocol analysis (p=0.04). The hazard ratio for relapse was 0.54 (p=0.02). CT showed no significant effects at 20 weeks but BDI scores predict an advantage (p=0.07).	"In this difficult-to-treat group of patients with residual depression who showed only partial response despite antidepressant treatment, cognitive therapy produced worthwhile benefit."	Unequal contact time between the two groups. Data suggest CBT is effective for treating residual depression but requires patient commitment to have efficacy.
Huang 2015 (score= 5.5)	Exercise (Aerobic, Strengthening, Flexibility)/Cognit	RCT	Sponsored by the Chang Gung University. No COI.	N = 57 patients with Geriatric Depressi	Mean age: 76.53 years; 27 males,	Three times per week 50 min physical fitness exercise sessions group	Follow up at 1 week (T1), 3	CBT group GDS-15 score at baseline was 7.78 vs 4.28 at T2 (P=0.009). Exercise group	"Immediately after a 12-week intervention, there were significant decreases in depressive symptoms and more perceived	Usual care bias. Data suggest both exercise and CBT decreased depressive symptoms but the exercise group had

	ive Behavioral Therapy			on Scale-15 scores ≥ 5	30 females	(n = 19) vs weekly 60-80 min cognitive behavioral therapy sessions group (n = 18) vs usual care group (n = 20)	months (T2), 6 months (T3), and 9 months (T4) after baseline.	GDS-15 score at baseline was 8.63 vs 4.63 at T2 (P=0.003). Exercise groups quality of life SF-36 score was 60.61 at baseline vs 76.12 at T2 (P<0.001).	social support amongst those in the CBT group. When considering the effectiveness in the decrease of depressive symptoms longer term, the increase in the 6-min walk distance and raising the patients' quality of life, physical fitness exercise program may be a better intervention for elderly adults with depressive symptoms."	decreased symptoms for a longer period with improved fitness and quality of life.
Schlögelhofer 2014 (score= 5.5)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 90 patients diagnosed with major depressive disorder according to DSM-IV-TR guidelines.	Mean age: 47.8 years; 30 males, 60 females.	Group 1 was assigned to read 'Feeling good' by Burns within 6 weeks and had one session with a psychotherapist (n=49) vs. group 2 only received outcome assessments and clinical management	Immediate follow-up.	There was no significant difference between HRSD-17 (p=0.129) and BDI-scores (p=0.16). There was a significant difference between in reducing negative strategies for coping with	"Guided self-help did not lead to a significant reduction in symptom severity in patients with partially remitted depressive disorder after a 6-week intervention. However, the intervention leads to a reduction of negative stress-coping strategies."	Data suggest lack of efficacy of CBT guided self-help for reducing symptom severity after 6 weeks of therapy.

						from psychiatrists (n=41).		stress (p=0.002).Positive strategies for coping with stress did not have an effect on HRSD-17 (p=0.689) and BDI scores (p=0.163).		
Weitz 2014 (score= 5.5)	Cognitive Behavioral Therapy/ Interpersonal Psychotherapy	RCT	No sponsorship or COI.	N=239 participants with current major depressive episode (RDC criteria)	Mean age: 35 years; 72 males, 167 females	CBT Group: received cognitive behavioral therapy (no specific duration or protocol mentioned) (n=33) vs IPT Group: receiving interpersonal psychotherapy treatments consisting of 50- min sessions (n=38) vs Imipramine+CM Group: received clinical management consisting of	6, 12, 18 months	Changes in HRSD scores showed an effect size of 0.43 for CBT Group, 0.56 for IPT Group, 0.55 for Imipramine Group, and 0.34 for the placebo group. IPT group and imipramine group showed the greatest reduction in suicide symptoms compared to placebo (imipramine vs placebo: b=0.47, p<0.05; IPT vs	"This study demonstrates the specific effectiveness of IPT and medications in reducing suicidal ideation (relative to placebo), albeit largely as a consequence of their more general effects on depression."	Data suggest medications to treat depression such as imipramine and IPT may reduce suicidal ideation.

						medication management and 150-300 mg of imipramine (n=37) vs Placebo+CM Group: received clinical management consisting of medication management and placebo medication (50-60min sessions) (n=40)		placebo: b=0.41, p<0.05).		
Cramer 2011 (score= 5.5)	Cognitive Behavioral Therapy	RCT	Sponsored by National Institute for Health Research School for Primary Care Research. No COI.	N = 73 female patients diagnosed with depression according to the PHQ-9 guidelines.	Mean age: 42.5 years; 0 males, 73 females.	Group 1 went through 12 sessions of cognitive behavioral therapy over 10 weeks that covered checking and raising activity levels, catching and balancing negative thoughts, managing	3 and 6 months.	The difference decreased over time but at 3 and 6 months the PHQ-9 scores were lower for group 1 (p>0.05). Group 2 had 10% to 38% improvement from baseline. Between 3 and 6 months 13% of group 1 and 44$ of group 2	"This study showed that a randomised controlled trial of group CBT for women with depression is feasible and the intervention is acceptable, and may possibly prove to be effective in a larger trial. The cost effectiveness of group CBT for depression should be explored further in a full trial."	Usual care bias. Data suggest CBT improved depression more than UC group. All subjects were female in this pilot stud

						anxiety, new ways to problem solve, etc. (n=52) vs. group 2 was given 2 information booklets that included support organizations and received usual care (n=21).		received counseling (p=0.01). At 3 and 6 months the mean number of health related consultations were 4.8 for group 1 and 4.2 in group 2 (p=0.75), 3.9 for group 1 and 6.0 for group 2 (p=0.06).		
Rohan 2004 (score= 5.0)	Light Therapy/ CBT	RCT	Sponsored by the Uniformed Services University of the Health Sciences. No mention of COI.	N = 23 individuals who met the SIGH-SAD criteria for a current Seasonal Affective Disorder (SAD) episode	Mean age: 50.5 ± 12.6 years; 2 males, 21 females	Group LT: received standard light therapy treatment protocol (10,000 lux in 45-min doses twice daily) for 2 weeks (n=9) vs Group CBT: received SAD-tailored group CBT intervention (1.5-hour session twice a week for 6 weeks) (n=7)	Follow up at 1 year	Remission rates (per SIGH-SAD criteria) were 42.86% in CBT group, 55.55% in LT group, and 71.43% in CBT+LT group (p<0.001) at the end of the 6-week treatment period. Remission rates (per SIGH-SAD criteria) were 42.86% in CBT group, 37.50% in LT	"The nearly half of SAD patients who do not remit with light alone may benefit from CBT as an adjunct or alternative treatment, especially as a prophylaxis against episode recurrence."	Data suggest improvement observed in all 3 therapies but during the subsequent winter, combination CBT and LT appeared to improve long-term outcomes of symptom severity, remission, and relapse rates.

						vs Group CBT+LT: received both standard light therapy and group CBT treatment (n=7)		group, and 83.33% in CBT+LT group (p=0.028) at the 1 year follow-up.		
Lam 2013 (score= 5.0)	CBT/Esc italopram	RCT	Sponsored by grant from Lundbeck Canada. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 99 patients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 43.3 years; 45 males, 54 females	CBT Group: received 10 mg/day escitalopram (increased to 20 mg/day at week 2) and telephone-based cognitive behavioral therapy consisting of 8 sessions (each 30-40 min) over 8-10 weeks including motivation-exercises, identify, challenge and distance negative thoughts training, and personal care	2, 4, 8, 12 weeks	Decrease in MADRS score was 63% in CBT group compared to 61% in control group (p=0.86). Remission rates were 56% in CBT group compared to 53% in control group (p=0.74). Work functioning LEAP total score and LEAPS productivity scale showed greater improvement in CBT group compared to control group (p=0.046,	"Combined treatment with escitalopram and telephone-administered CBT significantly improved some self-reported work functioning outcomes, but not symptom-based outcomes, compared with escitalopram alone."	Data suggest depression scores were most improved via escitalopram compared to telephone-delivered CBT although self-reported work functions showed improvement with telephone delivered CBT.

						and self-management skills (n=48) vs Control Group: received 10-minute structured phone call weekly for 8 weeks and received 10 mg/day escitalopram (increased to 20 mg/day at week 2) (n=51)		p=0.036, respectively).		
Jarrett 1999 (score= 5.0)	CBT/Phenelzine	RCT	Sponsored by grants from National Institute of Mental Health. No mention of COI.	N = 108 patients with major depressive disorder (DSM-IV)	Mean age: 39.6 years; 35 males, 73 females	CBT Group: received cognitive behavioral therapy consisting of 20 individual sessions 2 times weekly for 10 weeks (n=36) vs Phenelzine Group: received phenelzine sulfate (0.85 mg/kg to 1	4, 7, 10 weeks	Response rate was 58% in CBT group, 58% in phenelzine group, and 28% in placebo group. Phenelzine reduced the mean HRSD-21 scores more than the placebo group at 4 weeks (p=0.01). For weeks 7 and	"Cognitive therapy may offer an effective alternative to standard acute-phase treatment with a monoamine oxidase inhibitor for outpatients with major depressive disorder and atypical features."	Baseline data differs in terms of duration and type of depression. Data suggest both CBT and phenelzine had comparable efficacy and were both superior to placebo but high dropout rate in placebo group.

						mg/kg consisting of 11 sessions over 10 weeks (n=36) vs Placebo: received identical dosing as phenelzine of a placebo pill (n=36)		10, both CBT group and phenelzine group reduced the HRSD-21 group compared to placebo (CBT vs Placebo 7 weeks: F1,103=7.29, p<0.01; 10 weeks: F1,103=8.94, p<0.01; Phenelzine vs Placebo 7 weeks: F1,103=12.60, p<0.001; 10 weeks F1,103=9.30, p<0.01).		
Schramm 2015 (score=5.0)	CBT/Escitalopram	RCT	Sponsored by Lundbeck GmbH, Hamburg, Germany. No mention of COI.	N = 60 patients with chronic major depression (DSM-IV)	Mean age: 43.63±10.56 years; 28 males, 32 females	CBASP Group: received 22 sessions of cognitive behavioral analysis system of psychotherapy (n=29) vs ESC/CM Group:	8, 28 weeks	Improvement in MADRS scores was observed for both groups at 8 weeks (p<0.001) and at 28 weeks (p<0.001). Response rate was 68.4% in CBASP and	"CABSP and ESC/CM appear to be equally effective treatment options for chronically depressed outpatients. For nonimprovers to the initial treatment, it is efficacious to augment with medication in the case of nonresponse	Small sample size. Data suggest both CBT and escitalopram were effective in the treatment of chronic major depression.

						received 18 session over 28 weeks of escitalopram 10 mg/day for first week then increased to 20 mg/day for rest of study and clinical management consisting of psychoeducation, support and empathy intervention (n=30)		60.0% in ESC/CM group with neither group being superior.	to CBASP and vice versa."	
Lemmens 2015 (score= 5.0)	Interpersonal Psychotherapy (IPT)/Cognitive Behavioral Therapy	RCT	Sponsored by the research institute of Experimental Psychopathology (EPP), the Netherlands, and the Academic Community Mental Health Centre RIAGG. No COI.	N = 182 adult outpatients with a primary diagnosis of MDD (DSM-IV)	Mean age: 40.5 years; 66 males, 116 females	CT Group: received 16–20 individual sessions of 45 min cognitive therapy (n=76) vs IPT Group: received 16–20 individual sessions of 45 min of interpersonal psychotherapy (n=75) vs Waitlist Group:	3, 7, 9, 12 months	Improvement in depression severity was greater in both CT and IPT group compared to waitlist ($p<0.02$). IPT and CT group showed reduction in BDI-II from 28.4 to 12.6 in the CT group compared to 31.2 to 17.2 in the IPT group.	"Within our power and time ranges, CT and IPT appeared not to differ in the treatment of depression in the acute phase and beyond."	Waitlist control bias. Data suggest comparable efficacy.

						received waitlist control (n=31)				
Wiles 2013 (score= 5.0)	Cognitive Behavioral Therapy	RCT	Sponsored by National Institute for Health Research Health Technology Assessment (NIHR HTA). No mention of COI.	N = 469 participants with adequate adherence to antidepressant medication and classification of depression measured via Beck Depression Inventory (BDI-2) and International Classification of Disease (ICD-10)	Mean age: 49.6 years; 130 males, 339 females	Intervention group: participants received 12 sessions of Cognitive Behavioral Therapy (CBT) with possibility of extra-trial care from a therapist as well as usual care (n=234) vs. Control group: participants received usual care without access to CBT (n=235).	Follow-up at 3, 6, 9, and 12 months.	46% of intervention group met criteria for response compared to 22% in usual care group at 6 months (OR = 3.26, p < 0.001)	"CBT as an adjunct to usual care that included pharmacotherapy was effective in reducing depressive symptoms and improving quality of life in primary care patients with treatment-resistant depression. The beneficial effect of the intervention was also identified for the more stringent criteria of remission and improvements were maintained over 12 months."	Usual care bias, which was variable and up to the individual practitioners. Data suggest CBT as an adjunct to usual care which includes anti-depressants is effective in reducing depression.

Conradi 2007 (score= 5.0)	CBT/Education	RCT	Sponsored by grants from the Dutch Organization for Scientific Research (NOW), the Medical Sciences Program and Chronic Diseases Program, Research Foundations of the Health Insurance Company 'Het Groene Land', the Regional Health Insurance Company (RZG), National Fund Mental Health	N = 267 patients with major depressive episodes diagnosed by Composite International Diagnostic Interview (CIDI)	Mean age: 42.8±11.3 years; 93 males, 174 females	PEP: received psycho-educational prevention program (PEP) consisting of educational books, videos, and 3 sessions with a psychiatrist (n=112) CBT-enhanced PEP: received PEP and 10-12 individual 45-minute sessions of cognitive behavioral therapy (CBT) (n=44) vs Psychiatrist-enhanced PEP: received PEP as well as 1-hour session with 2 psychiatrists, antidepressant medication (n=39) vs UC: received usual care of brief	3, 6, 36 months	Enhanced PEP and Enhanced-CBT PEP groups showed better improvement compared to UC group in BDI score (enhanced PEP BDI=2.07, 95% CI 1.13-3.0; CBT-enhance BID=1.62, 95% CI 0.7-2.55) and compared to PEP group (enhanced PEP BDI=2.37, 95% CI 1.35-3.39; CBT-enhance BID=1.93, 95% CI 0.92-2.94). Of all the patients, 64% showed recurrence of depressive episode and a mean BDI score of 9.6.	"The PEP program had no extra benefit compared to UC and may even worsen outcome in severely depressed patients. Enhancing treatment of depression in primary care with psychiatric consultation or brief CBT seems to improve the long-term outcome, but findings need replication as the interventions were combined with the ineffective PEP program."	Usual care bias. At 3 years, data suggest lack of efficacy for PEP, but brief CBT or psychiatric consultation appear to improve long-term outcome.

			(NFGV), and the University Hospital Groningen to J. Ormel and H. Kluiter. No conflict of interest.			supportive counseling, anti-depressant prescription and eventual psychological referral (n=72)				
Stangier 2013 (score= 5.0)	Education/CBT	RCT	Sponsored by German Research Funding. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 180 participants with recurrent nonpsychotic major depressive disorder diagnosed by DSM-IV Criteria	Mean age: 48.6±11.6 years; 50 males, 130 females	Cognitive Behavior Therapy (CBT): received 50-minute maintenance CBT session weekly until final phase with monthly sessions (n=90) vs Manualized Psychoeducation: received 20-minute sessions of psychoeducation tailored to each participant (n=90)	2, 8 months, 1 year	Recurrence of major depressive episode was 607 days for CBT group compared to 531 days in psychoeducation group. Relapse rate was 51% for CBT group compared to 60% in psychoeducation group at 1 year. The hazard ratio comparing CBT to psychoeducation was 0.622 (95%	"The results indicate that maintenance CBT has significant effects on the prevention of relapse or recurrence only in patients with a high risk of depression recurrence. For patients with a moderate risk of recurrence, nonspecific effects and structured patient education may be equally effective."	Data suggest CBT maintenance prevents relapse in high-risk depression recurrence individuals.

								CI=0.356-0.850).		
Anderson 2013, a (score= 5.0)	Computer-based Cognitive Behavioral Therapy/ Cognitive Behavioral Therapy	RCT	Sponsored by grant from the Swedish Science Foundation. COI: First author published a book on self-help material based on the treatment material.	N = 69 patients diagnosed with major depression with or without dysthymia (DSM-IV)	Mean age: 42.3±13.5 years; 15 males, 54 females	ICBT Group: received internet based cognitive behavioral therapy consisting of 7 text modules for 114 pages including exercises (n=33) vs Group CBT: received group based face-to-face cognitive behavioral therapy consisting of 8 group sessions (2 hours) (n=36)	9 weeks, 1, 3 years	Mean differences in MADRS scores were -4.7 (95% CI -8.63 to -0.77) in the ICBT group compared to -4.55 (95% CI -8.60 to -0.54) (p=0.04). Between group standardized mean difference was d=0.58 (95% CI 0.09-1.05) favoring ICBT group.	"Guided ICBT is at least as effective as group-based CBT and long-term effects can be sustained up to 3 years after treatment."	Data suggest guided iCBT may be as effective as group based CBT with gains sustained at 3 years.
DeRubeis 2005 (score= 4.5)	Paroxetine/CBT	RCT	Sponsored by the National Institute of Mental Health.	N = 240 participants with moderate to severe major depressive disorder	Mean age: 40 years; 98 males, 142 females	Paroxetine 10-50 mg/day for 16 weeks (n=120) vs. Placebo 10-50 mg/day for 8 weeks (n=60) vs. Cognitive Therapy (CT) for 16 weeks,	Follow-up at weeks 2, 4, 6, 8, 10, 12, 14, and 16	At 8 weeks there was a significant difference in response rates between groups (paroxetine = 50%, placebo = 25%, CT = 43%, p =	"Cognitive therapy can be as effective as medications for the initial treatment of moderate to severe major depression, but this degree of effectiveness may depend on a high level of therapist	Data suggest at 8 weeks the response rates to both paroxetine and CBT were comparable.

				meeting DSM-IV major depressive disorder criteria		50-minute sessions twice weekly for 4 weeks then 1-2 times weekly for 8 weeks, then weekly for 4 weeks (n=60)		0.006). At 16 weeks there was no difference in response rates between groups (paroxetine = 58%, CT = 58%, p = 0.92)	experience or expertise."	
Hollon 2005 (score= NA)	Paroxetine/CBT	Secondary Analysis of DeRubeis 2005	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 104 participants with moderate to severe major depressive disorder meeting DSM-IV major depressive disorder criteria, met criteria for continuation phase portion of study	Mean age and gender distribution not reported	Continuation of paroxetine (cAMD) (n=34) vs. Withdrawal onto placebo (n=35) vs. Cognitive Therapy responders – given up to 3 booster sessions during 12-month continuation phase (n=35)	Follow-up at weeks 1, 2, 4, 6, and 8 and months 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12	Patients who withdrew from CT were less likely to relapse during the continuation phase than those who withdrew from medications (30.8%, 76.2%, p = 0.004). Patients who withdrew from CT were no more likely to relapse than those who kept taking medications (30.8%, 47.2%, p = 0.20)	"Cognitive therapy has an enduring effect that extends beyond the end of treatment. It seems to be as effective as keeping patients on medication."	Data suggest CT effects persist after treatment and is as effective as prolonged ADT.

Dunlop 2017 (score= 4.5)	CBT/Duloxetine/Escitalopram	RCT	Sponsored by NIH grants. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 344 patients with current major depressive disorder (DSM-IV)	Mean age: 40.0±11.7 years; 148 males, 196 females	CBT Group: received 16 individual sessions of cognitive behavioral therapy consisting of 50 min sessions (n=115) vs Escitalopram Group: received 10-20 mg/day escitalopram (n=114) vs Duloxetine Group: received 30-60 mg/day duloxetine (n=115)	2, 4, 6, 8, 10, 12 weeks	Mean HAM-D score reduction was 10.9 points, but did not differ across the groups (F=0.53, p=0.589). Remission rates were 41.9% for CBT group, 46.7% in escitalopram group, and 54.7% in duloxetine group (p=0.170).	"Treatment guidelines that recommend either an evidence-based psychotherapy or antidepressant medication for nonpsychotic major depression can be extended to treatment-naïve patients. Treatment preferences among patients without prior treatment exposure do not significantly moderate symptomatic outcomes."	Data suggest patient preference towards CBT or pharmacotherapy did not significantly impact treatment outcomes in patients not receiving prior treatment.
Lemmens 2018 (score= 4.5)	Interpersonal Psychotherapy/CBT	RCT	Sponsored by the research institute of Experimental Psychopathology (EPP) and the Academic Communit	N = 134 adult patients with a diagnosis of MDD (DSM-IV)	Mean age: 40.5 years; 66 males, 116 females	CPT Group: received 16–20 individual sessions of 45 min cognitive therapy (n=69) vs IPT Group: received 16–20 individual sessions of 45 min of	7, 8, 9, 10, 11, 12, 24 months	Mean BDI-II scores decreased from 13.8 to 11.7 in the CT group compared to 16.0 to 14.9 in the IPT group. Reduction in depressive symptoms was achieved in	"Patients who responded to IPT were no more likely to relapse following treatment termination than patients who responded to CT. Given that CT appears to have a prophylactic effect following successful treatment, our	Data suggest comparable outcomes between CBT and IPT with similar relapse rates.

			y Mental Health Centre (Netherlands). No COI.			interpersonal psychotherapy (n=65)		65.2% of CT group compared to 61.5% of IPT group (p=0.66).	findings suggest that IPT might have a prophylactic effect as well."	
Mohr 2012 (score= 4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by research grants from National Institute of Mental Health. No COI.	N = 325 female patients diagnosed with major depressive disorder according to HAM-D guidelines.	Mean age: 47.7 years; 0 males, 325 females.	Group 1 received 18 sessions of cognitive behavioral therapy (CBT) 45 min each, face to face where the first 2 weeks had two sessions each and subsequent 12 weeks only had 1 session weekly (n=162) vs. Group 2 used an identical protocol but received CBT entirely over the phone (n=163).	3 and 6 months.	Post treatment and at 6 months improvement was significant compared to baseline for both groups ($p<0.001$, $p<0.001$). There were no significant differences for Ham-D scores ($p=0.22$) or PHQ-9 scores ($p=0.89$) between group 1 and group 2 post treatment. At 6 months there was a significant difference for Ham-D scores ($p<0.001$) or PHQ-9 scores ($p=0.004$) between group 1 and group 2.	"TCBT can reduce attrition and is as effective as face-to-face CBT at post treatment for depression among primary care patients."	High attrition rate. Data suggest comparable efficacy at 6 months.

Stiles-Shields 2014 (score= N/A)	Cognitive Behavioral Therapy	Secondary Analysis of Mohr, 2012	Sponsored by research grants from National Institute of Mental Health. No COI.	N = 325 female patients diagnosed with major depressive disorder according to HAM-D guidelines	Mean age: 47.7 years; 0 males, 325 females.	Group 1 received 18 sessions of cognitive behavioral therapy (CBT) 45 min each, face to face where the first 2 weeks had two sessions each and subsequent 12 weeks only had 1 session weekly (n=162) vs. Group 2 used an identical protocol but received CBT entirely over the phone (n=163).	Baseline, 9 and 18 weeks, 6 and 12 months.	There was a significant difference between treatment assigned and presence of baseline comorbid anxiety for PHQ-9 ($p=0.002$), GAD-7 ($p=0.04$), and HAM-D ($p=0.001$). Patients that had comorbid anxiety disorders at baseline also had significant higher scores for PHQ-9 ($p<0.001$), GAD-7 ($p=0.003$), and HAM-D ($p<0.001$). There was no significant difference between T-CBT and F2F-	"The findings indicate that the presence of baseline anxiety impacts the overall effect of T-CBT for the treatment of depression."	Data suggest the presence of anxiety impacts T-CBT when treating depression. If anxiety is present with depression, T-CBT is much less effective than face-to-face CBT.

								CBT groups (p=0.99)		
Stiles-Shields 2015 (score= N/A)	Cognitive Behavioral Therapy	Secondary Analysis of Mohr, 2012	Sponsored by research grants from National Institute of Mental Health. No mention of COI.	N = 325 female patients diagnosed with major depressive disorder according to HAM-D guidelines	Mean age: 47.7 years; 0 males, 325 females.	Group 1 received 18 sessions of cognitive behavioral therapy (CBT) 45 min each, face to face where the first 2 weeks had two sessions each and subsequent 12 weeks only had 1 session weekly (n=162) vs. Group 2 used an identical protocol but received CBT entirely over the phone (n=163).	Baseline, 9 and 18 weeks, 6 and 12 months.	The coping self-efficacy (CSE) scale was able to help predict scores on the HAMD and PHQ-9 guidelines. High CSE scores tended to respond without other variables having an effect. Those with low CSE scores had depression severity impact their response. Delivery of treatment did not have an influence on the predicted outcome.	"[…] a moderate to high level of CSE significantly increases the chance of responding in both T-CBT and FtF-CBT. Among patients with low CSE, those with lower depressive symptom severity are more likely to do well in treatment."	Data suggest that individuals with moderate to high CSE are more likely to benefit from either T-CBT or face-to-face CBT.
Nakagawa 2017 (score= 4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by Japanese Ministry of Health,	N = 80 patients diagnosed with major	Mean age: 40.6 years; 51	Group 1 received usual treatment and 50 minutes CBT sessions	3, 6, and 12 months.	There was not a significant difference between the groups at 8	"Patients with pharmacotherapy-resistant depression treated in psychiatric specialty care settings	Treatment as usual bias. Data suggest CBT significantly improved symptoms

			Labour, and Welfare. COI, Dr. Ono received research support from Japanese Ministry of Health, Labour, and Welfare and royalties from Igaku-Shoin, Seiwa-Shoten, and Kongo-Shuppan, and Dr. Fujisawa received royalties from Seiwa-Shoten.	depressive disorder according to the DSM-IV guidelines.	males, 29 females.	weekly for 16 weeks and up to 4 additional sessions (n=40) vs. Group 2 only received usual treatment that consisted of medication visits every 2 weeks for 10-15 min (n=40).		weeks (p=0.11) but there was at 16 weeks (p<0.001). CBT had beneficial effects at 3 months (p=0.01), 6 months (p=0.02), and 12 months (p=0.002).	may benefit from supplementing usual medication management with CBT."	of depression at 16 weeks.
Berking 2013	Cognitive Behavior	RCT	Sponsored by the Vogelsber	N = 432 subjects with	Mean age: 46.44	CBT: 45 min session of individual	No follow up	Subjects in the CBT-ERT group were	"Integrating strategies that target emotion regulation	Data suggest the addition of ERT to CBT improve

(score= 4.5)	al Therapy		g Clinic and by grants PA001-113040 and PZ00P1-121576 from the Swiss National Science Foundation to Matthias Berking. COI: Hofmann is a paid consultant and is supported by NIMH grant.	MDD according to DSM-IV and a BDI score > 11	years; 76 males, 356 females	therapy and four 45 min session of group psychotherapy weekly, focused on depression. Then received four 45 min sessions of transdiagnostic group therapy focused on problem solving therapy (n=237) vs. CBT enriched with an intense emotion regulation skills training (CBT-ERT): For ERT, Affect Regulation Training (ART) was used. There were four 1.5 hour sessions and two 45	menti oned	depressed significantly less than CBT (response rates – CBT: 75.5%, CBT-ERT: 84.9%; remission rates – CBT: 51.1%, CBT-ERT: 65.1%). CBT-ERT also had a significantly bigger reduction in negative affect, and a greater increase of well-being and emotion regulation skills.	skills improves the efficacy of CBT for MDD."	treatment efficacy for MDD

						min sessions (n=195)				
Dimidjian 2006 (score= 4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by National Institute of Mental Health Grant. COI: Dunner is a consultant or on the advisory board for, and serves on the speaker's bureau of a number of pharmaceutical companies, including GlaxoSmithKline.	N = 241 subjects with major depression on the scale of DSM-IV.	Mean age: 39.9 years; 82 males, 159 females	Behavioral Activation (BA) group: received max twenty-four 50-minute sessions over 16 weeks, sessions twice weekly for first 8 weeks, and then only weekly after (n=43) vs. Cognitive Therapy (CT) group: same session schedule and frequency as BA group (n=45) vs. Antidepressants (ADM): received 16 weeks of paroxetine, started at 10mg/day, then 20mg/day at week 2, then 30mg/day	Follow up at 8 and 16 weeks	Subjects in BA improved significantly greater than participants in CT on both the BDI, t(81)=2.23 (p=.029), and the HRSD, t(188)= 2.09 (p=.038). Participants in ADM improved significantly greater than participants in CT on both the BDI, t(81)= 2.76, (p=.007), and the HRSD, t(188)=2.31, (p=.022). When comparing participants in BA and ADM, were no significant differences in the rates of improvement	"Among more severely depressed patients, behavioral activation was comparable to antidepressant medication, and both significantly outperformed cognitive therapy."	Data suggest BA comparable to ADM and better than CBT.

						at week 4, then 40mg/day at week 6, and 50mg/day dosage at week 12 (n=100) vs. Placebo (PLA) group: received 8 for weeks (n=53)		on the BDI, t(81)= 0.25, (p= .80), or on the HRSD, t(188)=0.05, (p=.96).		
Richards 2016 (score= 4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by the National Institute for Health Research. COI: one or more authors received funding from European Science Foundation, NIHR Collaborations for Leadership in Applied Health Research and Care	N = 440 subjects that are 18 years or older meeting DSM-IV criteria for MDD.	Mean age: 43.5 years; 150 males, 290 females.	Behavioral Activation (BA) group (n=221) vs. CBT group (n=219). All treatments maximum of 20 60-minute sessions over 16 weeks. Both set of treatments focused on core and supplementary techniques.	Follow up at 6, 12, and 18 months.	BA did not differ from CBT in anxiety (p=0.60), depression status, and SCID number of depression-free days (p=0.21)	"We found that BA, a simpler psychological treatment than CBT, can be delivered by junior mental health workers with less intensive and costly training, with no lesser effect than CBT."	Baseline difference in time on antidepressant between groups. Data suggest BA may show similar efficacy to CBT without being as costly or as intensive.

			and report NIHR panel memberships. WK receives fees from book royalties.							
Maddux 2009 (score= 4.0)	Nefazodone/CBT	RCT	Sponsored by Bristol-Myers Squibb. Author Thase serves on the Speakers Bureau and acts as a Consultant for the Bristol-Myers Squibb Company.	N = 681 participants meeting DSM-IV criteria for chronic major depressive disorder, major depressive disorder superimposed on antecedent dysthymic disorder, or	Mean age: 42.3 years; 236 males, 445 females	Nefazodone: 300-600 mg daily (n=227) vs. Cognitive behavioral analysis system of psychotherapy (CBASP): 16-20 sessions, 2 sessions weekly for 4 weeks, 1 session weekly for 8 weeks (n=227) vs. Combination of both treatments (n=227)	No follow-up	Patients with comorbid personality disorders (PDs) statistically lower Hamilton Depression Rating Scale scores (mean=12.2) compared to those without comorbid PDs (mean=13.5, partial n2 = 0.008).	"Comorbid Axis II disorders did not negatively affect treatment outcome and did not differentially affect response to psychotherapy versus medication. Treatment formulations for chronically depressed patients with certain PDs may not need to differ from treatment formulations of chronically depressed patients without co-occurring PDs."	Data suggest that chronic depression with comorbid personality disorders do not respond to treatment with nefazodone or psychotherapy differently than those who are chronically depressed without personality disorders.

				recurrent major depressive disorder with incomplete remission between episodes						
Chatwin 2016 (score= 4.0)	Cognitive Behavioral Therapy/ Emotional Freedom Techniques	RCT	No mention of sponsorship. No COI.	N = 17 participants screened positive for major depressive disorder (MDD) determined by MINI-international neuropsychiatric interview (MINI) 6.0 compare	No mention of mean age; 14 males, 53 females	EFT Intervention: received emotional freedom techniques program with 2 EFT therapists and standard protocols (n=11) vs CBT Intervention: received cognitive behavior therapy program (n=6) vs Controls: (n=57)	8 weeks, 3, 6 months	No differences in depression scores were observed between intervention groups (p=0.994); however, CBT group compared to the community control group showed lower depression scores (p=0.018), and also lower depression scores for EFT groups compared to community	"The findings of the present study have indicated that EFT may be an effective treatment strategy worthy of further investigation."	Data suggest comparable efficacy between CBT and EFT on reducing depressive symptoms but CBT group gains not maintained over time.

				d with N=57 controls				control group (p=0.003). At 8 week follow-up depression scores were higher in EFT groups compared to CBT group (p=0.003) and the community group (p<0.001), and the CBT group had higher depression scores than the control group (p=0.042). At 3 month follow-up depression scores were higher only when comparing EFT groups compared to community group (p=0.03). At 6 month follow-up similar results were observed for only higher depression		

								scores comparing EFT group to community group (p=0.022).		
Preschl 2011 (score= 4.0)	Compute r-based Cognitiv e Behavior al Therapy	RCT	No COI. Sponsored by the Werner Selo Foundatio n.	N = 53 participa nts with Beck Depressi on Inventor y (BDI) scores of 12+	Mean age: 36.7 years; 17 males, 36 females	Internet-based treatment – access to online content of CBT, with assignments lasting 45 minutes, 2 assignments each week, option to text therapist as well (n=25) vs. Face-to-face group – attended hourly sessions once per week of CBT with weekly assignments (n=28). Both groups completed 8 weeks of treatment.	No follow -up	Correlation analysis show working alliance ratings do not significantly predict BDI residual gain score in internet-based or face-to-face groups.	"Contrary to what might have been expected, the working alliance in the online group was comparable to that in the face-to-face group. However, the results showed no significant relations between the BDI residual gain score and the working alliance ratings in either group."	Data suggest comparable efficacy between online and face-to-face CBT.

Garnefski 2011 (score= 4.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 32 participants with depression symptoms as assessed via Hospital Anxiety Depression Scale (HADS).	Mean age: 47.28 years; 5 males, 27 females	Cognitive Behavioral Self-help program (CBS), including workbook, program, and CD, worked on 4 days per week for 4 weeks (n = 15) vs. Waitlist control (n = 17)	At baseline and 2 months.	Participants in the intervention group showed significant improvements of depressive symptoms from baseline to end of trial (p=0.021).	"The result of this pilot study showed that a self-help intervention program, working on relaxation, changing maladaptive cognitions, and attainment of personal life goals, might be effective in reducing depressed mood in people with acquired chronic physical impairments."	Wait list control bias. 2-month follow-up. Data suggest self-help CBT programs may reduce depressive symptoms
Forman 2007 (score= 4.0)	Acceptance and Commitment Therapy (ACT)/Cognitive Behavioral Thearpy	RCT	No mention of sponsorship or COI.	N = 101 subjects with Beck Anxiety Inventory score > 9 and Beck Depression Inventory-II score > 9, symptoms meeting DSM-	Mean age: 27.9 years; 8 males, 101 females.	Cognitive Therapy (CT) group: received traditional CT. Average of 15.27 sessions (n=44) vs ACT group: Received traditional ACT. Average of 15.60 sessions. (n=55). Only 99 of the 101 randomized were included in the analysis.	No follow up	For CT, mean scores for Beck Depression Inventory (BDI) was 18.92, Beck Anxiety Inventory (BAI) was 13.08, Global Assessment of Functioning (GAF) was 64.22, Clinical Global Impression (CGI) was 3.31, Quality of Life Inventory	"The results suggest that ACT is a viable and disseminable treatment, the effectiveness of which appears equivalent to that of CT, even as its mechanisms appear to be distinct."	High attrition rates in both groups (CT=42.4%, ACT=33.3%). Data suggest comparable efficacy between CT and ACT.

				IV-TR criteria		All subjects received semi-structured interviews using DSM-IV-TR and completed pre and post questionnaires.		(QOLI) was 0.49, and Subject Life Satisfaction Scale (SLS) was 11.21. For ACT, mean scores for BDI was 18.96, BAI was 13.22, GAF was 64.96, CGI was 3.23, QOLI was 0.73, and SLS was 12.75.		
Forman 2012 (score= N/A)	Acceptance and Commitment Therapy (ACT)/Cognitive Behavioral Therapy	Post-hoc long term follow up	No mention of sponsorship or COI.	N = 132 subjects with Beck Anxiety Inventory score > 9 and Beck Depression Inventory-II score > 9, symptoms meeting DSM-	Mean age: 26.7 years; 27 males, 105 females	CT group: received CT (automatic thoughts, core beliefs, and schemas, identification of cognitive distortions, cognitive disputation, and cognitive restructuring). Average of 16.37 sessions (n=63) vs ACT group: received ACT (experiential acceptance,	Follow up around 14-20 months	According to the BDI, 81.8% of CT patients recovered, but only 60.7% in ACT patients. BAI was 72.7% in CT and 56% in ACT. OQ was 46.4% in CT and 22.6% in ACT. QOLI was 37.8% in CT and 22.9% in ACT.	"The results reveal that the two treatments are equally effective in the short term: both were successful in maintaining improvements in depression, anxiety, and general functioning. Yet, statistical comparisons of long-term outcomes suggest that CT has a slight advantage over ACT in the long-term maintenance of gains, at least with respect to depressive	Data suggest long term results appear to favor CT over ACT for treatment of anxiety and depression

				IV-TR criteria		mindfulness training, clarification of personal values, and willingness to experience internal distress for the sake of living consistently with one's values). Average of 18.10 sessions. (n=69)			symptoms and general functioning."	
Driessen 2013 (score= 4.0)	Cognitive Behavioral Therapy/ Psychodynamic Therapy	RCT	Sponsored by Wyeth Pharmaceuticals, Arkin Mental Health Care, ProPersona Mental Health Care, VU University. COI, one or more of the authors have	N = 341 participants with DSM-IV classified major depressive order (MDD) as assessed via Hamilton Depression Rating	Mean age: 38.91 years; 102 males, 239 females.	16 sessions of individual manualized CBT within 22 weeks (n = 164) vs. 16 sessions of short-term psychodynamic supportive therapy within 22 weeks (n = 177)	Follow-up at one year.	No statistically significant treatment differences between groups (p>0.05).	"The findings extend the evidence base of psychodynamic therapy for depression but also indicate that time limited treatment is insufficient for a substantial number of patients encountered in psychiatric outpatient clinics."	Data suggest comparable efficacy for all primary outcome measures between CBT and psychodynamic therapy.

			received or will receive benefits for personal or professional use.	Scale (HAM-D).						
Paykel 2005 (score= 4.0)	Cognitive Behavioral Therapy	RCT	Sponsored by grants from the Medical Research Council. No COI.	N = 158 subjects with major depression of the DSM-III-R criteria.	Mean age: 49.2 years; 66 males, 69 females.	Clinical management (n=65) vs. 16 sessions of CBT for 20 weeks, also received clinical management (n=70). Clinical management included meeting with psychiatrist every 4 weeks for 20 weeks, and every 8 weeks for a further 48 weeks. All subjects on a mean daily dose of TCAs (amitriptyline or fluoxetine)	Follow up at 6 years after randomization and 4-6 years after treatment.	During the follow-up period, the hazard rate was 0.18 (CI 0.13-0.27). At 20 weeks the control group had a recurrence rate of 31% while the CBT group had a 6% recurrence rate (p=0.002). At 275 weeks the control group had a recurrence rate of 83% while the CBT group had a 75% recurrence rate (p=0.33).	"The effect of CBT in reduction of relapse and recurrence persists for several years. The potential value of subsequent additional CBT some time after cessation should be explored."	Data suggest prolonged benefits of CBT in the reduction of relapse and recurrence of depression.

Thompson 2001 (score= 4.0)	Cognitive Behavioral Therapy/ Desipramine	RCT	Sponsored by a grant from the National Institute of Mental Health. No mention of COI.	N = 102 subjects with MDD according to the Research Diagnostic Criteria.	Mean age: 66.8 years; 33 males, 67 women.	Desipramine 10mg and increased slowly (n=33) vs. CBT-Alone - group: each session was 50-60 minutes with a cognitive behavioral therapist (n=31) vs. Combined group – received same dosage of desipramine and amount of CBT as other groups (n=36). All participants seen for 16-20 sessions over 3-4 month period. Sessions twice a week for 1 week, then once per week for next 8-12 weeks	Follow up at 10 days	Reduction in depressive symptoms in the low severity group according to the BDI-SF was significantly greater in separate comparisons of Desipramine-Alone with CBT-Alone ($t[844]=2.45$; $p<0.05$) and with the Combined treatment ($t[844]=2.13$; $p<0.05$)	"The results indicate that psychotherapy can be an effective treatment for older adult outpatients with moderate levels of depression."	Data suggest all 3 treatment groups improved but combined treatment was best for severely depressed patients.

Zagorscak 2018 (score= 4.0)	Cognitive Behavioral Therapy	RCT	Sponsored by the German public health insurance company "Techniker Krankenkasse." No COI.	N = 1,089 subjects with mild-to-moderate depression according to BDI-II	Mean age: 45.7 years; 375 males, 714 females	Individual Counseling (IC) Group: subjects had a personal counselor that provided semi standardized written feedback after completing each module (n=555) vs. Contact on demand (CoD) group: feedback was given automatically in a nonstandardized way (n=534). Intervention had 7 modules for 6 weeks.	Follow up at 3, 6, and 12 months.	Both groups had a big pre-post effects on depression (Beck Depression Inventory-II: dIC = 1.53, dCoD = 1.37; Patient Health Questionnaire-9: dIC = 1.20, dCoD = 1.04)	"Adding semi standardized guidance in IBI for depression did not prove to be more effective than fully standardized feedback on primary and secondary outcomes, but it had positive effects on attrition."	High dropout rates in both groups. Data suggest lack of efficacy.
Gibbons 2016 (score= 4.0)	Cognitive Behavioral Therapy/ Insight-Oriented Therapy	RCT	Sponsored by Agency for Healthcare Research and Quality. No COI.	N = 237 patients with a diagnosis of MDD (DSM-IV)	Mean age: 36.2 years; 59 males, 178 females	DT Group: received supportive-expressive short-term dynamic psychotherapy (DT) consisting of	Follow up at 1, 2, and 5 months	Mean change in HAM-D score was 0.86 points between CT and DT group (95% CI -0.70-2.42). The only significant	"This study suggests that DT is not inferior to CT on change in depression for the treatment of MDD in a community mental health setting. The 95%CI suggests that the effects of DT are	5-month follow-up. Data suggest comparable efficacy between dynamic therapy and cognitive therapy.

						(n=118) vs. CT Group: received structured sessions focusing on behavioral activation and depressogenic beliefs (activity scheduling, evaluation of thoughts, behavioral experiments) of cognitive therapy (n=119)		differences between DT group compared to CT group were in supportive techniques (t120=2.48, p=0.02), competence in excessive techniques (t120=4.78, p=0.001), adherence to techniques (t120=-7.07, p=0.001), and competence in CT (t120=-7.07, p=0.001).	equivalent to those of CT."	
Omidi 2010 (score=3.5)	Cognitive Behavioral Therapy									Treatment as usual bias. Data suggest comparable efficacy between CBT and MBCT compared to TAU for MDD.33
Hegerl 2010 (score=3.5)	Cognitive Behavioral Therapy									Data suggest sertraline superior to placebo, cognitive behavioral therapy (CBT) superior to

33 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										self-help groups and CBT, sertraline and patient's choice arm are similar.34
Mergl 2018 (score= NA)	Cognitive Behavioral Therapy	1 year follow-up of Hegerl 2010								Data suggest sertraline and CBT have similar anti-depressive effects for mild to moderate depression but sertraline seems slightly better than CBT.
Furukawa 2012 (score= 3.5)	Cognitive Behavioral Therapy									Study terminated early due to poor participation. Data suggest T-CBT may provide access to those with subthreshold depression
Hollon 2016 (score= 3.5)	Cognitive Behavioral Therapy									Data suggest CBT augments ADM and speeds up recovery compared to ADM alone
Tadic 2010 (score= 3.5)	Cognitive Behavioral Therapy									Significant difference in age on baseline characteristic. Data suggest EI may be

34 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										predictive for early treatment decision in mild, minor, major and subsyndromal depression
Perlis 2002 (score= 3.5)	Cognitive Behavioral Therapy									Data suggest a lack of efficacy when adding CBT to fluoxetine as compared to fluoxetine alone
Elkin 1989 (score= 3.0)	Cognitive Behavioral Therapy									High dropout rate. Data suggest lack of efficacy of all 3 treatment groups versus placebo.35
Christensen 2004 (score= 3.0)	Cognitive Behavioral Therapy									Data suggest comparable efficacy in both interventions.
Gallagher-Thompson 1994 (score= 3.0)	Cognitive Behavioral Therapy									Data suggest depressed family caregivers who had been providing care for at least 44 months improved with CBT
Wuthrich 2015	Cognitive Behavior									Data suggest improvement in both groups but faster and

35 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score= 3.0)	al Therapy									sustained results in CBT
Shapiro 1994 (score= 2.5)	Cognitive Behavioral Therapy									Data suggest comparable efficacy with a trend towards CBT being better per Beck Depression Inventory.
Mackinnon 2008 (score= 2.5)	Cognitive Behavioral Therapy									Data suggest both interventional groups saw benefits.
Murphy 1985 (score= 2.5)	Cognitive Behavioral Therapy									Sparse methods. Data suggest comparable efficacy for all 4 treatment arms.
Fournier 2013 (score= 2.5)	Cognitive Behavioral Therapy									Data suggest medications and CBT lead to different response patterns in symptoms.
Fournier 2015 (score= 2.0)	Cognitive Behavioral Therapy									Data suggest CBT likely provides greater and sustained improvements versus medications.36

36 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Computer-Assisted Cognitive Behavioral Therapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hoorelbeke 2017 (score= 7.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the Ghent University. No COI.	N = 68 with remitted depression via Mini-International Neuropsychiatric Interview (MINI)	Mean age: 46.97 years; 23 males; 45 females	10 online sessions of adaptive Paced Auditory Serial Addition Task (PASAT, internet-delivered cognitive control training - CCT) (n=34) vs. Low cognitive load training (n=34). All sessions given within a 2-week period	Follow-up at 3 months	Mixed ANOVA results – main effect of time for Brooding: $F(2, 65) = 12.1$ ($p<0.001$), for Depressive symptomatology: $F(2, 65) = 0.79$ ($p = 0.459$). Main effect of group for Brooding: $F(91, 66) = 7.85$ ($p = 0.007$), for Depressive symptomatology: $F(1, 66) = 2.56$ ($p = 0.115$). Time x Group Interaction effect for Brooding: $F(2, 65) = 4.7$ ($p = 0.012$), Depressive	"These findings demonstrate the effectiveness of CCT as an intervention to reduce cognitive vulnerability, residual symptomatology, and foster resilience following recovery from depression. CCT thus holds potential as a preventive intervention for RMD patients."	Data suggest internet-delivered cognitive control training may act as a preventive strategy in recovered depressed patients by fostering resilience.

								symptomatology: F(2, 65) = 7.04 (p = 0.002)		
Vernmark 2010 (score= 6.0)	Computer-based Cognitive Behavioral Therapy	RCT	COI: Five authors published a Swedish self-help book that includes text tested in current study. Sponsored by the Swedish Research Council	N = 88 with major depression via DSM-IV criteria, total of <31 on Montgomery Åsberg Depression Rating Scale-self rated (MADRS-S), total of >14 on MADRS-S, <4 on Item 9 (suicidal thoughts) on	Mean age: 36.82 years; 28 males, 60 females	Guided self-help depression program – seven text modules with exercises (n=29) vs. Email therapy – manual based on CBT-principles, received at least 1 treatment per week along with assistant mails used to answer shorter questions of practical/technical nature (n=30) vs. Waiting list control (n=29)	Follow-up at 6 months	Repeated measures ANOVA for Beck Depression Inventory score: significant interaction effect for group and time – F(2, 85) = 6.47 (p < 0.001). Tukey's HSD showed email therapy (p=0.002) and self-help (p=0.06) groups significantly improved depressive symptoms compared to waitlist control. Email therapy and self-help were not statistically different (p = 0.41)	"Overall, the difference between guided self-help and e-mail therapy was small, but in favour of the latter. These findings indicate that both guided self-help and individualized e-mail therapy can be effective."	Waitlist control bias. Data suggest comparable efficacy between interventional groups.

				MADRS-S						
Andersson 2013 b (score= N/A)	Computer-based Cognitive Behavioral Therapy	3.5-year follow-up of Vernmark 2010.	No COI. Sponsored by the Swedish research council.	N = 88 with major depression via DSM-IV criteria, total of <31 on Montgomery Åsberg Depression Rating Scale-self rated (MADRS-S), total of >14 on MADRS-S, <4 on Item 9 (suicidal thoughts) on MADRS-S	Mean age: 36.82 years; 28 males, 60 females	Guided self-help depression program – seven text modules with exercises (n=29) vs. Email therapy – manual based on CBT-principles, received at least 1 treatment per week along with assistant mails used to answer shorter questions of practical/technical nature (n=30) vs. Waiting list control (n=29)	Follow-up at 3.5 years	55% of participants sought for additional treatment during follow-up period. Piecewise growth model showed negative mean estimate of slope (estimate = -10.8, $p < 0.001$) to show continued low Beck Depression Inventory scores	"People with mild to moderate major depression may benefit from ICBT 3.5-years after treatment completion."	Data suggest individuals suffering from mild to moderate depression may benefit from iCBT even 3.5 years post treatment.

Klein 2016 (score= 5.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the German Federal Ministry of Health. Klein received payments for presentations, workshops and books on psychotherapy and chronic depression and Meyer is employed by GAIA AG.	N = 1,013 with mild to moderate depressive symptoms via Patient Health Questionnaire (PHQ-9 score 5—14)	No mean age listed, age range 18-65 years; 0 males, 1,013 females	Internet intervention – 12 week CBT-based programme (Deprexis), 11 modules, email supporters were also utilized, also had access to usual care (n=509) vs. Care as Usual (n=504)	Follow-up at 3 and 6 months	PHQ-9 score changes from baseline differed between groups ($t_{825} = 6.12$, $p < 0.001$). Post-assessment between-group effect size for intervention (d = 0.39 [95% CI (0.13-0.64)], at follow-up (d = 0.32 [0.06-0.69]	"The Internet intervention examined in this trial was superior to CAU alone in reducing mild to moderate depressive symptoms. The magnitude of the effect is clinically important and has public health implications."	EVIDENT trial and use of Deprexis internet. Care as usual bias. Data suggest self-rated depression improved at 6 months in internet interventional group for those with mild to moderate depression.
Buntrock 2017 (score= 5.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the European Union and the BARMER GEK. COI: one or more of the authors	N = 406 with subthreshold depression (Centre for Epidemiological Studies	Mean age: 45 years; 106 males, 300 females	Intervention Group: received web-based guided self-help intervention consisting of 6 sessions (30 minutes) of cognitive behavioral	6, 12 months	Intervention group showed a mean depression-free survival time of 43 weeks (95% CI 41-46) compared to 37 weeks in the control group (95% CI 36-	"Our study supports guidelines recommending Web-based treatment for sD and adds that this not only restores health in people with sD, but additionally reduces the risk of developing a MDD. Offering the	GET-ON Study. Data suggest web-based self-guided CBT with problem solving therapy for subthreshold depression led to more depression free years and quality of life adjusted years than usual care plus

			have received or will receive benefits for personal or professional use.	Depression Scale (CES-D ≥ 16) not meeting criteria for full blown major depressive disorder (MDD) (DSM-IV)		therapy and problem solving therapy and received online written feedback after each session (n=202) vs Usual Care Group: received enhanced usual care consisting of access to web-based psychoeducational intervention that showed patients treatments for depression (n=204)		40). Differences in EQ-5D QALY gains were 0.78 for intervention group compared to 0.77 in the control group (p=0.32). Differences in SF-6D QALY gain were 0.71 for intervention group compared to 0.67 in control group (p<0.001).	intervention has an acceptable likelihood of being more cost-effective than enhanced usual care and could therefore reach community members on a wider scale."	access to health care professionals group and was more cost-effective.
Anderson 2013, a (score= 5.0)	Computer-based Cognitive Behavioral Therapy/ Cognitive Behavior	RCT	Sponsored by grant from the Swedish Science Foundation. COI: First author published	N = 69 patients diagnosed with major depression with or without dysthym	Mean age: 42.3±13.5 years; 15 males, 54 females	ICBT Group: received internet based cognitive behavioral therapy consisting of 7 text modules for 114 pages including	9 weeks, 1, 3 years	Mean differences in MADRS scores were -4.7 (95% CI -8.63 to -0.77) in the ICBT group compared to -4.55 (95% CI -8.60 to -0.54)	"Guided ICBT is at least as effective as group-based CBT and long-term effects can be sustained up to 3 years after treatment."	Data suggest guided iCBT may be as effective as group based CBT with gains sustained at 3 years.

	al Therapy		a book on self-help material based on the treatment material.	ia (DSM-IV)		exercises (n=33) vs Group CBT: received group based face-to-face cognitive behavioral therapy consisting of 8 group sessions (2 hours) (n=36)		(p=0.04). Between group standardized mean difference was d=0.58 (95% CI 0.09-1.05) favoring ICBT group.		
Montero-Marín 2016 (score= 5.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by Instituto de Salud Carlos II of the Spanish Ministry of Economy and Competitiveness grant, and the Network for Prevention and Health Promotion in primary care grant,	N = 296 patients diagnosed with major depression (DSM-IV)	Mean age: 42.9 years; 72 males, 224 females	CSG Group: received internet-delivered self-help program consisting of 10 cognitive behavioral therapy modules of completely self-guided program without therapist (n=98) LITG Group: received low-intensity therapist-guided internet-based program	3, 6, 15 months	BDI-II scores showed improvement at 6 months [TAU vs CSG (B=-4.22, p=.007); TAU vs LITG (B=-4.34, p=.005)] and at 15 months [TAU vs CSG (B=-5.10, p=.001); TAU vs LITG (B=-4.62, p=.002)].	Treatment as usual bias. Data suggest neither CSG nor LITG was better than iTAU at 3 months but at 6 months, both interventions showed benefits over iTAU.	"An Internet-based intervention for depression combined with iTAU conferred a benefit over iTAU alone in the Spanish primary health care system."

			and European Union ERDF funding. No COI.			consisting of 10 cognitive behavioral therapy modules (n=96) vs TAU Group: received treatment as usual from general practitioners consisting of antidepressant prescription, or referral to mental health facilities if necessary (n=102)				
Gilbody 2015 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the UK National Institute for Health Research Health Technology Assessment programme. No COI.	N = 691 participants with symptoms of depression (PHQ-9)	Mean age: 39.86±12.65 years; 229 males, 462 females	Group 1: received Beating the Blues (interactive, multimedia, cCBT package) consisting of 15 min intro video with 8 therapy sessions each 50 minutes and usual care	4, 12, 24 months	Difference between Group 1 and Usual care group was observed (OR=1.19, 95% CI 0.75-1.88) and between Group 2 and usual care group (OR=0.98, 95% CI 0.62-1.56). Non-inferiority comparison	"Supported cCBT does not substantially improve depression outcomes compared with usual GP care alone. In this study, neither a commercially available nor free to use computerised CBT intervention was superior to usual GP care.	Usual care bias. Data suggest cCBT was not superior to usual GP care for depression.

						(n=210) vs Group 2: received MoodGYM (web-based CBG program) consisting of 5 modules on a weekly basis and usual care (n=242) vs Usual Care Only: received usual GP care only (n=239)		between Group 2 and Group 1 showed OR=0.91 (95% CI 0.62-1.34, p=0.69).		
Buntrock 2015 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by European Union. COI: Some of the authors are stakeholders of the 'Institute for Online Health Trainings'.	N = 406 patients with subthreshold depression (sD) (CES-D)	Mean age: 45.04±11.89 years; 106 males, 300 females	Intervention Group: received web-based cognitive behavioral intervention consisting of 6 30-minute interactive sessions (n=202) vs Control Group: received web-based psycho-educational intervention (n=204)	6 weeks, 6 months	A mean reduction in CES-D scores of 8.73 points (p<0.001) was observed in the intervention group compared to 2.81 points in the control group (p<0.001). An effect size was d=0.69 (95% CI 0.49-0.89) in favor of the intervention (p=0.003).	"This study lends support to the idea that problem solving coupled with behavioral activation is an effective treatment for sD. In addition, the delivery of this intervention over the Internet might be a promising strategy for the dissemination of psychological interventions for sD on a large scale."	Usual care bias. Data suggest problem solving in tandem with behavioral activation may benefit subthreshold depression if delivered via the internet.

Johansson 2012 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by a grant from the Swedish Research Council. No COI.	N = 121 participants diagnosed with major depressive disorder (DSM-IV)	Mean age: 44.7±12.1 years; 35 males, 86 females	Standard Group: received 8 self-help chapters (behavioral activation, cognitive restructuring, sleep management, general health advice, and relapse prevention) for 10 weeks (n=40) vs Tailor Group: received 25 chapters (material on depression, panic, social anxiety, stress management, problem solving strategies, mindfulness, etc.) for 10 weeks (n=39) Active Control: received online access	6 months	Effect size for BDI-II was 0.23 comparing tailor versus standard group and 0.84 comparing tailor and standard versus control group ($p<0.001$). Subgroup analyses suggests an improvement favoring tailor group over standard group.	"This study shows that tailored Internet-based treatment for depression is effective and that addressing comorbidity by tailoring may be one way of making guided self-help treatments more effective than standardized approaches in the treatment of more severe depression."	Data suggest both treatment groups led to improvement in depression but subgroup analysis showed the tailored group was best for those with higher levels of depression.

						to a discussion group about depression and were encouraged to participate for 10 weeks (n=42)				
Noguchi 2017 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the RIETI, Japan.	N = 974 participants with symptoms of at least mild depression via Center for Epidemiological Studies Depression scale score ≥ 16 and Patient Health Quesitonnaire-9 score ≥ 5	Mean age: 43.7 years; 486 males, 488 females	Internet-based cognitive behavioral therapy (iCBT), sent emails every day for 5 weeks to encourage participants to access website for exercises (n=326) vs. Simplified emotion-focused mindfulness (sEFM), sent emails every day for 5 weeks to encourage participants to access website for exercises (n=323) vs. Waiting list	Follow-up at 6 and 12 weeks	Decreased Center for Epidemiological Studies Depression scale (CES-D) from baseline to post-intervention (t=3.97, p<0.001). Mixed-effects model analysis at post-intervention showed non-significant intervention effects for CES-D (95% CI [-2.58, 0.02], p=0.05).	"Although both iCBT and sEFM have the potential to temporarily reduce depressive symptoms, substantial improvements are required to enhance and maintain their effects."	Waitlist control bias. Data suggest both interventional groups temporarily improved depressive symptoms but at 6 weeks there was no significant differences in any of the 3 groups suggesting ongoing intervention is required to maintain gains.

						control (n=325)				
Christensen 2004 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the National Health and Medical Research Council Australia programme grant to the Centre for Mental Health Research, Australian National University.	N = 525 participants with depressive symptoms, diagnostic criteria not described	Mean age: 36.43 years; 150 males, 375 females	BluePages - educational website about depression, contacted weekly to guide usage of website (n=166) vs. MoodGYM – Cognitive Behavior Therapy website, contacted weekly to guide usage of website, also included 5 interactive modules (n=182) vs. Control intervention (n=178)	Follow-up at 6 weeks after baseline assessment	Significantly decreased Center for Epidemiological Studies depression scale scores for MoodGYM (mean difference: 3.2, $p<0.05$) and BluePages (2.9, $p<0.05$) compared to control. No statistical difference between BluePages and MoodGYM (-0.3, $p>0.05$)	"Both cognitive behaviour therapy and psychoeducation delivered via the internet are effective in reducing symptoms of depression."	Data suggest both cognitive behavioral therapy (Mood GYM) and psychoeducation (Blue Pages) decreased depression symptoms compared to control.
Moritz 2012 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. No mention of sponsorship.	N = 105 with depression, diagnostic criteria	Mean age: 38.57 years; 45 males,	Deprexis – online program available for 8 weeks, encompasses ten content	Follow-up at 4 and 8 weeks	Beck Depression Inventory (BDI) total scores at post-treatment: Waitlist =	"The results of this trial suggest that online treatment can be beneficial for people with depression, particularly for those	Waitlist control bias. Data suggest internet-based therapy, in this case, Deprexis may benefit those with

				not specified	165 females	modules with evidence-based CBT, with each lasting between 10-60 minutes (n=105) vs. Delayed-treatment (waitlist group) – program access 8 weeks after post-survey (n=105)		25.67, Deprexis = 20.51 (Intention to treat analysis, between group difference pre-post ANCOVA: p = 0.03, d = 0.36) (Per protocol between-group difference pre-post ANCOVA: F(1,167) = 5.51, p = 0.02, d = 0.36)	with moderate symptoms."	moderate depression symptoms.
Kessler 2009 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the BUPA Foundation.	N = 297 participants with Beck depression inventory (BDI) score of ≥ 14 and confirmed depression diagnosis via ICD-10	Mean age: 34.95 years; 95 males, 202 females	Online Cognitive Behavioral Therapy (CBT) – with therapist online in real time, ten 55-minute sessions, completed within 16 weeks, along with usual care (n=149) vs. Waiting List – placed on waiting list	Follow-up at 4 and 8 months	BDI scores and adjusted odds ratio at 4 months: CBT – 113, Waiting-list – 97 (OR=-7.1, p<0.0001). BDI scores and adjusted odds ratio at 8 months: CBT – 109, Waiting-list – 101 (OR=-6.2, p=0.0002).	"CBT seems to be effective when delivered online in real time by a therapist, with benefits maintained over 8 months. This method of delivery could broaden access to CBT."	IPCRESS study. Waitlist control bias. Data suggest therapist delivered internet CBT appears to be effective and gains maintained at 8 months.

						for 8-months, along with usual care (n=148)				
Button 2012 (score= N/A)	Computer-based Cognitive Behavioral Therapy	Secondary analysis of Kessler 2009	No COI. Sponsored by the BUPA Foundation.	N = 297 participants with Beck depression inventory (BDI) score of ≥ 14 and confirmed depression diagnosis via ICD-10	Mean age: 34.95 years; 95 males, 202 females	Online Cognitive Behavioral Therapy (CBT) – with therapist online in real time, ten 55-minute sessions, completed within 16 weeks, along with usual care (n=149) vs. Waiting List – placed on waiting list for 8-months, along with usual care (n=148)	Follow-up at 4 and 8 months	There was an interaction between marital status and treatment (p = 0.046), between baseline severity and intervention (interaction coefficient = -8.0, 95% CI (-14.7, -1.2), and week interaction between life stressors within the past 6 months and intervention (p=0.056)	"Secondary analyses of trials comparing two or more treatments allow factors that may moderate treatment response to be distinguished from more general prognostic indicators, although caution is needed in interpreting such exploratory analyses."	Data suggest online CBT more likely to benefit more severely depressed patients and those separated, widowed and divorced. Education, age or depression history were not found to be associated with treatment response.
Terides 2018 (score= 4.5)	Computer-based Cognitive Behavioral Therapy	RCT	Titov and Dear are developers of the Wellbeing Course and funded by the	N = 148 participants seeking treatment for anxiety, depression, or	Mean age: 44.67 years; 25 males, 113 females, 2 other.	Online Cognitive Behavioral Therapy (CBT) – Wellbeing Course, 8-week program with 5 lessons	Follow-up at 3 months	Mixed models analyses showed significant time by group interaction for Patient Health Questionnaire-9 (F1, 234 =	"Although skills usage and symptom outcomes were assessed concurrently, these findings support the notion that iCBT increases the frequency of skills	Study not blinded as the allocation was revealed pre-intervention. Waitlist control bias. Data suggest iCBT improved depression via symptom reduction and

			Australian Government to develop and provide a free national internet and telephone-delivered treatment service, the Mind Spot Clinic. Sponsored by the eCentreClinic, Macquarie University.	both, Generalized Anxiety Disorder 7-Item score ≥ 5 or Patient Health Questionnaire 9-Item score ≥ 5, confirmed diagnosis via Mini International Neuropsychiatric Interview (MINI) version 5		(n = 65) vs. Waitlist control group, offered Wellbeing course after 8 weeks (n = 75)		6.23, $p < 0.05$), the Generalized Anxiety Disorder 7-Item Scale ($F1, 221 = 12.24$, $p < 0.01$), and the Satisfaction With Life Scale ($F1, 206 = 5.67$, $p < 0.05$)	usage behaviours and suggest that this may be an important mechanism of change."	increased overall satisfaction with life.
Imamura 2014 (score= 4.0)	Cognitive Behavioral Therapy	RCT	Sponsored by a Grant-in-Aid for Scientific Research.	N = 1790 workers who were not diagnos	Mean age: 37.6 years; 639 males,	Internet CBT program (iCBT): 6 weekly lessons, training on	Follow up at 3 and 6 months	There was a significant intervention effect on BDI-II with the iCBT program	"The present study first demonstrated that a computerized cognitive behavior therapy delivered via the Internet was	Data suggest iCBT better than control for improving symptoms of depression

			COI: One or more authors are employed at Chugai Pharmaceutical Company and Medical Care Toranomon, received lecture fees, royalties, consultancy fees, or on the advisory board.	ed with MDD in the past month under the WHO-Composite International Diagnostic Interview version 3.0	123 females.	stress management skills, self-monitoring skills, and more, given 10 weeks to complete (n=381) vs. Received 500 word email message once a month that had useful information on stress management, access to an internal employee assistance program service and an e-learning program (n=381)		(t=-1.99, P<0.05) with small effect sizes (Cohen's d: 20.16, 95% Confidence Interval: 20.32 to 0.00, at six-month follow-up).	effective in improving depression in the general working population."	
Imamura 2015 (score= N/A)	Cognitive Behavioral Therapy	12 month follow up of Imamura 2014	Sponsored by a Grant-in-Aid for scientific research and the Grant-in-Aid for	N = 1790 workers who were not diagnosed with MDD in the past	Mean age: 37.6 years; 639 males, 123 females	Internet CBT program (iCBT): 6 weekly lessons, training on stress management skills, self-	Follow up at 3, 6 and 12 months	At 12 months, the intervention group has a significantly lower incidence of MDE than control group (Log-rank $\chi 2 = 7.04$, $p < 0.01$).	"The present study demonstrates that an iCBT program is effective in preventing MDE in the working population. However, it should be noted that MDE was	Data suggest iCBT may be beneficial for the prevention of MDE in the workplace

			Young Scientists. COI: One or more authors are employed at Chugai Pharmaceutical Company and Medical Care Toranomon, received lecture fees, royalties, consultancy fees, or on the advisory board.	month under the WHO-Composite International Diagnostic Interview version 3.0		monitoring skills, and more, given 10 weeks to complete (n=381) vs. Received 500 word email message once a month that had useful information on stress management, access to an internal employee assistance program service and an e-learning program (n=381)			measured by self-report, while the CIDI can measure the episodes more strictly following DSM-IV criteria."	
Titov 2015 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the National Priority Driven Research Program Grant from beyondblu	N = 52 with symptoms of depression, diagnosis criteria not used	Mean age: 65.31 years; 14 females, 38	Online Cognitive Behavioral Therapy – Managing Your Mood Course, 8 week course, five lessons and homework	Follow-up at 3 and 12 months	Statistically lower scores on the Patient Health Questionnaire-9 (d = 2.08, 95% CI [0.61-1.79]) in treatment group	"The results support the potential efficacy and cost-effectiveness of therapist-guided iCBT as a treatment for older adults with symptoms of depression."	Small sample. Waitlist control bias. Data suggest iCBT beneficial for the treatment of depression in older adults and gains were maintained at both 3 months and

			e. Author Dear is supported by the National Health and Medical Research Council (NHMRC) Australian Public Health Fellowship.			assignments (n=29) vs. Waitlist Control Group (n=25)		versus waitlist control		12 months post-intervention.
Buhrman 2015 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the Multidisciplinary Pain Centre at Uppsala University hospital.	N = 52 with chronic pain for over 3 months and problems with depression and anxiety defined by score > 10 on Montgomery Åsberg Depressi	Mean age: 50.69 years; 8 males, 44 females	Online Cognitive Behavioral Therapy, 1 weekly session for 8 weeks (n=28) vs. Waitlist Control (n=24)	Follow-up at 12 months	Significant effect between groups on MADRS-S (F1,49=8.95, p=0.004), favor for online CBT. Significant treatment effect on Pain Disability Index (F149=4.96, p = 0.031), favor for online CBT	"One-year follow-up showed maintenance of improvements. We conclude that an individualized guided internet-delivered treatment based on cognitive-behavior therapy can be effective for persons with chronic pain comorbid emotional distress."	Data suggest at 1 year post intervention gains were maintained in the internet-guided CBT group.

				on Rating Scale (MADRS-S) and depression diagnosis via Primary Care Evaluation of Mental Disorders (PRIME-MD)						
Proudfoot 2003 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	Authors Proudfoot and Gary are minority partners in the commercial exploitation of Beating the Blues and author Goldberg is an occasional	N = 167 with depression, mixed anxiety/ depression, or anxiety disorder via ICD diagnosis codes	Mean age: 44.63 years; 44 males, 123 females	Beating the Blues – computer therapy with nine sessions, followed by eight therapy sessions, each being 50 minutes, taken once weekly, along with treatment as usual (n=89) vs. Treatment as Usual group (n=78)	Follow-up at 1, 3, and 6 months	Beck Depression Inventory – estimated treatment effect shows greater reduction in BDI after Beating the Blues over TAU (95% CI ~ [2-9]). No treatment and visit interaction more treatment and drug interaction	"These results demonstrate that computerized interactive multimedia cognitive-behavioural techniques under minimal clinical supervision can bring about improvements in depression and anxiety, as well as in work and social adjustment, with and without pharmacotherapy and in patients with pre-	Beating the Blues (BtB) Trial. Treatment as usual bias. Data suggest computerized CBT clinically supervised improves depression and anxiety with and without concomitant antidepressant medication.

			consultant to Utrasis plc. Sponsored by the NHS Executive London, Research & Development, Responsive Funding Programme.						treatment illness of durations greater or less than 6 months."	
Proudfoot 2004 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	Authors Proudfoot and Gray are minority partners in the exploitation of Beating the Blues and Goldberg and Shapiro are occasional consultants to	N = 274 participants with anxiety and/or depression with a General Health Questionnaire score of 4+ and Clinical Interview Schedule –	Mean age: 43.51 years; 72 males, 202 females	Beating the Blues – computer therapy with nine sessions, followed by eight therapy sessions, each being 50 minutes, taken once weekly, along with treatment as usual (n=146) vs. Treatment as Usual (n=128)	Follow-up at 2, 3, 5, and 8 months	Beck Depression Inventory scores lower in the computerized CBT group compared to TAU (p=0.0006).	"Computer-delivered CBT is a widely applicable treatment for anxiety and/or depression in general practice."	Beating the Blues (BtB) Trial. Treatment as usual bias. Data suggest computer-delivered CBT may be appropriated for treatment of anxiety or depression in general practice.

			Ultrasis plc. Sponsored by the NHS Executive London Research and Development, Responsive Funding Programme and Ultrasis UK Ltd.	Revised score of 12+						
Preschl 2011 (score= 4.0)	Computer-based Cognitive Behavioral Therapy/ Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the Werner Selo Foundation.	N = 53 participants with Beck Depression Inventory (BDI) scores of 12+	Mean age: 36.7 years; 17 males, 36 females	Internet-based treatment – access to online content of CBT, with assignments lasting 45 minutes, 2 assignments each week, option to text therapist as well (n=25) vs. Face-to-face group – attended hourly sessions once	No follow-up	Correlation analysis show working alliance ratings do not significantly predict BDI residual gain score in internet-based or face-to-face groups.	"Contrary to what might have been expected, the working alliance in the online group was comparable to that in the face-to-face group. However, the results showed no significant relations between the BDI residual gain score and the working alliance ratings in either group."	Data suggest comparable efficacy between online and face-to-face CBT.

						per week of CBT with weekly assignments (n=28). Both groups completed 8 weeks of treatment.				
Newby 2014 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	No mention of sponsorship. Author Newby and Williams supported by two Australian National Health and Medical Research Council Fellowships.	N = 99 with major depressive disorder or generalized anxiety disorder according to DSM-IV criteria	Mean age: 44.0 years; 22 males, 77 females	Internet-delivered CBT (iCBT) – six online lessons with homework assignments, given 10 weeks to complete (n=49) vs. Waitlist Control (WLC) (n=60)	Follow-up at 3 months	Mean Patient Health Questionnaire-9 scores at baseline, mid-treatment post-treatment and at 3 month follow-up – iCBT: 10.39, 7.93, 5.76, 4.05 (within-group comparison: $t(229.84) = 1.31$, $p < 0.001$), WLC: 11.62, 11.24, 10.41 ($t(228.66) = 1.94$, $p = 0.15$). Between-group comparison: $F(1,166.32) = 26.51$ ($p < 0.001$)	"These findings indicate that iCBT is an effective treatment for RNT and positive metacognitive beliefs."	Mixed population of general anxiety disorder (GAD), major depressive disorder (MDD), or mixed GAD/MDD. Data suggest iCBT reduced repetitive negative thinking compared to WLC group and gains were maintained at 3 months.

Richards 2015 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by SilverCloud Health Ltd and Aware Charity, Ireland.	N = 262 with mild to moderate distress, no official depression diagnosis used other than others with Beck Depression Inventory scores of <14 or >29 were excluded	Mean age: 39.86 years; 51 males, 137 females	Computerized CBT (iCBT) – Space from Depression, 7 modules with interactive videos, quizzes, as well as homework (n=133) vs. Waitlist Control (WLC) (n=129)	Follow-up at 3 and 6 months	Beck Depression Inventory-II Scores significantly decreased in iCBT group (95% CI on Effect Size (d) [0.14, 2.45]) but not significant in WLC (-0.78, 1.50). BDI-II scores in iCBT group: 3-months = 11.86, 6-months = 14.91	"The study supports a model for delivering online depression interventions population-wide using trained supporters."	Space from Depression Trial. Waitlist control bias. Data suggest significant improvement in the interventional group using trained supporters and online delivery of CBT.
Mira 2017 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	No COI. Sponsored by the Ministry of Economy and Competitiveness	N = 124 participants with at least 1 stressful event in their lives	Mean age: 35.6 years; 41 males, 83 females	Computerized CBT (iCBT) – Sonreír es Divertido, 8 interactive modules, given 12 weeks to complete	Follow-up at 12 months	Intention-to-treat results: Mean BDI-II scores at pre- and post-treatments, respectively – iCBT: 9.14, 5.03,	"The Internet-based program was effective and well accepted, with and without human support, showing that ICT-based automated support may be useful. It is essential	Data suggest internet-based program appeared to be effective and accepted whether or not there was concomitant human support. Waitlist control bias.

			and the CIBERobn, Institute of Health Carlos III.	and Beck Depression Inventory-II score of 28+		modules (n=36) vs. iCBT with human support (iCBT+HS) – included 2-minute weekly calls to give positive reinforcement or encouragement (n=44) vs. Waitlist Control (WLC) (n=44)		iCBT+HS: 10.91, 6.16, WLC: 9.11, 8.45. Between-group effect size: iCBT vs. iCBT+HS = 0.20 (95% CI [-0.63 – 0.25]), iCBT vs. WLC = 0.50 (-0.49, -0.05), iCBT+HS vs. WLC = 0.34 (-0.76, 0.07)	to continue to study other ICT strategies for providing support."	
Phillips 2014 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the British Occupational Health Research Foundation. Thornicroft supported by a National Institute for Health Research (NIHR) Applied Programm	N = 637 participants with Patient Health Questionnaire-9 score of 2+ on five of the nine items	Mean age: 42.45 years; 296 males, 328 females, 13 were missing gender	MoodGYM – online form of CBT, developed at Australia National University, with five 1-hour modules, usually taken weekly, given 5 weeks to complete all modules, also received 10 minute weekly phone calls (n=318) vs.	Follow-up at 6 and 12 weeks	Mean Work and Social Adjustment Scale (WSAS) scores at baseline, 6 and 12 weeks, respectively – control: 20.0, 16.5, 15.9, MoodGYM: 19.9, 16.0, 15.0 (effect size = -0.470, 95% CI [-1.837, 0.897), p = 0.50)	"This study found no evidence that MoodGYM was superior to informational websites in terms of psychological outcomes or service use, although improvement to subthreshold levels of depression was seen in nearly half the patients in both groups."	Low completion rate. Data suggest Mood GYM, a computerized CBT intervention, is no better than other informational websites.

			e grant awarded to the South London and Maudsley NHS Foundation Trust and in relation to the NIHR Specialist Mental Health Biomedical Research Centre at the Institute of Psychiatry, King's College London and the South London and Maudsley NHS Foundation Trust.			Control group (n=319)				

Høifødt 2013 (score= 4.0)	Computer-based Cognitive Behavioral Therapy	RCT	Sponsored by the Research Council of Norway. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 106 participants with mild to moderate depressive symptoms via Beck Depression Inventory-II scores between 14-29	Mean age: 36.1 years; 29 males, 77 females	Waitlist control – received treatment as usual (n=54) vs. Guided self-help intervention – internet-delivered iCBT (MoodGYM), including 5 modules lasting 45-60 minutes, along with face-to-face therapist support and tailored emails between sessions (n=52)	Follow-up at 6 months	Beck Depression Inventory-II mean scores revealed significant time x treatment group interaction ($F1,244.83 = 9.55$, $p = 0.002$, $d = 0.65$)	"The intervention could potentially be used in a stepped-care approach, but remains to be tested in regular primary health care."	Waitlist control bias. MOODGYM with brief therapist support may decrease depressive symptoms and improve anxiety.
Smith 2017 (score= 4.0)	Bibliotherapy/Computer-assisted Cognitive Behavioral Therapy	RCT	Sponsored by the Australian National Health and Medical Research Council. No mention of COI.	N = 270 participants with score 5-23 on Patient Health Questionnaire 9-item scale (PHQ-9)	Mean age: 39.91 years; 45 males, 225 females	iCBT – sadness program, 6 online lessons over 12 week period, completion of one lesson every 1-2 weeks, illustrated story about	Follow-up at 3 months	PHQ-9 score within-group effect sizes for baseline to 3 month follow-up and 95% confidence intervals: iCBT – 1.51 (1.00-2.00), bCBT – 1.09 (0.70-1.48), bMED –	"Self-help based interventions could be beneficial in treating depression, however vigilance needs to be applied when selecting from the range of materials available."	Waitlist control bias. Data suggest all 3 interventional groups improved with some relapse in the bMED group at 3 months.

				and met criteria on the Mini International Neuropsychiatric Interview (MINI) for DSM-IV MDD criteria		character who overcomes depression with CBT skills (n=61) vs. bCBT – Beating the Blues, self-help book, 12 chapters of CBT skills to be read over 12 weeks (n=77) vs. bMED – Silence Your Mind, self-help book about meditating with instructional DVD, 13 chapters to be completed over 12 weeks (n=64) vs. Wait list control – 12 week waiting period (n=68)		1.55 (1.10-2.00), WLC – 0.50 (0.11-0.89). Between-group effect sizes: iCBT vs. WLC = 0.86 ($p < 0.001$), bCBT vs. WLC ($p < 0.001$), bMED vs. WLC ($p < 0.001$), iCBT vs. bCBT ($p > 0.05$), iCBT vs. bMED ($p > 0.05$), bCBT vs. bMED ($p > 0.05$)		
Calkins 2015 (score= 4.0)	Computer-based Cognitive	RCT	No mention of COI or	N = 48 participant with Beck	Mean age: 35.73 years;	Cognitive Control Training (CCT) – three	No follow-up	Significant large effect sizes found with BDI-II (d	"Our results suggest that CCT is effective in altering depressed mood, although it	Data suggest CCT improved depressed mood.

	Behavioral Therapy		sponsorship.	Depression Inventory-II scores ≥17 and <35	22 males, 26 females	60-minute sessions of modified Paced Auditory Serial Addition Task (PASAT) and Attention Control Intervention (ACI) exercises via computer (n=24) vs. Peripheral Vision Training (PVT) – 3 sessions lasting 25-30 minutes (n=24)		= 0.73, p < .05), suggesting CCT more effective than PVT	may be specific to select mood dimensions."	
de Graaf 2009 (score= 3.5)										Treatment as usual bias. Data suggest lack of efficacy of iCBT as not superior to treatment as usual.37
de Graaf 2011		One-year follo								Data suggest unsupported iCBT

37 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score= N/A)		w-up of de Graaf 2009.								not better than treatment as usual.
Anders son 2005 (score= 3.5)										Waitlist control bias. Data suggest iCBT plus minimal therapist contact plus discussion group participation resulted in improved depressive symptoms which were largely maintained at 6 months compared to controls.38
Holländ dare 2011 (score= 3.5)										Data suggest a trend towards higher remission in internet CBT treated individuals.
Holländ dare 2013 (score= N/A)		2 year follo w-up of Holländare 2011								2-year follow-up of Holländare 2011. Data suggest at 2 years, iCBT was better than controls via relapse rates (13.7% vs. 60.9%) and remission was higher in iCBT group.

38 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Spek 2007 (score= 3.5)										Waitlist control bias. Data suggest iCBT may be as effective as group CBT for subthreshold depression in those 50+ years old.
Spek 2008 (score= N/A)		1 year follow-up of Spek 2007								1-year follow-up of Spek 2007. Data suggest individuals 50 years and older with subthreshold depression likely still benefit from iCBT one year later.
Clarke 2009 (score= 3.5)										Treatment as usual bias. Data suggest trend towards benefit from intervention.39
Clarke 2002 (score= 3.5)										Overcoming Depression on the Internet (ODIN) trial. Usual care bias. Data suggest lack of efficacy.
Clarke 2005 (score= 3.5)										Usual care bias. Both treatment groups showed some benefit of those using the ODIN site.

39 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Farrer 2011 (score= 3.5)										Data suggest iCBT effective both with and without telephone tracking.
Christensen 2006 (score= 3.5)										Data suggest brief CBT not as effective as longer CBT but with increasing treatment duration, dropout rates escalate.
Wright 2005 (score= 3.5)										Waitlist control bias. Small sample size. Data suggest computer-assisted CBT may increase access while decreasing costs.
Dear 2013 (score= 3.5)										Data suggest iCBT may benefit those with depression, anxiety, and chronic pain.
Wagner 2014 (score= 3.5)										Data suggest comparable efficacy between iCBT and face-to-face CBT but 3 months post intervention gains found only in iCBT group via continued

										symptom reduction.40
McBride 2006 (score= 3.5)										Data suggest in individuals with higher attachment avoidance scores, CBT was better than interpersonal psychotherapy for reducing depression symptom severity and predictive of less remission.
Luty 2007 (score= 3.5)										Data suggest comparable efficacy but CBT best in severely depressed patients.
Ekeblad 2016 (score= 3.0)										Data suggest comparable efficacy between interpersonal psychotherapy and CBT but CBT group had a high dropout rate.
Warmerdam 2008 (score= 3.0)										Waitlist control bias. Data suggest both internet delivered CBT and PST were effective in

40 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										decreasing symptoms of depression but the effect of PST occurred faster.
Warmerdam 2010 (score= N/A)		Post-hoc analysis of Warmerdam 2008								Data suggest no evidence that the 2 online treatments work with different mechanisms.41
Eriksson 2017 (score= 3.0)										Treatment as usual bias. Data suggest iCBT as effective as treatment as usual at 6 months.
Hardy 1995 (score= 2.5)										Data suggest CBT was initially rated higher than interpersonal psychotherapy pre-treatment but after randomization the treatments were similar in ratings.
Gerhards 2010										Treatment as usual bias. Data suggest CBT was best but all treatments had

41 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score= 2.5)										improvement but low adherence.
Barkham 1999 (score= 2.0)										Data suggest comparable efficacy initially but at 1 year, CBT was superior to psychodynamic-interpersonal (PI) therapy.
Hadjistavropoulos 2017 (score= 2.0)										Data suggest at 3 months, optional therapist support in addition to iCBT may be effective.
Kelders 2015 (score= 2.0)										Significant dropouts. Data suggest automated internet delivered support may be as effective as human support for mild to moderate depression.42
Acceptance and Commitment Therapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:

42 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Carlbring 2013 (score= 5.0)	Acceptance and Commitment Therapy (ACT)	RCT	Sponsored in part by grants from the Swedish Science Foundation, the Swedish Council for Social Research and the Swedish Council for Work Life Research. COI: two of the authors are employed by Psykology partners, which develops and sells products related to this research.	N = 80 patients with Montgomery Asberg Depression Rating Scale (MADRS-S) score in the range of 15-30	Mean age: 44.4 years; 14 males, 66 females.	"Depressionshjülphen" program – 7 sessions of acceptance and commitment therapy (ACT), access to internet-therapist every week that was limited to ~15 min (n=40) vs Receiving no treatment until after post treatment assessment (n=40)	Follow up at 8 weeks and 3 months	25% reached remission (BDI score less than or equal to 10) in the treated group and 5% in the control group. Mean number of modules finished was 5.1	"We conclude that there is initial evidence that BA with components of ACT can be effective in reducing symptoms of depression."	Waitlist control bias, short follow-up time internet-based BA may reduce depressive symptoms.

Kohtala 2013 (score= 4.5)	Acceptance and Commitment Therapy (ACT)	RCT	No mention of sponsorship or COI.	N = 60 subjects who had subjective depressive symptoms, no diagnosis necessary, no diagnostic criteria used	Mean age: 46.2 years; 12 males, 45 females.	Four 1-hour sessions of acceptance and commitment therapy (ACT) (n=28) vs waiting list control (WLC) (n=29)	Follow up at 6 months	The ACT group's level of depression lowered by 47%, compared to the WLC group (4%). From pre to post follow up, psychological flexibility was t(56)=−4.91, p = .000, meanwhile pre to follow-up was t(56)=−6.56, p = .000. At post treatment, 30% recovered, 14% improved, 33% remained unchanged and 2% deteriorated when regarding the subject's self-reported depressive mood based on the BDI.	"The results support the brief ACT-based intervention for sub-clinical depressive symptoms when treatment was conducted by briefly trained psychology students. It also contributes to the growing body of evidence on brief ACT-based treatments and inexperienced therapists."	Waitlist control bias. Data suggest individuals with sub-clinical depressive symptoms who participated in a 4-session ACT program showed significant improvement in depressive mood and symptoms.
Folke 2012 (score= 4.5)	Acceptance and Commitment	RCT	No mention of sponsorship or COI.	N = 35 subjects with a diagnosis of	Mean age: 46.3 years; 4 males,	Contact with physician for different treatment options or	Follow up at 18 months	ACT showed significant improvement (mean improvement=	"The results indicate that ACT is a promising treatment for depression."	Small sample. Data suggest no observed benefit in ACT for depressed patients returning to work

	Therapy (ACT)			unipolar depressive disorder as defined by DMS-4	30 females.	renewed certificate for sick leave (n=16) vs Acceptance and Commitment Therapy (ACT) – 1 60-90 minute session, followed by 5 group 120-180 minute sessions (n=18)		−4.78, SE = 1.81, t(48.09) =−2.64, p = .011, effect size = 0.71) and from pretreatment to follow up (mean improvement= 5.27, SE=2.73, t(29.72)=−1.93, p=.063, effect size=0.77). Controls had non-significant decrease from pretreatment to post treatment ([mean deterioration=2 .75, SE = 1.95, t(48.54) = 1.41, p = .165) and pretreatment to follow up (mean improvement =−1.62, SE = 2.84, t(29.32) =−.57, p = .57)		and terminating long-term sick leave compared to control.
Lang 2017 (score= 4.5)	Acceptan ce and Commit ment	RCT	No mention of	N = 160 veterans with anxiety	Mean age: 34 years; 128	Acceptance and Commitment Therapy	Follo w up at 3, 6, 9,	No differences between two groups according to	"ACT's efficacy in this group was modest and generally did not differ from	Data suggest comparable efficacy between ACT and PCT.

	Therapy (ACT)/Psychotherapy		sponsorship or COI	or depressive disorder according to DMS-4	males, 32 females	(ACT) – twelve 1-hr sessions (n=80) vs Present-centered Therapy (PCT) – twelve 1-hr sessions (n=80)	and 12 months	MRMM analyses on BSI-18 GSI (between groups effect size = 0.16, 95% CI [0.23, 0.56]), SDS (between groups effect size = 0.33, 95% CI [0.07, 0.72]), or AUDIT (between-groups effect size = 0.24, 95% CI [0.21, 0.68]).	that for PCT. Additional work is needed to understand the reasons that ACT did not perform as well as predicted in this veteran sample"	
Lappalainen 2015 (score= 4.0)	Acceptance and Commitment Therapy (ACT)	RCT	No sponsorship or COI.	N = 39 subjects who fulfill at least five of the DSM-IV-TR criteria for major depressive episode.	Mean age: 51.9 years; 11 males, 28 females	iACT group: used the "Good Life Compass" online program for 6 weeks (n=19) vs WLC group: wait list control, received no treatment (n=20)	Follow up at month 12	There was a significant effect in the iACT group regarding psychological and physiological symptoms (g = .60), psychological flexibility (g = .67), mindfulness skills (g = .53), frequency of	"We conclude that an ACT-based guided Internet-delivered treatment with minimal contact can be effective for people with depressive symptoms."	Waitlist control bias. Data suggest internet delivered ACT with minimal contact may be effective for individuals with depressive symptoms.

								automatic thoughts (g = .57) and thought suppression (g = .53).		
Bohlmeijer 2011 (score= 4.0)	Acceptance and Commitment Therapy (ACT)	RCT	Sponsored by Innovation Fund Health Insurers. No mention of COI.	N = 140 subjects with mild to moderate depressive symptomatology according to the CES-D scale	Mean age: 49 years; 17 males, 76 females.	Acceptance and Commitment Therapy (ACT) intervention: eight two-hour weekly sessions that is based on the 6 core processes of ACT. Session 1 was an exploration of their values. Session 2 and 3 was reflection on avoidance and control strategies. Session 4, 5, and 6 was how deal with experiences. Session 7 and 8 was becoming aware of	Follow up at 3 months	ACT had a significantly decrease in depressive symptomatology (Cohen's d=60). There was also a decrease in anxiety and fatigue in the ACT group.	"These findings suggest that an early intervention based on ACT, aimed at increasing acceptance, is effective in reducing depressive symptomatology."	Waitlist control bias. Mostly female participants. Data suggest early intervention. ACT improved depression anxiety and fatigue and these benefits were maintained at 3 months.

						values and decisions (n=49) vs waiting list: received no intervention (n=44)				
Fledderus 2012 (score= 4.0)	Acceptance and Commitment Therapy (ACT)	RCT	Sponsored by the Netherlands Foundation for Mental Health. No COI.	N = 625 subjects with mild to moderate depressive symptoms of <39 on the CES-D.	Mean age: 42 years; 114 males, 262 females	ACT-E: Self-help book and standardized emails, able to ask questions (n=125) vs ACT-M: Self-help book and standardized email with questions on progress (n=125) vs Self-help book but no email support (n=126). Self-help book called 'Living to the full' – nine modules, 1 module per week	Follow up at 3 months	In the ACT-E group, 34% reached a clinically significant change on the CES-D, meanwhile waitlist was 6% [OR 8.60, 95% confidence interval (CI) 3.69–20.08, p<0.001, NNT=3.57]. Moreover, ACT-M was 39% (OR 10.96, 95% CI 4.72–25.46, p<0.001, NNT=2.98). ACT-E and ACT-M had significant reductions in depression, anxiety,	"The ACT-based self-help programme with minimal email support is effective for people with mild to moderate depressive symptomatology."	Waitlist control bias. Data suggest self-help ACT may help mild to moderate depressed individuals

								fatigue, experiential avoidance and improvements in positive mental health when compared with the waitlist (effect sizes Cohen's d=0.51–1.00).		
Forman 2007 (score= 4.0)	Acceptance and Commitment Therapy (ACT)/Cognitive Behavioral Thearpy	RCT	No mention of sponsorship or COI.	N = 101 subjects with Beck Anxiety Inventory score > 9 and Beck Depression Inventory-II score > 9, symptoms meeting DSM-IV-TR criteria	Mean age: 27.9 years; 8 males, 101 females.	Cognitive Therapy (CT) group: received traditional CT. Average of 15.27 sessions (n=44) vs ACT group: Received traditional ACT. Average of 15.60 sessions. (n=55). Only 99 of the 101 randomized were included in the analysis. All subjects received semi-structured interviews using DSM-	No follow up	For CT, mean scores for Beck Depression Inventory (BDI) was 18.92, Beck Anxiety Inventory (BAI) was 13.08, Global Assessment of Functioning (GAF) was 64.22, Clinical Global Impression (CGI) was 3.31, Quality of Life Inventory (QOLI) was 0.49, and Subject Life Satisfaction Scale (SLS)	"The results suggest that ACT is a viable and disseminable treatment, the effectiveness of which appears equivalent to that of CT, even as its mechanisms appear to be distinct."	High attrition rates in both groups (CT=42.4%, ACT=33.3%). Data suggest comparable efficacy between CT and ACT.

						IV-TR and completed pre and post questionnaires.		was 11.21. For ACT, mean scores for BDI was 18.96, BAI was 13.22, GAF was 64.96, CGI was 3.23, QOLI was 0.73, and SLS was 12.75.		
Forman 2012 (score= N/A)	Acceptance and Commitment Therapy (ACT)/Cognitive Behavioral Thearpy	Post-hoc long term follow up	No mention of sponsorship or COI.	N = 132 subjects with Beck Anxiety Inventory score > 9 and Beck Depression Inventory-II score > 9, symptoms meeting DSM-IV-TR criteria	Mean age: 26.7 years; 27 males, 105 females	CT group: received CT (automatic thoughts, core beliefs, and schemas, identification of cognitive distortions, cognitive disputation, and cognitive restructuring). Average of 16.37 sessions (n=63) vs ACT group: received ACT (experiential acceptance, mindfulness training, clarification of personal values, and	Follow up around 14-20 months	According to the BDI, 81.8% of CT patients recovered, but only 60.7% in ACT patients. BAI was 72.7% in CT and 56% in ACT. OQ was 46.4% in CT and 22.6% in ACT. QOLI was 37.8% in CT and 22.9% in ACT.	"The results reveal that the two treatments are equally effective in the short term: both were successful in maintaining improvements in depression, anxiety, and general functioning. Yet, statistical comparisons of long-term outcomes suggest that CT has a slight advantage over ACT in the long-term maintenance of gains, at least with respect to depressive symptoms and general functioning."	Data suggest long term results appear to favor CT over ACT for treatment of anxiety and depression

						willingness to experience internal distress for the sake of living consistently with one's values). Average of 18.10 sessions. (n=69)				
Dindo 2012 (score= 3.5)	Acceptance and Commitment Therapy (ACT)									Waitlist control/ treatment as usual bias. Data suggest at 3 months there were improvement seen in the ACT-ED group.43
Pots 2016 (score= 3.5)	Acceptance and Commitment Therapy (ACT)									Waitlist control bias. Data suggest decreases in symptoms of depression greatest in web-based intervention
Interpersonal Therapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:

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Souza 2016 (score= 6.5)	Interpersonal Psychotherapy (IPT)	RCT	No mention of sponsorship or COI.	N=40 adult patients with MDD (DSM-IV)	Mean age: 49.2 years; 6 males, 34 females	IPT+TAU: received interpersonal psychotherapy consisting of 16 individual 40-minute weekly sessions for 16-19 weeks (n=17) vs TAU: (n=23)	8, 12, 19, 24 weeks	HDRS scores improved by 4.57 points in TAU (95% CI 0.59-8.55) compared to 5.86 points in IPT+TAU group (95% CI 1.50-10.22).	"Both treatments lead to equal improvements in depressive symptoms. We found no evidence to support adding IPT to pharmacotherapy in patients with TRD."	TAU bias, small sample. Data suggest comparable efficacy with no added benefit of adding IPT to TAU.
Schramm 2011 (score= 6.0)	Interpersonal Psychotherapy (IPT)	RCT	Sponsored by the Research Committee of the University Medical Centre Freiburg. No COI.	N=30 patients with current episode of chronic MDD or MDD superimposed on a pre-existing dysthymic disorder	Mean age: 40.2±11.5 years; 14 males, 16 females	CBASP: received cognitive behavioral analysis system of psychotherapy (CBASP) consisting of behavioral, cognitive, and interpersonal strategies to teach interpersonal problem solving skills (2 weekly 50-min sessions for first 6 weeks and weekly sessions	12 months	Mean HRSD-24 scores dropped from 23 to 11.21 in CBASP group and 23.27 to 18.87 in the IPT group. CBASP group showed better improvement in depressive symptoms (T[13]=3.53, p=.004) and a similar observation was made for BDI scores (CBASP: T[13]=5.01, p<.001; IPT:	"In summary, while limited by some factors, the results of this study suggest that with intensive CBASP early-onset chronically depressed patients have a good chance of remission. However, to maintain the effects a longer course of therapy might be necessary."	Small sample pilot study. Initially there were higher remission rates in CBASP (57%) versus IPT (20%) but at 1 year, post treatment no differences were found between groups.

						following until 8 weeks then 1 extra session per week for 2 more weeks—max 24 sessions) (n=14) vs IPT: received interpersonal psychotherapy focusing on interpersonal and psychosocial problem areas (2 weekly 50-min sessions for first 6 weeks and weekly sessions following until 8 weeks then 1 extra session per week for 2 more weeks—max 24 sessions) (n=15)		T[14]=2.34, p=.034).		
Weitz 2014 (score= 5.5)	Interpersonal Psychotherapy (IPT)/CB	RCT	No sponsorship or COI.	N=239 participants with current major	Mean age: 35 years; 72 males,	CBT Group: received cognitive behavioral therapy (no	6, 12, 18 months	Changes in HRSD scores showed an effect size of 0.43 for CBT	"This study demonstrates the specific effectiveness of IPT and medications in	Data suggest medications to treat depression such as imipramine and IPT

	T/Imipramine			depressive episode (RDC criteria)	167 females	specific duration or protocol mentioned) (n=33) vs IPT Group: receiving interpersonal psychotherapy treatments consisting of 50- min sessions (n=38) vs Imipramine+CM Group: received clinical management consisting of medication management and 150-300 mg of imipramine (n=37) vs Placebo+CM Group: received clinical management consisting of medication management and placebo		Group, 0.56 for IPT Group, 0.55 for Imipramine Group, and 0.34 for the placebo group. IPT group and imipramine group showed the greatest reduction in suicide symptoms compared to placebo (imipramine vs placebo: b=0.47, p<0.05; IPT vs placebo: b=0.41, p<0.05).	reducing suicidal ideation (relative to placebo), albeit largely as a consequence of their more general effects on depression."	may reduce suicidal ideation.

						medication (50-60min sessions) (n=40)				
Zobel 2011 (score= 5.5)	Interpersonal Psychotherapy (IPT)	RCT	Sponsored by grant from the German Research Society. COI: Calker has received honoraria for lecturing from AstraZeneca, Pfizer, Eli Lilly, Merz, Sanofi, Organon, Neuraxpharm, Wyeth, and Squibb have served in an Advisory Board of Bristol-	N=124 in-patients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 41.9 years; 16 males, 81 females	IPT Group: received interpersonal psychotherapy plus pharmacotherapy (15 individual sessions and 8 group sessions) 3x weekly over 5 weeks (IPT) (n=50) vs Clinical Management Group: received 3 weekly sessions of psychoeducative, supportive, and empathic intervention of 20-25 minutes of clinical management(n =47) Both groups received pharmacothera	5 weeks, 3, 12, 75 months	HAM-D scores were improved from 4.56 to 4.36 in the IPT group compared to 7.81 to 8.40 in the clinical management group (p=0.038).	"In the long-term, a combination of psycho- and pharmacotherapy was superior in terms of sustained remission rates to standard psychiatric treatment. Early trauma should be assessed routinely in depressed patients."	Standard care bias. Data suggest that at 5 years, combination psychotherapy and pharmacotherapy were superior to the clinical management plus medication (standard care) group for sustained remission rates.

			Myers Squibb.			py of sertraline (switched to amitriptyline or amitriptyline-N-oxide if nonresponse 50-250 mg/day)				
Reynolds 1999 (score=5.0)	Interpersonal Psychotherapy (IPT)/Nortriptyline	RCT	Sponsored by National Institute of Mental Health. No mention of COI.	N=180 patients with recurrent non-psychotic unipolar major depression (MINI, Hamilton)	Mean age: 67.6±5.8 years; 45 males, 135 females	Nortriptyline+IPT Group: received 80-120 ng/mL nortriptyline hydrochloride and biweekly interpersonal psychotherapy (n=25) vs Nortriptyline+MC Group: received medication clinic consisting of 30 minute visits by a nonphysician clinician and a psychiatrist as well as 80-120 ng/mL of nortriptyline hydrochloride	1, 2, 3 years	The Nortriptyline+IPT group, Nortriptyline+MC group, and the IPT+Placebo group were better at preventing recurrence of depression compared to placebo ($p<.001$, $p<.001$, $p=.03$; respectively.)	"In geriatric patients with recurrent major depression, maintenance treatment with nortriptyline or IPT is superior to placebo in preventing or delaying recurrence. Combined treatment using both appears to be the optimal clinical strategy in preserving recovery."	Data suggest the 3 active treatment arms showed decreased time to recurrence versus placebo. Combined treatment of nortriptyline and IPT showed the lowest recurrence rates at 3 years.

						(n=28) vs Placebo+IPT: received placebo medication and biweekly interpersonal psychotherapy (n=25) vs Placebo+MC: received medication clinic consisting of 30 minute visits by a nonphysician clinician and a psychiatrist as well as placebo medication (n=29)				
Lemmens 2015 (score= 5.0)	Interpersonal Psychotherapy (IPT)/Cognitive Behavioral Thearpy	RCT	Sponsored by the research institute of Experimental Psychopathology (EPP), the Netherlands, and the Academic	N=182 adult outpatients with a primary diagnosis of MDD (DSM-IV)	Mean age: 40.5 years; 66 males, 116 females	CT Group: received 16–20 individual sessions of 45 min cognitive therapy (n=76) vs IPT Group: received 16–20 individual sessions of	3, 7, 9, 12 months	Improvement in depression severity was greater in both CT and IPT group compared to waitlist ($p<0.02$). IPT and CT group showed reduction in	"Within our power and time ranges, CT and IPT appeared not to differ in the treatment of depression in the acute phase and beyond."	Waitlist control bias. Data suggest comparable efficacy.

			Community Mental Health Centre RIAGG. No COI.			45 min of interpersonal psychotherapy (n=75) vs Waitlist Group: received waitlist control (n=31)		BDI-II from 28.4 to 12.6 in the CT group compared to 31.2 to 17.2 in the IPT group.		
Lemmens 2018 (score= 4.5)	Interpersonal Psychotherapy/CBT	RCT	Sponsored by the research institute of Experimental Psychopathology (EPP) and the Academic Community Mental Health Centre (Netherlands). No COI.	N=134 adult patients with a diagnosis of MDD (DSM-IV)	Mean age: 40.5 years; 66 males, 116 females	CPT Group: received 16–20 individual sessions of 45 min cognitive therapy (n=69) vs IPT Group: received 16–20 individual sessions of 45 min of interpersonal psychotherapy (n=65)	7, 8, 9, 10, 11, 12, 24 months	Mean BDI-II scores decreased from 13.8 to 11.7 in the CT group compared to 16.0 to 14.9 in the IPT group. Reduction in depressive symptoms was achieved in 65.2% of CT group compared to 61.5% of IPT group (p=0.66).	"Patients who responded to IPT were no more likely to relapse following treatment termination than patients who responded to CT. Given that CT appears to have a prophylactic effect following successful treatment, our findings suggest that IPT might have a prophylactic effect as well."	Data suggest comparable outcomes between CT and IPT with similar relapse rates.
Reynolds 2010 (score= 4.0)	Interpersonal Psychotherapy IPT)	RCT	Sponsored by the National Institute of Mental Health. No	N=124 outpatients with current major depressive episode	Mean age: 72.3 years; 40 males, 84 females	Depression Care Management: received depression care management and 10 mg	6, 16 weeks	Improvement in HRSD scores showed improvement for both groups (OR=1.69, 95% CI 0.76-3.77, p=0.20). The	"No added advantage of IPT over DCM was shown. Depression care management is a clinically useful strategy to achieve full remission in	Data suggest there was no added benefit of IPT over DCM as remission rates suggesting comparable efficacy.

			mention of COI.	(DSM-IV)		escitalopram daily (consisting of education about depression, medications, sleep, suicide—and review of symptoms and side effects and encouragement to stay the course) (45-minute sessions for 16 sessions) (n=64) vs IPT Group: received interpersonal psychotherapy (60-75 minutes) and 10-20 mg of escitalopram (n=60) All patients received DCM for 6 weeks and then were randomized to		groups did not differ in speed of symptom decrease (F=2.59, df=1, 108; p=0.11).	about 50% of partial responders."	

						either DCM or IPT.				
van Schaik 2006 (score= 4.0)	Interpersonal Psychotherapy (IPT)	RCT	Sponsored by the Netherlands Organization for Health Research and Development. No mention of COI.	N = 143 MDD subjects with a score of greater than or equal to 5 on the GDS-15	Mean age: 67.9 years; 44 males, 99 females	IPT group: 10 sessions of interpersonal psychotherapy that focuses on exploring either complicated grief, interpersonal conflict, role transition, or interpersonal deficit (n=69) vs CAU group: received no treatment unless suicidal (n=74)	Follow up at month 2 and 6.	IPT was better than usual care in reducing the number of patients diagnosed with MDD post treatment (RD: 17%). Remission rates did not differ between the two groups but remission rates in IPT was low (32%-33%). MDRS in IPT was 19.4 (7.9) while in the usual care group it was 19.3 (8.6)	"IPT was more effective than CAU for elderly patients with moderate to severe major depressive disorder in general practice."	Care as usual bias. Data suggest IPT superior to CAU.
Menchetti 2014 (score= 4.0)	Sertraline/Citalopram/Interpersonal Psychotherapy	RCT	No COI. Sponsored by the Italian Ministry for University and Research as	N = 287 participants meeting s DSM-IV criteria for major	Mean age: 44.9 years, 76 males, 211 females	Interpersonal counseling – six 30-minute sessions (initial session being 60-minutes) (n=143) vs. SSRI treatment –	No long-term follow-up	At 2 months significantly higher percentage of patients who reached remission in interpersonal group compared to	"We identified some patient characteristics predicting a differential outcome with pharmacological and psychological interventions. Should our results be confirmed in future studies, these	Data suggest a significantly greater number of patients reached remission (58.7%) in the interpersonal counseling group compared to the SSRI group (45.1%), suggesting

			Research Program of National Interest in 2005.	depression		given either sertraline or citalopram, patients met with psychiatrist every 2 to 3 week intervals, dosages not specified (n=144). Treatments given over a 2-month period		SSRI group (58.7%, 45.1%, p = 0.021)	characteristics will help clinicians to define criteria for first-line treatment of depression targeted to patients' characteristics."	IP counseling better than either sertraline or citalopram.
Schramm 2007 (score= 4.0)	Interpersonal Psychotherapy (IPT)	RCT	Sponsored by grants from the German Research Society, Bonn, Germany. COI: one of more authors have received honoraria for lectures.	N = 124 patients with DSM-IV MDD	Mean age: 42.5 years; 43 males, 81 females	IPT group: 15-fifty minute sessions 3 times per week for 5 weeks (n=65) vs clinical management group: three 20-25 minute weekly sessions according to the "Guideline for Medication Clinic" (n=61). Both groups received	Follow up at month 3 and 12.	After 5 weeks, clinician-rated depression improved (intent-to treat: F=343.27, df=1, 122, p<0.001; effect size: interpersonal psychotherapy, d=3.17, clinical management, d= 2.53) and self-rated depression also improved	"An inpatient treatment program with both brief and intensive psychotherapy plus pharmacotherapy is superior to standard treatment."	Data suggest both brief and intensive psychotherapy plus pharmacotherapy superior to usual care.

						pharmacotherapy		(intent-to-treat: F=246.30, df=1, 122, p<0.001; effect size: interpersonal psychotherapy, d=1.91, clinical management, d=1.46).		
Toth 2013 (score=3.5)										Data suggest interpersonal psychotherapy (IPT) group showed decreased depressive symptoms.44
Schulberg 1996 (score=3.5)										Usual care bias. Both interpersonal psychotherapy and nortriptyline groups showed significant symptom improvement over placebo (70% versus 20%).
McBride 2006 (score=3.5)										Data suggest in individuals with higher attachment avoidance scores, CBT was better than interpersonal psychotherapy for

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										reducing depression symptom severity and predictive of less remission.
Brown 1996 (score= 3.5)										Data suggest both psychotherapy and pharmacotherapy for individuals with MDD with or without a generalized anxiety disorder.
Luty 2007 (score= 3.5)										Data suggest comparable efficacy but CBT best in severely depressed patients.
Miller 2002 (score= 3.5)										Data suggest interpersonal psychotherapy over the telephone may benefit women who are at high risk for recurrent depression.
Schulberg 2007 (score= 3.0)										Usual care bias. Baseline differences between groups so that randomization unequal. Data suggest interpersonal psychotherapy may

										benefit late life depression.45
Ekebla d 2016 (score= 3.0)										Data suggest comparable efficacy between interpersonal psychotherapy and CBT but CBT group had a high dropout rate.
Rucci 2011 (score= 2.5)										Data suggest SSRI was better than interpersonal psychotherapy for delaying time to suicidal ideation.
Hardy 1995 (score= 2.5)										Data suggest CBT was initially rated higher than interpersonal psychotherapy pre-treatment but after randomization the treatments were similar in ratings.
de Mello 2001 (score= 2.5)										Small sample size with high dropout rate. Data suggest a slight trend for lower Hamilton Rating Scale for

45 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS) scores in the interpersonal psychotherapy group.
DiMascio 1979 (score=2.5)										Data suggest comparable efficacy.
Barkham 1999 (score=2.0)										Data suggest comparable efficacy initially but at 1 year, CBT was superior to psychodynamic-interpersonal (PI) therapy.46

Evidence for the Use of Bibliotherapy/Cognitive Bibliotherapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Joling 2011 (score=4.5)	Bibliotherapy	RCT	Sponsored by the Netherlands Organization for Health	N = 170 patients with subthreshold	Mean age: 81.45 years; 45 males,	Usual care – unrestricted access to usual care for depression or	Follow-up at 3 months	No difference in significant improvement (5+ decrease in CES-D score)	"Bibliotherapy as a stand-alone intervention for the elderly (aged 75 years and older) did not reduce depressive symptoms	Usual care bias. Data suggest lack of efficacy as stand-alone therapy for depression.

46 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

			Research and Development. No mention of COI.	depression and/or anxiety (score of 16 on the Center for Epidemiologic Studies Depression Scale [CES-D] for two subsequent measurements, which were at least 3 months apart)	125 females	anxiety symptoms (n=84) vs. Bibliotherapy – CBT-based therapy, visited for maximum of 60 minutes by home health nurse three times during 12 week period, also had access to usual care (n=86)		between bibliotherapy and usual care groups (OR = 0.86, 95% CI: 0.447–1.657, p = 0.704)	more than usual care. This might indicate that bibliotherapy can only be effective for patients who are motivated and acknowledge their depression."	
Jamison 1995 (score=4.0)	Bibliotherapy	RCT	No mention of sponsorship and COI.	N = 80 participants who scored 10+ on Hamilton Rating Scale for Depression 21-item version (HRSD), scored 10+ on 21-item Beck Depression Inventory (BDI),	Mean age: 40.0 years; 13 males, 67 females	Bibliotherapy – self-help book to treating depression, *Feeling Good* by David Burns (1980), requested to read book within 4 weeks, also received a weekly phone call from research assistant (n=40) vs. Delayed cognitive bibliotherapy (n=40)	Follow-up at 3 months	Significant group x time interaction [F(5, 64) = 15.3, p < 0.05] in MANOVA for overall treatment effectiveness (independent variables being HRSD, BDI, Symptom Checklist 90—Revised Positive Symptom Total, Automatic Thought Questionnaire, and Dysfunctional Attitude Scale—Form A)	"The results of this study suggest that cognitive bibliotherapy for depression was an effective treatment for depression with a general adult population."	Waitlist control bias. Data suggest minimal contract bibliotherapy superior to waitlist group with gains maintained at 3 months.

				and met DSM-III-R criteria for mild or moderate major depressive episode						
Smith 2017 (score=4.0)	Bibliotherapy/Computer-assisted Cognitive Behavioral Therapy	RCT	Sponsored by the Australian National Health and Medical Research Council. No mention of COI.	N = 270 participants with score 5-23 on Patient Health Questionnaire 9-item scale (PHQ-9) and met criteria on the Mini International Neuropsychiatric Interview (MINI) for DSM-IV MDD criteria	Mean age: 39.91 years; 45 males, 225 females	iCBT – sadness program, 6 online lessons over 12 week period, completion of one lesson every 1-2 weeks, illustrated story about character who overcomes depression with CBT skills (n=61) vs. bCBT – Beating the Blues, self-help book, 12 chapters of CBT skills to be read over 12 weeks (n=77) vs. bMED – Silence Your Mind, self-help book about meditating with instructional DVD, 13 chapters to be completed over 12 weeks (n=64) vs. Wait list control – 12 week waiting period (n=68)	Follow-up at 3 months	PHQ-9 score within-group effect sizes for baseline to 3 month follow-up and 95% confidence intervals: iCBT – 1.51 (1.00-2.00), bCBT – 1.09 (0.70-1.48), bMED – 1.55 (1.10-2.00), WLC – 0.50 (0.11-0.89). Between-group effect sizes: iCBT vs. WLC = 0.86 ($p < 0.001$), bCBT vs. WLC ($p < 0.001$), bMED vs. WLC ($p < 0.001$), iCBT vs. bCBT ($p > 0.05$), iCBT vs. bMED ($p > 0.05$), bCBT vs. bMED ($p > 0.05$)	"Self-help based interventions could be beneficial in treating depression, however vigilance needs to be applied when selecting from the range of materials available."	Waitlist control bias. Data suggest all 3 interventional groups improved with some relapse in the bMED group at 3 months.

Moldovan 2013 (score=4.0)	Bibliotherapy	RCT	No mention of sponsorship or COI.	N = 96 participants who scored between 10-16 on Beck Depression Inventory and not being in psychotherapy or on psychotropic medication	Mean age: 23.04 years; 12 males, 84 females	Bibliotherapy – *Feeling Good* (Burns, 1980), self-help book with CBT techniques, 1 month treatment with 5 minute weekly telephone calls (n=24) vs. Delayed Treatment – placed on waiting list for 1 month (n=24) vs. Placebo – received book similar to bibliotherapy material, 1 month treatment, 5 minute telephone calls (n=24) vs. No treatment – told they could not participate, invited to complete all measures, at all assessment times (n=24)	Follow-up at 3 months	ANOVA showed significant difference between groups – $F(3, 92) = 3.43$ ($p < 0.05$). Repeated measures ANOVA for baseline, post-treatment and follow-up showed significant decline in depressive symptoms for bibliotherapy group – $F(2, 21) = 8.21$ ($p < 0.05$)	"This study provided compelling evidence for the efficacy of cognitive bibliotherapy in subthreshold depression and showed that changes in automatic thoughts mediated the effect of bibliotherapy on depressive symptoms."	Data suggest bibliotherapy better than placebo.
Songprakun 2012 (score=3.5)										Standard care bias. Control group was statistically older than intervention group. Data suggest self-help manuals may be used as

										an adjunct to other depression treatments.[47]
Songprakun 2012 (score= N/A)										Same as Songprakun 2011. Standard care bias. Control group was statistically older than intervention group. Data suggest intervention group had lower psychological distress scores at 1-month follow-up.
Songprakun 2015 (score= N/A)										Post hoc analysis of Songprakun 2011. Data suggest use of bibliotherapy could be added to other treatments for depression.
Scogin 1989 (score=3.0)										Waitlist control bias. Data suggest bibliotherapy better than control.
Bilich 2008 (score=3.0)										Waitlist control bias. Data suggest both interventional groups improved levels of depression compared to controls.
Naylor 2010 (score=2.5)										Usual care bias. Data suggest lack of efficacy.

[47] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Short Term Psychodynamic Psychotherapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Jakobsen 2014 (score=6.5)	Cognitive Behavioral Therapy/Psychotherapy	RCT	Sponsored by Health Science Fund, Region Zealand, Denmark. COI, the principal investigator developed a treatment manual and a consultant developed a mentalisation-based treatment manual.	N = 44 patients diagnosed with depression according to the DSM-IV-TR guidelines	Mean age: 39.4 years; 6 males, 38 females.	Group 1: third-wave cognitive therapy with one 45 min psychotherapy session and one 1.5-hour mindfulness-skills training group every week for 18 weeks (n=22) vs. Group 2: mentalisation based 45 min psychotherapy session and one 1.5 hour mentalisation-based group therapy session every week for 18 weeks (n=22)	18 weeks	After adjustment with baseline there was a significant difference in Hamilton Depression Rating Scale scores (p=0.039), Beck's Depression Inventory scores (p=0.46), and WHO 5 scores (p=0.46). There was no statistical difference between Global Severity Index scores (p=0.66).	"Third-wave cognitive therapy may be more effective than mentalisation-based therapy for depressive symptoms measured on the HDRS."	Small sample. Data suggest third-wave CBT may be better than MBT for treatment of depression.
Knekt 2004 (score=5.5)	Short-term psychodynamic psychotherapy /Problem Solving Therapy	RCT	Sponsored by Social Insurance Institution. No mention of COI.	N = 367 in patients suffering from depressive or anxiety disorders (DSM-IV)	Mean age: 32.1 years; 92 males, 275 females	Short-term Psychodynamic Psychotherapy: received therapeutic interventions of 20 sessions, once per week over 5-6 months (confrontation, clarification, and interpretation) (n=101) vs Solution-Focused Therapy: received brief therapy approach (goal-setting, questioning, exploration of exceptions, positive feedback) of 12 sessions one every second or third week over 8 months (n=97) vs Long-Term Psychodynamic Psychotherapy: received 2-3 sessions a week up to 3 years of psychotherapy (exploration of	3, 7, 9 months, 1, 1.5, 2, 3, 4, 5 years	Mean BDI scores decreased 48% in short-term psychotherapy group compared to 42% in the solution-focused therapy group (p=0.65). Mean HDRS scores were reduced in both short-term psychotherapy group and the solution-focused therapy group (p=0.84).	"[B]oth solution-focused therapy and short-term psychodynamic psychotherapy are thus effective in the treatment of depressive and anxiety disorders in clinical practice, but they are not uniformly suitable and sufficient for inducing recovery for all patients."	Data suggest at 1-year post intervention both short term psychotherapy and solution focused therapy showed considerable improvement in decreasing depressive symptoms. Solution focused therapy was favored by therapists but not patients.

						conflicts, conflict resolution, clarification and interpretation of major elements, etc.) (n=128) vs Psycho-analysis: received analysis of interpersonal and intrapsychic conflicts (enhancement of self-awareness of motives, impulses, fears and conflicts) for 4 sessions a week up to 5 years (n=41)				
Lindfors 2014 (score= N/A)	Short-term psychodynamic psychotherapy	3 year follow-up of Helsinki Psychotherapy Study (Knecht and Lindfors 2004)	Sponsored by the Finnish Academy and the Social Insurance Institution, Finland. No mention of COI.	N = 326 patients suffering with depressive or anxiety disorders (DSM-IV)	Mean age: 32.3 years±6.9 years; 78 males, 248 females	Short-Term Therapy: received short-term psychodynamic psychotherapy (working through specific intrapsychic and interpersonal conflicts) 20 weekly treatment session over 5-6 months (n=198) vs Long-Term Psychodynamic Therapy: received long-term psychodynamic psychotherapy 2-3 sessions a week for up to 3 years (n=128)	7, 12, 24, 36 months	A greater decrease in SCL-9—GSI values was observed at 40.0% in short-term therapy compared to 26.3% in long-term therapy (p=0.80). Symptom levels were lower in the long-term therapy group in social support variables at 3 year follow-up (global index: 28.6% short-term vs 48.4% long-term; network size: 26.1% short-term vs 50.4% long-term; support satisfaction: 23.7% short-term vs 43.1% long-term).	"[P]atients who had a high level of social support and integration before entering psychotherapy seemed to benefit more from long-term therapy than from short-term therapy, whereas patients with a low level of social support experienced no such benefit."	Post hoc. Data suggest those patients with high social support prior to entering psychotherapy appear to benefit the most from long-term therapy.
Knekt 2016 (score= N/A)	Short-term psychodynamic	10-year follow-up of Helsink	Sponsored by the Academy	N = 326 patients suffering with	Mean age: 32.3 years±6.9 years; 78	Long-term therapy: received long-term psychodynamic psychotherapy 2-3 sessions a week for up to 3 years (n=128)	10 years	Depressive symptoms and psychiatric symptoms were	"After 10 years of follow-up, the benefits of LPP in comparison with	Data suggest LPP more effective than SPP but neither therapy guaranteed

	psychotherapy	i Psychotherapy Study Knecht and Lindfors 2004	of Finland. No COI.	depressive or anxiety disorders (DSM-IV)	males, 248 females	vs Short-term therapy: received short-term psychodynamic psychotherapy (working through specific intrapsychic and interpersonal conflicts) 20 weekly treatment session over 5-6 months (n=101) vs Solution-Focused Therapy: received 12 sessions of solution-focused therapy (goal and resource oriented strategies to facilitate behavior change) (n=97)		more greatly reduced in long-term therapy (53.2% to 57.0%) group compared to short term therapy group (38.1% to 43.7%); and 42.7% to 49.2% in the solution focused therapy.	the short-term therapies are rather small, though significant in symptoms and work ability, possibly due to more frequent use of auxiliary therapy in the short-term therapy groups. Further studies should focus on the choice of optimal length of therapy and the selection of factors predicting outcome of short- v. long-term therapy."	remission benefits of LPP are small but significant for symptom decline and work ability.
Schatzberg 2005 (score=5.0)	Nefazodone/ Psychotherapy	Crossover trial	Sponsored by Bristol-Myers Squibb Co, New York, NY. Author Borian was associate with Bristol-Myers Squibb Co.	N = 140 patients meeting DSM-IV criteria for chronic major depressive disorder, "double depression" (current major depressive episode superimposed on antecedent dysthymic disorder),	Mean age: 43.1 years; 48 males, 92 females	Received nefazodone first: 100-600 mg daily, for 12 weeks (n=61) vs. Received CBASP first: cognitive behavioral analysis system of psychotherapy, twice weekly for 4 weeks, then once weekly for 8 weeks (n=79)	No long term follow-up	Switching from nefazodone to CBASP and from switch from CBASP to nefazodone resulted in statistically significant improvements in symptoms ($p = 0.03$). Response and remission rates were not significantly different between completers	"Among chronically depressed individuals, CBASP appears to be efficacious for nonresponders to nefazodone, and nefazodone appears to be effective for CBASP nonresponders. A switch from an antidepressant medication to psychotherapy or vice versa appears to be useful for	Data suggest in chronically depression non-responders, switching from CBASP to nefazodone or nefazodone to CBASP results in similar therapeutic efficacy in treatment of depressive symptoms.

				or recurrent major depressive disorder with incomplete interepisode recovery					nonresponders to the initial treatment."	
Bastos 2015 (score=5.0)	Fluoxetine/ Psychotherapy	RCT	No mention of COI or sponsorship.	N = 272 participants meeting DSM-IV-TR criteria for major depressive disorder or depressive disorder not otherwise specified	Mean age: 29.61 years; 104 males, 168 females	Long-term psychotherapy – one weekly session (LTPP) (n=90) vs. Fluoxetine – 20-60 mg/day (n=91) vs. Combination of both treatments (n=91). All groups received treatment for 24 months.	Follow-up at 6, 12, 18, and 24 months	Mean Beck Depression Inventory (BDI) scores at the end of 24 months: LTPP = 22.08, Combination = 22.04, Fluoxetine = 12.53). Mixed analysis showed significant decrease in BDI scores among all groups($F_{8;\,479}$ = 45, 96, $p < 0.001$)	"These findings have implications for patients with depression who may benefit from long-term psychodynamic psychotherapy or combined treatment, or for depression patients who do not wish to take medication such as fluoxetine."	Data suggest long-term psychodynamic psychotherapy (LTPP) and combination LTPP plus fluoxetine are better than fluoxetine alone.
Guthrie 1999 (score=5.0)	Short-term psychodynamic psychotherapy	RCT	Sponsored by a grant from the North West Regional Health Authority. No mention of COI.	N = 110 patients with nonpsychotic disorders (ICD-10)	Mean age: 41.4±9.8 years; 41 males, 69 females	PIT Group: received psychodynamic interpersonal therapy for 8 sessions (emphasis on patient-therapist relationship as tool for resolving interpersonal issues) (n=55) vs TAU Group: received treatment as usual under care of their consultant psychiatrist (n=55)	6 months	PIT group showed greater improvement than TAU group on GSI (p=0.03) and depression scales (p=0.03).	"These preliminary findings suggest that brief psychodynamic-interpersonal therapy may be cost-effective relative to usual care for patients with enduring nonpsychotic symptoms who are not helped by conventional	Usual care bias, 6-month follow-up. Data suggest brief psychodynamic-interpersonal therapy may benefit patients not responding to routine care and may be cost-effective as reflected in the 6 months of costs post treatment.

									psychiatric treatment."	
De Jonghe 2001 (score=5.0)	Short-term psychodynamic psychotherapy	RCT	Sponsored by grant from Eli Lilly Nederland. No mention of COI.	N = 167 patients with major depression (DSM-III)	Mean age: 34 years; 49 males, 80 females	Pharmacotherapy Group: received fluoxetine 20 mg/d, if intolerance or inefficacy, received 50 mg/day amitriptyline—if intolerance or inefficacy, received 300 mg/day moclobemide (n=57) vs Combined Therapy: received both medication same as pharmacotherapy group and short psychodynamic supportive psychotherapy (16 45-minute sessions) consisting of focused behavioral and cognitive aspects of actual relationships (n=72)	8, 16, 24 weeks	Reduction in depressive symptoms was achieved at each follow-up time favoring combined therapy group in 23% at 8 weeks, 31% at 16 weeks, and 62% of patients at 24 weeks. Reduction of depressive symptoms was achieved in 40.7% of pharmacotherapy group and 59.2% in combined therapy group.	"Patients found combined treatment significantly more acceptable, they were significantly less likely to drop out of combined therapy and, ultimately, significantly more likely to recover. Combined therapy is preferable to pharmacotherapy in the treatment of ambulatory patients with major depression."	6-month efficacy evaluation. Data suggest combination psychotherapy with anti-depressants for treating depression best as patient adherence to treatment is better as well as statistically better than pharmacotherapy alone (59.2% vs 40.7%).
De Jonghe 2004 (score=5.0)	Short-term psychodynamic psychotherapy	RCT	Sponsored by grant from Wyeth Nederland. No mention of COI.	N = 208 patients with mild or moderate major depressive disorder (DSM-IV)	Mean age: 35.5±10.7 years; 33 males, 67 females	Psychotherapy: received short psychodynamic supportive psychotherapy (SPSP) consisting of 16 sessions within 6 months (n=106) vs Combined Therapy: received psychotherapy and pharmacotherapy consisting of 6 months of venlafaxine unless intolerable then changed to nortriptyline, if intolerable switched to lithium (SPSP and antidepressant medication) n=85)	6 months	Psychotherapy group showed a decrease in HRSD score from 18.14 to 11.35 compared to combined therapy group from 17.99 to 9.53 (F=3.04, p=0.083). Success rate was achieved in 32%-69% of psychotherapy group compared to 42%-79% in	"In summary, we investigated the possible advantages of combining antidepressants with psychotherapy in ambulatory patients with mild to moderate major depressive disorder. We found that psychotherapy is more acceptable	Data suggest comparable efficacy.

								the combined group. Between group differences were observed for HRSD scores (p<0.046).	than combined therapy."	
Dekker 2005 (score=5 .0)	Short-term psychodynamic psychotherapy	RCT	Sponsored by grant from Eli Lilly Nederland. No COI.	N = 90 patients with major depression (DSM-IV)	No mention of mean age (range: 19-59); 32 males, 58 females	Group 1: received 8 sessions short psychodynamic supportive psychotherapy (SPSP) (n=45) vs Group 2: received 16 sessions short psychodynamic supportive psychotherapy (SPSP) (n=45) All patients received antidepressant medication (fluoxetine 20 mg/day, if intolerable switched to nortriptyline 50-150 mg/day, if intolerable switched to mirtazapine 15-45 mg/day), psychoeducation and limited supportive contact	4, 8, 12, 16, 24 weeks	HDRS remission was achieved in 33.3% of Group 1 compared to 28.9% of Group 2 (p=0.65). HDRS reduction of greater than 50% was achieved by 42.4% in Group 1 compared to 42.4% in Group 2 (p=1.0).	"In the light of the outcome analysis (faster remission after fewer sessions), a short version of the psychotherapy treatment in a combined course of treatment seems to be justified."	At 6 months there was comparable efficacy between both the 8 session and the 16 session groups but the rate of change was faster in the fewer 8 sessions of psychotherapy.
Bressi 2010 (score=5 .0)	Short-term psychodynamic psychotherapy	RCT	No mention of sponsorship or COI.	N = 60 patients with depressive or anxiety disorders (DSM-IV-TR)	Mean age: 37.2 years; 14 males, 46 females	Intervention Group: received 40 weekly sessions (each session 45 minutes) of Short-Term Psychodynamic Psychotherapy (STPP) (n=30) vs Control Group: received drug treatment combined with interviews by psychiatrist (1-4 sessions per month) for up to 40 weeks (n=30)	12 months	Symptom distress improved in intervention group compared to controls (t=3.16, p=0.004). SCL-90-R scores decreased where IIP scores did not (t=1.306, p=0.204).	"This study corroborated evidence that STPP is an effective treatment for patients with depressive and anxiety disorders, and it could be more effective than TAU in improving interpersonal functioning as measured by IIP. However, further research with larger sample and prospective design is needed	TAU bias. 12-month evaluation post treatment. Data suggest STPP is effective for treating depression and/or anxiety.

									to evaluate stability of outcome in the longer term."	
Rosso 2013 (score=5.0)	Short-term psychodynamic psychotherapy	RCT	No sponsorship or COI.	N = 88 outpatients with depressive disorders (DSM-IV-TR)	Mean age: 39.8 years; 27 males, 63 females	BDT Group: received brief dynamic therapy for 15-30 sessions (n=33) vs BSP Group: received brief supportive psychotherapy for 15-30 sessions (n=55)	End of treatment, 6 months	$HAM\text{-}D_{17}$ remission was achieved by 75.8% in BDT group and 47.3% in BSP group (p=0.008). Remission rate at 6 months was 90.5% in BDT group compared to 34.8% in BSP group (p<.002).	"The efficacy of BDT in treating depressive disorders is higher in moderate than in mild depression."	6-month follow-up assessment. Data suggest BDT more effective for treating moderate vs mild depression.
De Roten 2016 (score=5.0)	Short-term psychodynamic psychotherapy	RCT	Sponsored by a grant from the Swiss National Science Foundation. No COI.	N = 149 patients with major depressive episode (DSM-IV)	Mean age: 43.2±10.4 years; 41 males, 108 females	IBPP Group: received inpatient brief psychodynamic psychotherapy (IBPP) consisting of 12 sessions over 4 weeks focused on bringing a change in patients and bringing patient's psychiatric problems to remission (n=76) TAU Group: received psychosocial treatment as usual for depression consisting of 6 sessions of psychoeducation and pharmacotherapy as prescribed by psychiatrist (n=73)	3, 12 months	Greater reduction in depressive symptom severity was observed in IBPP group compared to TAU group (ES=0.32, 95% CI 0.01-0.64). Response rate was greater in IBPP group compared to TAU group (OR=2.26, 95% CI 1.02-4.97).	"IBPP decreased observer-rated depression severity up to 12 months after the end of treatment. IBPP demonstrated immediate and distant treatment responses as well as substantial remissions at follow-up. IBPP appears to be a valuable adjunct in the treatment of depressed inpatients."	TAU bias. 12-month follow-up. Data suggest IBPP reduced observed depression up to 12 months post treatment.
Maina 2010 (score=4.5)	BDT/Fluvoxamine/Sertraline	RCT	No mention of sponsorship or COI.	N = 57 patients with OCD concurrent with	Mean age: 31.5 years; 24 males, 30 females	PT-alone Group received either 100 mg/day of fluvoxamine increased to a daily dose of 300 mg/day or 50 mg/day sertraline increased to a daily dose of 200 mg/day: (n=30) vs PT+BDT	16 weeks, 12 months	HAM-D-17 remission was not significant between groups (p=0.463). Mean HAM-D-score	"Supplemental BDT in the treatment of patients with OCD with concurrent MDD	Lack of efficacy of BDT. Data suggest combining BDT with either fluvoxamine or sertraline is no

				MDD (DSM-IV)		Group: received weekly 45 min sessions of brief dynamic therapy (10-16 sessions) (n=27)		improved from 17.56±4.9 to 13.40±5.3 in BDT group compared to 20.48±5.1 to 15.10±5.5 in PT alone group.	who are receiving effective medication has no significant clinical effect on both obsessive and depressive symptoms."	better than administration of either medication alone in patients with MDD and concurrent OCD.
Lang 2017 (score=4.5)	Acceptance and Commitment Therapy (ACT)/Psychotherapy	RCT	No mention of sponsorship or COI	N = 160 veterans with anxiety or depressive disorder according to DMS-IV	Mean age: 34 years; 128 males, 32 females	Acceptance and Commitment Therapy (ACT) –twelve 1-hr sessions (n=80) vs Present-centered Therapy (PCT) – twelve 1-hr sessions (n=80)	Follow up at 3, 6, 9, and 12 months	No differences between two groups according to MRMM analyses on BSI-18 GSI (between groups effect size = 0.16, 95% CI [0.23, 0.56]), SDS (between groups effect size = 0.33, 95% CI [0.07, 0.72]), or AUDIT (between-groups effect size = 0.24, 95% CI [0.21, 0.68]).	"ACT's efficacy in this group was modest and generally did not differ from that for PCT. Additional work is needed to understand the reasons that ACT did not perform as well as predicted in this veteran sample"	Data suggest comparable efficacy between ACT and PCT.
Zilcha-Mano 2014 (score=4.5)	Short-term psychodynamic psychotherapy	RCT	Sponsored by a NIMH grant, grant from Pfizer Corp. and from the Fulbright Program. COI: One or more of the authors have received or will receive benefits for personal or	N = 156 patients diagnosed with MDD (DSM-IV)	Mean age: 37.5±12.2 years; 64 males, 92 females	SET Group: received 20 sessions of manualized psychodynamic therapy 2 times weekly for 4 weeks, then weekly for rest of treatment (n=51) vs MED Group: received sertraline (unless don't respond then switched to venlafaxine after 8 weeks) no mention of dose (n=55) vs Placebo: received placebo (if no response then switched to a different placebo after 8 weeks) no mention of dosing (n=50)	4, 6, 8, 12, 16 weeks	Depressive symptoms were reduced in all groups ($p<0.001$). No between group differences were observed (ps≥.09).	"Current treatments for depression significantly improve patients' QOL and well-being. No significant differences were found between the three conditions examined in this study. The current study highlights the role	Data suggest comparable efficacy between treatment groups.

			professional use.						of well-being in predicting subsequent symptomatic change.“	
Maina 2009 (score=4.5)	Short-term psychodynamic psychotherapy	RCT	No sponsorship or COI.	N = 92 patients with major depressive disorder (DSM-IV-TR)	Mean age: 35.9 years; 36 males, 56 females	BDT Group: received weekly sessions each 45 minutes (15-30 sessions total) brief dynamic therapy (enhance patient's insight about repetitive conflicts and trauma that underlie problems) and antidepressant (same dosing as pharmacotherapy group) (n=41) vs Pharmacotherapy Group: received antidepressant only consisting of 20 mg/day of paroxetine or citalopram then upped to 60 mg/day and was managed by a psychiatrist (12 appointments 20 min each) (n=51)	48 months	Patients in BDT group showed greater sustained remission to depressive symptoms compared to pharmacotherapy group (HAM-D, p=0.0425). Remission rate was 64.1% in BDT group compared to 61.4% in pharmacotherapy group.	“The significant lower recurrence rates in a 48-month follow-up in the group of patients treated with the addition of BDT to medication in the acute phase support the view of the advantage in the long-term outcome of adding psychotherapeutic intervention to pharmacotherapy in the acute therapy of unipolar major depression.”	Contact time bias as BDT group had additional time with therapist. Data suggest combined BDT and pharmacotherapy had lower depression recurrence rates at 4 years post treatment.
Johansson 2012 (score=4.5)	Short-term psychodynamic psychotherapy	RCT	Sponsored by the Swedish Research Council and Linköping University. No COI.	N = 92 patients diagnosed with MDD (DSM-IV)	Mean age: 45.6±14.0 years; 23 males, 69 females	Psychodynamic Group: received psychodynamic psychotherapy (PDT) consisting of guided self-help textbook and online support from a therapist focused on observing and breaking unhelpful affective cognitive and behavioral patterns for 10 weeks and feedback was given within 24 hours (n=46) vs Structured Support Group: received psychoeducation and scheduled online support for 10 weeks (n=46)	10 months	Psychodynamic group showed greater improvement in BDI-2 scores (F(1, 109.8)=37.2, p<.001). Depression measured by MADRS-S was reduced from 23.07 to 12.5 in the psychodynamic	“Internet-based psychodynamic guided self-help is an efficacious treatment for MDD that has the potential to increase accessibility and availability of PDT for MDD.”	Data suggest internet guided self-help group may be efficacious for MDD.

								group compared to 23.48 to 18.61 in the structured support group (p<.001).		
Burnand 2002 (score=4.5)	Short-term psychodynamic psychotherapy	RCT	Sponsored by grant from the Swiss National Fund for Scientific Research. No mention of COI.	N = 74 patients with a diagnosis of major depressive episode (DSM-IV)	Mean age: 36.4 years; 29 males, 45 females	Combination Group: received psychodynamic psychotherapy(n=35) vs Clomipramine Group: received 25 mg of clomipramine on the first day and increased gradually to 125 mg on fifth day (received 2 electrocardiograms prior to treatment) and were switched to 20-40mg of citalopram per day if patients refused or had severe adverse effects for 10 weeks (n=39)	2, 4, 6, 8, 10 weeks	Mean HDRS scores showed a negative effect of time (8.9±7 in the combination group compared to 9.7±7.3 in the clomipramine group (F=286.4, p<.001). Nine percent of combination group showed treatment failure compared to 28% of clomipramine group (p=0.04).	"Provision of supplemental psychodynamic psychotherapy to patients with major depression who are receiving antidepressant medication is cost-effective."	Data suggest adding psychodynamic psychotherapy to antidepressant medication in the treatment of depression is associated with lower hospitalizations, lost workdays, improved global functioning, and may be cost effective.
Driessen 2013 (score=4.0)	Cognitive Behavioral Therapy/ Short-term psychodynamic psychotherapy	RCT	Sponsored by Wyeth Pharmaceuticals, Arkin Mental Health Care, ProPersona Mental Health Care, VU University. COI, one or more of the authors have received or will receive benefits for personal or	N = 341 participants with DSM-IV classified major depressive order (MDD) as assessed via Hamilton Depression Rating Scale (HAM-D).	Mean age: 38.91 years; 102 males, 239 females.	16 sessions of individual manualized CBT within 22 weeks (n = 164) vs. 16 sessions of short-term psychodynamic supportive therapy within 22 weeks (n = 177)	Follow-up at one year.	No statistically significant treatment differences between groups (p>0.05).	"The findings extend the evidence base of psychodynamic therapy for depression but also indicate that time limited treatment is insufficient for a substantial number of patients encountered in psychiatric outpatient clinics."	Data suggest comparable efficacy for all primary outcome measures between CBT and psychodynamic therapy but due to the time-limited psychodynamic therapy sessions it may be inappropriate for large numbers of patients in outpatient clinics.

			professional use.							
Maina 2007 (score=4.0)	Short-term psychodynamic psychotherapy	RCT	No mention of sponsorship or COI.	N = 35 patients with a diagnosis of major depressive disorder (DSM-IV-R)	Mean age: 35.94±11.17 years; 12 males, 23 females	BDT Group: received brief dynamic therapy consisting of weekly 45-min session (15-30 sessions total) (n=18) vs BSP Group: received brief supportive psychotherapy consisting of weekly 45 min sessions (20-30 sessions total) (n=17)	6, 12 months	Mean HAM-D scores decreased from 20.94±3.24 to 6.19±3.92 in the BDT group compared to 19.41±1.81 to 12.75±4.42 in the BSP group ($p<0.001$).	"BDT combined with antidepressants is preferable to supportive psychotherapy combined with medication in the treatment of outpatients with major depression."	Baseline differences between groups. Data suggest BDT plus antidepressant better than supportive psychotherapy plus antidepressants for outpatients with MDD.
Gibbons 2016 (score=4.0)	Short-term psychodynamic psychotherapy /CBT	RCT	Sponsored by Agency for Healthcare Research and Quality. No COI.	N = 237 patients with a diagnosis of MDD (DSM-IV)	Mean age: 36.2 years; 59 males, 178 females	DT Group: received supportive-expressive short-term dynamic psychotherapy (DT) consisting of (n=118) vs CT Group: received structured sessions focusing on behavioral activation and depressogenic beliefs (activity scheduling, evaluation of thoughts, behavioral experiments) of cognitive therapy (n=119)	1, 2, 5 months	Mean change in HAM-D score was 0.86 points between CT and DT group (95% CI -0.70-2.42). The only significant differences between DT group compared to CT group were in supportive techniques ($t_{120}=2.48$, $p=0.02$), competence in excessive techniques ($t_{120}=4.78$, $p=0.001$), adherence to techniques ($t_{120}=-7.07$, $p=0.001$), and competence in CT ($t_{120}=-7.07$, $p=0.001$).	"This study suggests that DT is not inferior to CT on change in depression for the treatment of MDD in a community mental health setting. The 95%CI suggests that the effects of DT are equivalent to those of CT."	5-month follow-up. Data suggest comparable efficacy.

Salmine n 2008 (score=4 .0)	Short-term psychodyna mic psychother apy	RCT	Sponsored by the Social Insurance Institution of Finland, and the Signe and Ane Gyllenberg Foundation . No mention of COI.	N = 51 patients with major depressive disorder of mild or moderate severity (DSM-IV)	Mean age: 42.4 years; 16 males, 35 females	PSY Group: received 16 weekly psychodynamic psychotherapy sessions (n=26) vs Fluoxetine Group: received 20 mg/day of fluoxetine for 3-4 weeks then increased to 40 mg/day of fluoxetine if no response was achieved (total16 weeks) (n=25)	4 months	Both groups achieved reduction in HDRS score ($p<0.0001$), but no between group differences were found. Fluoxetine group showed 68% remission compared to 71% in the PSY group ($p=0.84$).	"Both STPP and pharmacological treatment with fluoxetine are effective in reducing symptoms and in improving functional ability of primary care patients with mild or moderate depression. This study suggests no marked differences in the therapeutic effects of these two treatment forms in a primary care setting."	Data suggest comparable efficacy.
Thomps on 1987 (score=3 .5)										Delayed treatment (waitlist control bias). Data suggest comparable efficacy between all 3-treatment groups compared to delayed treatment group.[48]
Gallaghe r-Thomps on 1990 (score= N/A)		2-year follow-up of Thomps on 1987								Data suggest post treatment non-depressed patients likely to remain depression free longer than those patients with MDD

[48] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										or minor depression.[49]
Dekker 2013 (score=3.0)										Data suggest patients receiving PDT prior to antidepressant may be best but due to significant baseline differences between medication use 3 months prior to study make conclusions difficult.
Barkham 1996 (score=3.0)										Data suggest initial comparable efficacy between treatments but at 3 months and 1 years, the CPP group failed to maintain gains and the 16 session treatment group showed better progress compared to the 8 session treatment group.
Høglend 2006 (score=3.0)										Data suggest lack of efficacy.[50]
Høglend 2008		Secondary								Data suggest that transference

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(score= N/A)		analysis of Høglend 2006								interpretations are important for those patients who have severe, long-standing problems.
Ulberg 2009 (score=n/a)		Secondary analysis of Høglend 2006								Data suggest women with poor relational functioning but men with good relational functioning showed the best as well as sustained treatment responses to transference interpretations.
Ahola 2017 (score=3.0)										Small sample, waitlist control bias. Data suggest scheduled waiting should be only combined as a prep treatment for MDD.
Ahola 2017 (score=3.0)										Small sample, waitlist control bias. Data suggest scheduled waiting should be only considered as a prep treatment for MDD.[51]
Elkin 1989 (score=3.0)	Cognitive Behavioral Therapy									High dropout rate. Data suggest lack of efficacy of all 3 treatment groups versus placebo.

[48] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Shapiro 1994 (score=2.5)										Data suggest comparable efficacy with a trend towards CBT being better per Beck Depression Inventory.

Evidence for the Use of Problem-Solving Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Knekt 2004 (score=5.5)	Insight-Oriented Psychotherapy/Problem Solving Therapy	RCT	Sponsored by Social Insurance Institution. No mention of COI.	N = 367 in patients suffering from depressive or anxiety disorders (DSM-IV)	Mean age: 32.1 years; 92 males, 275 females	Short-term Psychodynamic Psychotherapy: received therapeutic interventions of 20 sessions, once per week over 5-6 months (confrontation, clarification, and interpretation) (n=101) vs Solution-Focused Therapy: received brief therapy approach (goal-setting, questioning, exploration of exceptions, positive feedback) of 12 sessions one every second or third week over 8 months (n=97) vs Long-Term Psychodynamic Psychotherapy: received 2-3	3, 7, 9 months, 1, 1.5, 2, 3, 4, 5 years	Mean BDI scores decreased 48% in short-term psychotherapy group compared to 42% in the solution-focused therapy group (p=0.65). Mean HDRS scores were reduced in both short-term psychotherapy group and the solution-focused therapy group (p=0.84).	"[B]oth solution-focused therapy and short-term psychodynamic psychotherapy are thus effective in the treatment of depressive and anxiety disorders in clinical practice, but they are not uniformly suitable and sufficient for inducing recovery for all patients."	Data suggest at 1-year post intervention both short term psychotherapy and solution focused therapy showed considerable improvement in decreasing depressive symptoms. Solution focused therapy was favored by therapists but not patients.

						sessions a week up to 3 years of psychotherapy (exploration of conflicts, conflict resolution, clarification and interpretation of major elements, etc.) (n=128) vs Psycho-analysis: received analysis of interpersonal and intrapsychic conflicts (enhancement of self-awareness of motives, impulses, fears and conflicts) for 4 sessions a week up to 5 years (n=41)				
Mynors-Wallis 2000 (score=5.5)	Problem Solving Therapy	RCT	Sponsored by Medical Research Council. No COI.	N = 80 patients with major depression (HAMD)	Mean age: 35 years; 35 males, 116 females	Problem Solving Group: received 6 sessions (1st session 1 hour, subsequent sessions lasting 30 minutes) of problem solving treatment	1,2, 3, 5, 7, 11, 12 weeks, 52 weeks	All groups improved at follow-up in the Hamilton rating scale for depression. Drug treatment group improved from 20.2 to 7.2 points compared to combination group	"Problem solving treatment is an effective treatment for depressive disorders in primary care. The treatment can be delivered by suitably trained practice nurses or	Data suggest all groups showed improvement at 12 weeks. Data suggest combination problem solving with anti-depressants no

						(focus on functioning better, and own skills for goals, solutions) either followed by general physicians (n =39) or followed by nurse (n=41) vs Combined treatment: received 6 sessions of problem solving treatment and 6 sessions of drug treatment (received medication) (n=35) vs Drug Treatment: received either fluvoxamine 100 mg or paroxetine 20 mg (n=36). All patients received 6 sessions over 12 weeks.		from 19.8 to 5.7 points, and from 20.5 to 5.8 points in the problem solving group (p=0.77). BDI scores improved from 30.2 to 11.5 in the drug group compared to 30.0 to 8.6 in the combination group, and 29.6 to 8.2 in the problem solving group (p=0.71). No significant differences between groups were observed.	general practitioners. The combination of this treatment with antidepressant medication is no more effective than either treatment alone."	better than either treatment alone.
Buntrock 2016 (score=5.0)	Problem Solving Therapy/Education	RCT	Sponsored by the European Union and the BARMER CEK. COI: One or more of the authors have received or will receive benefits	N = 406 patients with major depressive episode, bipolar disorder, psychotic disorder or	Mean age: 45.04±11.89 years; 106 males, 300 females	Intervention Group: received guided-web based psychoeducation, behavior therapy, and problem	6, 12 months	Incidence of MDD was 32% in the intervention group (95% CI 25-39%) compared to 47% (95% CI 40-55%) in the control group (p=0.002). Depression	"Among patients with subthreshold depression, the use of a web-based guided self-help intervention compared with enhanced usual	Data suggest at the 12 month assessment the web based self-help intervention decreased the incidence of MDD in

			for personal or professional use.	not having a history of MDD in the past 6 months (DSM-IV)		solving therapy consisting of 6 30-minute sessions (n=202) vs Control Group: received enhanced usual care consisting of psychoeducation offering more information than just from the primary care physician (n=204)		symptom severity had a HR=0.59 (95% CI 0.42-0.82, p=.002).	care reduced the incidence of MDD over 12 months."	individuals with subthreshold depression.
Ebert 2014 (score=5.0)	Problem Solving Therapy	RCT	Sponsored by the European Union. No COI.	N = 150 teachers with elevated depressive symptoms (CES-D)	Mean age: 47.1±8.2 years; 25 males, 125 females	iPST Group: received internet-based problem-solving training consisting of 5 lessons (behavioral activation, solvable problem procedure, coping techniques, written feedback) (n=62) vs WLC Group: received waitlist (n=63)	6 weeks, 3, 6 months	iPST group showed a greater reduction in depressive symptoms compared to WLC group (d=0.38, 95% CI 0.05-0.7).	"iPST is effective in reducing symptoms of depression among teachers. Disseminated on a large scale, iPST could contribute to reducing the burden of stress-related mental health problems among teachers. Future studies should evaluate iPST approaches for use in other working populations."	Waitlist control bias. Data suggest iPST was effective in reducing symptoms of depression in teachers, follow-up at 6 months.
Geraedts 2014 (score=5.0)	Problem Solving Therapy	RCT	Sponsored by Body@Work Research Center	N = 231 participants with	Mean age: 43.4±9.2 years; 87	Intervention Group: received web-	8 weeks	Improvement in depressive symptoms was	"This study showed that a Web-based	Care as usual (CAU) bias. Data suggest

			for Physical Activity, Work and Health, TNO VUMC< Amsterdam and the EMGO Institute for Health and Care Research. No COI.	elevated depressive symptoms (CES-D, DSM-IV)	males, 144 females	based problem solving treatment, cognitive therapy, and a stress guideline for 8 weeks with 2 treatment sessions (n=116) vs CAU Group: received care as usual (n=115)		observed for the intervention group (d=1.03, 95% CI 0.76-1.30, p=.001) and for the CAU group (d=0.98, 95% CI 0.71-1.25, p<.001). There were no difference between groups (d=0.16, 95% CI -0.1-0.41, p=0.29)	guided self-help course for employees with depressive symptoms was not more effective in reducing depressive symptoms among employees than CAU. Large improvements in depressive symptoms in the CAU group were unforeseen and potential explanations are discussed."	lack of efficacy compared to CAU.
Geraedts 2014 (score=N/A)	Problem Solving Therapy	RCT	Sponsored by Body@Work Research Center for Physical Activity, Work and Health, TNO VUMC< Amsterdam and the EMGO Institute for Health and Care Research. No COI.	N = 231 participants with elevated depressive symptoms (CES-D, DSM-IV)	Mean age: 43.4±9.2 years; 87 males, 144 females	Intervention Group: received web-based problem solving treatment, cognitive therapy, and a stress guideline for 8 weeks with 2 treatment sessions (n=116) vs CAU Group: received care as usual (n=115)	8 weeks	Improvement in depressive symptoms was observed for both the intervention group and the CAU group (d=0.16, 95% CI -0.10-0.41, p=.29 There were no difference between groups (d=0.16, 95% CI -0.09-0.42, p=0.29)	"This study showed that a Web-based guided self-help course for employees with depressive symptoms was not more effective in reducing depressive symptoms among employees than CAU. Large improvements in depressive symptoms in the CAU group were unforeseen and potential	1-year follow-up of Geraedts 2014. Data suggest lack of efficacy.

									explanations are discussed."	
Mynors-Wallis 1995 (score=4.5)	Problem Solving Therapy/Amitriptyline	RCT	Sponsored by the Wellcome Trust. No mention of COI.	N = 91 patients with major depression (Hamilton rating scale for depression)	Mean age: 37.1±11.4 years; 21 males, 70 females	PST Group: received problem solving treatment for 6 sessions over 3 months (n=29) vs Amitriptyline Group: received 50 mg amitriptyline for 2 nights, then increased 25 mg per night until 150 mg total taken for 6 sessions over 3 months (n=27) vs Placebo Group: received placebo in same dosing as amitriptyline group (n=26)	6, 12 weeks	Hamilton rating scale improved for all groups (p=0.037). PST group was superior to placebo in Ham-D score mean difference=4.69 (95% CI 0.41-8.96) but not superior to amitriptyline (M=0.94, 95% CI -3.28-5.15). Amitriptyline was superior to placebo in HAM-D score (M=3.75, 95% CI -0.59-8.09).	"As a treatment for major depression in primary care, problem solving treatment is effective, feasible, and acceptable to patients."	At 12 weeks, there was a significant improvement for depressive scores in the PST group.
Kleiboer 2015 (score=4.0)	Problem Solving Therapy	RCT	Sponsored by ZonMW. No mention of COI.	N = 537 participants with mild to moderate depression symptoms or anxiety (CES-D)	Mean age: 44.5±13.7 years; 187 males, 348 females	Condition 1: received internet-based brief problem-solving therapy (PST) (5 weekly sessions) without support from a coach (n=107) vs Condition 2:	6 weeks	Depressive symptoms were reduced in all groups with favor towards condition 3 (CESD: ES=0.34, p<.01, PHQ: ES=0.64, p<.01). Condition 1 (ES=0.25, p<.05) and condition 3	"…These findings are in line with the evidence showing the importance of support in Internet-based interventions for anxiety and depression to reach optimal	Waitlist control bias. 6-week follow-up evaluation. Data suggest internet based PST is effective with structured support in order to benefit

						received internet-based brief problem-solving therapy (PST) (5 weekly sessions) with an option to contact a coach for completion of each session (n=108) vs Condition 3: received internet-based brief problem-solving therapy (PST) (5 weekly sessions) with a coach actively giving weekly support by email after completion of each session (n=106) vs Condition 4: received non-specific support via chat or email with no access to internet-based intervention (weekly coaching sessions) (n=110) vs Condition 5: received access		(ES=0.31, p<.05) showed greater HADS improvement compared to condition 5.	treatment effects. Compared to WLC, we did not find evidence for the effectiveness of Internet-based interventions when delivered 'without support' or 'with support on request', nor did the results show that 'non-specific support' without providing actual treatment is effective."	symptoms of depression.

						to a website with psycho-education about depression and anxiety (n=106)				
Kenter 2016 (score=4.0)	Problem Solving Therapy	RCT	Sponsored by ZonMW. No COI.	N = 269 patients with major depressive disorder (DSM-IV)	Mean age: 38.0±11.4 years; 124 males, 145 females	Intervention Group: received problem solving therapy (6 steps: identify the problem, finding solutions, selecting 1 solution, creating a plan, executing the plan, and evaluation) consisting of 5 weekly sessions with weekly online feedback from a coach (n=136) vs Control Group: received self-help book without any form of guidance (n=133)	8 weeks	Both groups depression scores improved (control group: B=0.56, 95% CI 0.34-0.78, p<.001; intervention group: B=0.61, 95% CI 0.38-0.84, p<.001). Between group effect was d=0.07.	"Internet-based problem solving therapy is not more effective in reducing symptoms of depression than receiving an unguided self-help book during the waitlist period at outpatient mental health clinics."	Waitlist control bias. Data suggest lack of efficacy.
Mynors-Wallis 2002 (score=3.5)										Data suggest lack of efficacy of problem-solving

										treatment showing superiority over antidepressant nor better self-control after treatment.[52]
Warmerdam 2008 (score=3.0)										Waitlist control bias. Data suggest both internet delivered CBT and PST were effective in decreasing symptoms of depression but the effect of PST occurred faster.
Warmerdam 2010 (score= N/A)		Post-hoc analysis of Warmerdam 2008								Data suggest no evidence that the 2 online treatments work with different mechanisms.
Vázquez González 2013 (score=3.0)										Usual Care bias. Data suggest intervention group showed greater improvement than UC group.

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Arean 1993 (score=2.5)										Waitlist control bias, 3 month follow-up self-report. Data suggest both PST and RT groups resulted in significant reductions in depressive symptoms but the PST group improved most.
Dowrick 2000 (score=2.5)										Data suggest PST may prevent depression but both interventional group improved.[53]

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Evidence for the Use of Peer Support

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Cook 2012 (score=5.0)	Peer Support	RCT	Sponsored by US Department of Education, National Institute on Disability and Rehabilitation Research, the Substance Abuse & Mental Health Services Administration, Center for Mental Health Services. No COI.	N = 519 adults with severe and persistent mental illness (DSM-IV criteria)	Mean age: 45.8±9.88 years; 177 males, 342 females	Experimental Group: received wellness recovery action planning (WRAP) intervention for 8 weekly session (2.5 hours each) consisting of lectures, group discussions, individual and group exercises (n=251) vs Control Group: received waitlist, but guaranteed WRAP intervention (n=268)	2, 3, 6, 12 months	Experimental group showed greater symptom reduction in BSI global symptom severity (0.34 vs 0.26) and positive symptom total (8.4 vs 6.64) compared to control group (OR=0.95, 95% CI 0.91-0.98). Total HS score odds ratio for condition by time interaction was 1.49 (95% CI 1.47-1.51).	"These results indicate that peer-delivered mental illness self-management training reduces psychiatric symptoms, enhances participants' hopefulness, and improves their QOL over time. This confirms the importance of peer-led wellness management interventions, such as WRAP, as part of a group of evidence-based recovery-oriented services."	Waitlist control bias. Data would suggest that peer led wellness programs decreases psychiatric symptoms.
Cook 2012 (score=N/A)	Peer Support	Secondary analysis of Cook 2012 WRAP Study	Sponsored by National Institute on Disability and Rehabilitation Research, U.S. Department of Education, and by Center for Mental Health Services, Substance Abuse and	N = 519 adults with severe and persistent mental illness (DSM-IV criteria)	Mean age: 45.8±9.88 years; 177 males, 342 females	Experimental Group: received wellness recovery action planning (WRAP) intervention for 8 weekly session (2.5 hours each) consisting of lectures, group	2, 8 months	Experimental group showed greater reductions in BSI depression and anxiety subscale scores and showed greater improvement in total RAS score compared to control group (p=0.01 for both)	"Our findings build on prior evidence of the positive impact of WRAP on recovery from serious mental illness (6–9) and go further in demonstrating the longitudinal effectiveness of this intervention	Waitlist control bias. Data suggest self-perceived recovery was observed in the intervention group over time.

			Mental Health Services Administration. No COI.			discussions, individual and group exercises (n=251) vs Control Group: received waitlist, but guaranteed WRAP intervention (n=268)			when subjected to rigorous testing. Results of the analysis show that participation in WRAP reduced symptoms of depression and anxiety and enhanced perceived recovery."	
Jonikas 2013 (score=N/A)	Peer Support	Secondary Analysis of Cook 2012 WRAP Study	Sponsored by National Institute on Disability and Rehabilitation Research, U.S. Department of Education and by Center for Mental Health Services, Substance Abuse and Mental Health Services Administration. No COI.	N = 519 adults with severe and persistent mental illness (DSM-IV criteria)	Mean age: 45.8±9.88 years; 177 males, 342 females	Experimental Group: received wellness recovery action planning (WRAP) intervention for 8 weekly session (2.5 hours each) consisting of lectures, group discussions, individual and group exercises (n=251) vs Control Group: received waitlist, but guaranteed WRAP intervention (n=268)	6 months	Experimental group showed greater improvement in total PSAS score, mindful non-adherence subscale and self-advocacy compared to control group.	"These findings provide additional support for the positive impact of peer-led illness self-management on mental health recovery."	Wait-list control bias. Data support a positive impact of peer-led illness self-management (such as WRAP) on mental health recovery.
Valenstein 2016 (score=4.0)	Peer Support	RCT	Sponsored by grants from Division of Health Services	N = 443 patients with a clinical diagnosis of	Mean age: 54.9±10.9 years; no mention of	Patients matched on basis of gender and age, pairs	3, 6, 12 months	BDI-2 scores decreased 7.0 in peer support group compared to 6.7 in	"This study did not support the effectiveness of a less-structured,	Usual care bias. Data suggest lack of efficacy over

			Research and Development, U.S. Department of Veterans Affairs. No COI.	depression (PHQ-9 criteria)	gender (majority male)	randomly assigned. Received brief training on being a peer partner, along with peer-support manual and list of telephone discussion topics (Depression Intervention, Actively Learning and Understanding With Peers (DIAL-UP)) for 6 months (n=200) vs Usual Care Group: received usual mental health care and assigned partner during enrollment (n=243)		usual care group. Mental health functional scores (VR-36 MCS) showed improvements in both groups.	telephone-delivered mutual peer support intervention for VA patients with depression over enhanced usual care. Interventions that use more professionalized peers who provide unidirectional support and a structured curriculum might be more effective."	usual care as both groups showed improvement.
Lindfors 2014 (score=3.0)										Data suggest those patients having good social support pre-therapy seemed to benefit best from long term therapy compared to

										short term therapy.[54]
Baker 1999 (score=3.0)										Sparse methods. Data suggest comparable efficacy between CBT and MSG for treatment of depression and therapy adherence was predictive for best results.

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Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Celano 2017 (score=6.0)	Suicide Prevention	RCT	Sponsored by American Foundation for Suicide Prevention, National Heart, Lung and Blood Institute, National Institute of Mental Health. No COI.	N = 65 adults diagnosed with major depressive disorder (MDD) with a current major depressive episode confirmed by mini international neuropsychiatric interview (MINI)	Mean age: 44.0±16.6 years; 17 males, 38 females	PP Group: received 1 weekly session for 6 weeks of positive psychology intervention (gratitude training, review of past success, acts of kindness, identifying personal strength) (PP) (n=32) vs CF Group: received cognition-focused intervention (CF) consisting of emotional memory recall, and daily activity repeating for 1 weekly session for 6 weeks (n=33)	6, 12 weeks	CF group showed greater reduction in hopelessness compared to PP group at 6 weeks (BHS=-3.15, 95% CI -6.280- -0.12, p=.04), as well as suicidal ideation (CHRT=-9.88, 95% CI -15.69 - -4.08, p=0.001) and depressive symptoms (QIDS-SR_{16}=-4.58, 95% CI -8.26 - -0.91, p=0.02).	"In sum, relative to a PP intervention, a 6-week CF intervention led to greater reductions in hopelessness and other suicide risk factors in a cohort of recently-hospitalized patients with MDD and suicidal ideation."	Data suggest a cognition-focused intervention is superior to a positive psychology intervention for improving a feeling of hopelessness and other risk factors for suicide.
Sahraian 2015 (score=6.0)	Vitamin C	RCT	Sponsored by Shiraz University of Medical Sciences. No COI.	N = 43 patients with major depressive disorder according to DSM-IV criteria	Mean age: 33.5±9.4 years; 11 males, 32 females	Vitamin C Group: received citalopram (up to 60 mg/day) and vitamin C (up to 1000 mg/day)	2, 4, 8 weeks	Decline of HDRS in vitamin C group was 60.0% compared to placebo of 59.2% (p=0.9). ANOVA HDRS score decreased by	"Treating MDD with vitamin C adds nothing to the short-term efficacy of citalopram. This combination is not effective	Data suggest lack of efficacy.

						(n=21) vs Placebo: received citalopram and placebo (n=22) Citalopram started 10 mg/day and increased 20 mg/day over 7 days		F(3,120)=154.6, (p<0.001).	regarding suicidal behavior. However, this combination seems to be safe and well-tolerated."	
Gysin-Maillart 2016 (score=5.5)	Novel Brief Therapy/Suicide Prevention	RCT	No sponsorship. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 120 patients that had attempted suicide defined according to Silverman et. Al.	Mean age: 37.8 years; 54 males, 66 females	ASSIP Group: received 3 60-90-min sessions on a weekly basis and a 4th session if necessary of Attempted Suicide Short Intervention Program (ASSIP) (n=60) vs TAU Group: received treatment as usual of 1 single clinical interview of suicide risk assessment and in patient, day patient, or outpatient care as considered by clinicians in patient management (SSF-3)(n=60)	12 and 24 months	ASSIP group had 5 reattempted suicides at follow-up compared to control with 41 reattempted suicides (p<0.001). Mean suicide-attempt-free survival rate was 0.99 (95% CI 0.98-1.00) in ASSIP group compared to 0.93 (95% CI 0.89-0.96) in the control group at 12 months and 0.95 (95% CI 0.90-1.00) compared to 0.79 (95% CI 0.71-0.87) respectively at 24 months. Mean hazard ratio was 0.17 (95% CI 0.07-0.46) showing ASSIP group had 83% reduced risk of	"ASSIP, a manual-based brief therapy for patients who have attempted suicide, administered in a real-world clinical setting, was efficacious in reducing suicidal behavior over 24 months."	Data suggest TAU plus ASSIP reduced total members of suicide attempts compared to TAU (5 versus 41).

								suicide attempt (p<0.001).		
Lauterbach 2008 (score=5.0)	Lithium/Suicide Prevention	RCT	Sponsored by grants from German Ministry for Education and Research, German Research Foundation, Sanofi-Aventis. No COI.	N = 167 patients with a recent suicide attempt in the context of an depressive spectrum disorder according to DSM-IV criteria	Mean age: 39.5 years; 71 males, 96 females	Lithium: received lithium carbonate in blood levels of 0.6-0.8 mmol/l (increasing 200 mg/week) (n=84) vs Placebo: received same dosing as treatment group of placebo (n=83)	12 months	There were 7 suicide attempts in the lithium group compared to 10 in the placebo group. Incidence rate in lithium group was IR=0.13 (95% CI 0.05-0.26) compared to placebo IR=0.22 (95% 0.10-0.40) (p=0.049).	"Results indicate that lithium treatment might be effective in reducing the risk of completed suicide in adult patients with affective disorders. Our findings contribute to the growing body of evidence suggesting a specific ant suicidal effect of lithium."	High dropout rates. Dissimilar numbers of suicide attempts between lithium and placebo groups (48 vs 26). The hazard ratio initially showed no difference between groups, but at 12 months data suggest all suicides occurred in placebo group.
Rombold 2014 (score=N/A)	Lithium/Suicide Prevention	Post-hoc analysis of Lauterbach 2008	Sponsored by grants from German Ministry for Education and Research, German Research Foundation, Sanofi-Aventis. No COI.	N = 19 patients diagnosed with depressive spectrum disorder as well as a personality disorder (PD) according to SKID-2 for DSM-IV criteria	Mean age: 30.5 years; 7 males, 12 females	Lithium: received lithium carbonate in blood levels of 0.6-0.8 mmol/l (increasing 200 mg/week) (n=8) vs Placebo: received same dosing as treatment group of placebo (n=11)	12 months	Lithium group had 3 patients attempt suicide compared to 2 patients in the placebo group (p=0.1). Hamilton 17 scores decreased from 16.0 to 11.0 in the lithium group compared to 15.36 to 9.0 in the placebo group (t=0.4, p=0.71).	"On the basis of the small sample size, among patients with comorbid PD, lithium does not seem to have an effect on suicidal behavior in contrast to patients with affective disorders without comorbid PD."	Data suggest lithium appear not to be effective in those with comorbid personality disorders in preventing suicidal behavior in contrast to individuals with affective disorders, but no comorbid personality

										disorder where it has benefit.
Currier 2010 (score=5.0)	Suicide Prevention	RCT	Sponsored by grant from National Institute of Mental Health and in part by grant to NIMH/NIDA-funded Center for Public Health and Population Interventions for Preventing Suicide. No mention of COI.	N = 120 participants with suicidal thoughts, plans, or behaviors on Spectrum of Suicidal Behavior (five-tem scale rating suicidal behavior)	Mean age: 32.7±10.8 years; 52 males, 68 females	MCT Group: received mobile crisis team intervention consisting of community assessment and triage, psychiatric evaluation within 48 hours of discharge in 1 hour sessions over 2 week and 3 month intervals (n=56) vs OPC Group: received outpatient psychiatric clinic care of treatment as usual by referral from physicians within 5 days of emergency department discharge in 1 hour sessions over 2 week and 3 month intervals (n=64)	2 weeks, 3 months	Successful first clinical contact was observed in 69.6% of MCT group compared to 29.6% of OPC group (RR=2.35, 95% CI 1.55-3.56, p<0.001). No differences observed between groups for symptom or functional outcome measures.	"Community-based mobile outreach was a highly effective method of contacting suicidal patients who were discharged from the ED."	Data suggest no difference between groups.

Brown 2005 (score=4.5)	Cognitive Therapy/Suicide Prevention	RCT	Sponsored by grants from the National Institute of Mental Health and grant from the Centers for Disease Control and Prevention. No COI.	N = 120 individuals who attempted suicide within 48 hours	Mean age: 35.0 years; 47 males, 73 females	Cognitive Therapy Group: received 10 sessions of cognitive therapy as well as usual care treatment (n=60) vs Usual Care Group: received usual care of case management, referrals to community mental health treatment (n=60)	6, 12, 18 months	Cognitive therapy group had 24.1% of participants attempt at least 1 suicide compared to usual care group with 41.6% of participants (p=0.049). Probability of reattempt was 0.86 (95% CI 0.74-0.93) for cognitive therapy group compared to usual care group of 0.68 (95% CI 0.54-0.79). Cognitive group therapy were 50% less likely to attempt suicide compared to usual care group (HR=0.51, 95% CI 0.26-0.997).	"Cognitive therapy was effective in preventing suicide attempts for adults who recently attempted suicide."	Usual care bias. Data suggest cognitive therapy reduced suicide attempts by approximately 50% compared to usual care.
Bruce 2004 (score=4.0)	Suicide Prevention	RCT	Sponsored by the National Institute of Mental Health (NIMH). COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 598 patients diagnosed with major depressive disorder according to DSM-IV Criteria	No mention of mean age, range 60-94 years; 170 males, 428 females	Intervention Group: received physician and treatment management of medications, monthly interpersonal therapy, and appropriate follow-up with nurses, psychologists, and social workers with	4, 8, 12 months	Intervention patients that received depression treatment was 89.2% of the group compared to 52.5% of usual care patients (p<.001). Suicide ideation declined 12.9% points in intervention group compared to usual care group with 3.0% points	"Evidence of the intervention's effectiveness in community-based primary care with a heterogeneous sample of depressed patients introduces new challenges related to its sustainability and dissemination. The	Prospect Study. Usual care bias. Baseline numbers of suicidal ideation different between groups (29.4% vs 20.1%). Data suggest a specific care management program was better than

						no mention of duration of treatments (n=320) vs Usual Care: received depression treatment and management without mention of duration (n=278)		(p=0.01). A decrease in HDRS score was observed at 4 months (p<0.001), 8 months (p<0.001), and 12 months (p=0.006) for intervention compared to usual care group.	intervention's effectiveness in reducing suicidal ideation, regardless of depression severity, reinforces its role as a prevention strategy to reduce risk factors for suicide in late life."	usual care for decreasing suicidal ideation.
Alexopoulos 2009 (Score=N/A)	Suicide Prevention	2-year follow-up of Prospect Study (Bruce 2004).	Sponsored by NIMH. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 599 patients with major or minor depression defined according to DSM-IV criteria	No mention of mean age, range 60-94 years; 170 males, 429 females	Intervention Group: received physician and treatment management of medications, monthly interpersonal therapy, and appropriate follow-up with nurses, psychologists, and social workers with no mention of duration of treatments (n=320) vs Usual Care: received depression treatment and management with no mention of duration of	4, 8, 12, 18, 24 months	More patients in the intervention group received treatment for depression (antidepressants, psychotherapy, etc.) compared to usual care group (p<0.001). Suicide attempts were made by 2 patients in the intervention and 3 in the usual care group. Remission was achieved by 45.4% of intervention group at 24 months compared to 31.5% of usual care group.	"Sustained collaborative care maintains high utilization of depression treatment, reduces suicidal ideation, and improves the outcomes of major depression over 2 years."	Data suggest at 2 years the interventional group utilized depression treatment strategies (antidepressants, psychotherapy, etc.) much more than usual care group which reduced suicidal ideation.

						treatments (n=279)				
Gallo 2015 (score= N/A)	Suicide Prevention	Post-hoc analysis of Prospect Study (Bruce 2004).	Sponsored by grants from the National Institute of Mental Health. No COI.	N = 20 patients with major depressive disorder (MDD) defined under DSM-IV criteria	No mention of mean age, range 60-94 years; 170 males, 428 females	Intervention Group: received physician and treatment management of medications, monthly interpersonal therapy, and appropriate follow-up with nurses, psychologists, and social workers (no mention of specific treatment duration) (n=320) vs Usual Care: received depression treatment and management (no mention of specific treatment duration) (n=278)	No mention of follow-up.	Patients in the usual care group were at an increased risk of mortality (HR=3.02, 95% CI 1.32-8.72) compared to the intervention group risk of mortality (HR=1.73, 95% CI 0.86-3.96).	"Depression management mitigated the combined effect of multimorbidity and depression on mortality. Depression management should be integral to optimal patient care, not a secondary focus."	Data suggest depression management reduced the combined risks of multimorbidity and depression (hazard ratio) on mortality.
Bruce 2015 (score=3.5)										Usual care bias. Significantly fewer patients in CAREPATH group were less likely to

										be diagnosed with MDD, but had more limitations. Data suggest at 3 and 6 months there were no differences between groups but at 12 months, the difference in HAM-D scores reached statistical significance. Benefits of HHC nurses for CAREPATH suicide prevention appears limited to those with moderate to severe depression.[55]
Lohman 2016 (score=N/A)		Secondary analysis of Bruce 2015								Data suggest Care path was associated with reduced SI ideation at one year.
Motto 2001 (score=3.0)										Data suggest long-term follow-up of individuals at risk for suicide

[55] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										has a preventive benefit (lower suicide rate) than those with no long-term contact. These differences were significant during the first 2 years, but gradually diminished over time to no observable difference at year 14.
Gewirtz 2016 (score=3.0)										Usual treatment bias. Data suggest some benefit of ADAPT vs usual treatment for reduction of suicidal ideation in military personnel at 12 months.[56]

[56] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Watkins 2012 (score=5.5)	Mind Body Interventions	RCT	No COI. No mention of sponsorship.	N = 121 participants meeting the DSM-IV criteria for a current episode of major depression or subthreshold	Mean age: 46.27 years; 43 males, 78 females	Treatment as usual (TAU) for 8 weeks (n = 42) vs. TAU with concreteness training (CNT) guided self-help for 8 weeks (n = 40) vs. TAU with relaxation training (RT) guided self-help for 8 weeks (n = 39). Guided self-help included 1.5 hours of face-to-face sessions, training exercises recorded on audio, detailed workbook for 15-30 minutes daily for at least 6 weeks, and three 30-minute telephone sessions.	Follow-up at 3 and 6 months	Hamilton Rating Scale for Depression scores at post-treatment: TAU+CNT – 9.36, TAU+RT – 11.33, TAU – 13.00. Mean difference between TAU and TAU+CNT: 4.28 (p=0.006). Mean difference between TAU+RT and TAU+CNT: 1.98 (p=0.21)	"This study provides preliminary evidence that CNT guided self-help may be a useful addition to TAU in treating major depression in primary care, although the effect was not significantly different from an existing active treatment (RT) matched for structural and common factors."	Usual care bias. Data suggest a non-significant improvement in depressive symptoms in treatment as usual plus concreteness training (CNT) group.
Chan 2017 (score=4.5)	Mind & Body Interventions	RCT	No sponsorship or COI.	N = 185 with mild to moderate depression	Mean age: 55.3 years; 46	Integrative body-mind-spirit (I-BMS) group which	Follow up pre-treatment, post-	Remission rate of depression was 57% in the I-BMS group vs 28% for	"Our findings indicate the effectiveness of I-BMS in	Waitlist control bias. Data suggest I-BMS has a role in facilitating

				(scored 10 to 34 on the Center for Epidemiologic Studies Depression Scale) and insomnia (scored over 5 on the Pittsburgh Sleep Quality Index)	males, 139 females	consisted of eight 3-hour weekly group sessions with culturally relevant mind-body exercises, mindfulness practices, self-reflection and group discussion and sharing (n = 92) vs waitlist control group (n = 93)	treatment and at 3 months.	the control at 3 months (p=0.004).	facilitating sleep and alleviating depression, as well as reducing IL-6 levels (at T 1 only). In line with previous findings, the current results support the interconnectivity between the body and the mind, as well as the efficacy of I-BMS in relieving distress in these two reciprocating faculties of human existence. The lack of effect of IL-6 at T 2 could be due to normal fluctuation and variations of plasma IL-6 concentration of the participants"	sleep and decreasing depression as well as reducing IL-6 levels.
Sreevani 2013 (score=4.0)	Mind Body Interventions	RCT	No mention of COI or sponsorship.	N = 30 participants with depressive disorder via ICD-10 criteria	Mean age: 27.97 years; 12 males, 18 females	Usual care – including antidepressant use and psycho-education for 1 month (n = 15) vs. Integrated body-mind-spirit therapy – sessions on health and	Follow-up at 2 and 3 months	Beck Depression Inventory II (BDI II) scores at baseline, post-treatment, 2 month and 3 months, respectively: integrated body-mind-spirit therapy – 28.20, 12.20, 6.80, 6.27, usual care – 26.13,	"The integrated body-mind-spirit group intervention model appears to reduce depressive symptoms and improve well-being in patients with depression."	Usual care bias. Pilot study. Data suggest interventional group appears to show decreased symptoms of depression and improved well-being.

						emotional management strategies and stress reduction paired with acupressure, breathing techniques and medication, sessions held once a week for over 3 hours for 1 month (n = 15)		22.33, 18.87, 18.60. Therapy intervention caused higher decrease in depressive symptoms than usual care (F = 20.55, p < 0.001)		
Chan 2017 (score=3.5)										High dropout rate. Waitlist control bias. Sparse methods. Data suggest Integrative body-mind-spirit treatment may positively benefit depression and sleep disturbance as well as reducing interleukin-6 levels.[57]
Chan 2012 a (score=3.5)										Waitlist control bias. Data suggest comparable efficacy between interventional groups with Chan-based Dejian Mind-Body Intervention (DMBI) group

[57] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										resulting in reduced anti-depressant consumption.
Chan 2012 b (score=N/A)		Secondary analysis of Chan 2012 a								Data suggest both cognitive behavioral therapy and DMBI improved sleep compared to waitlist group.
Chen 2015 (score=3.5)		Non-RCT design								Data suggest both groups (major depressive disorder and healthy controls) were influenced by body-mind relaxation meditation induction (BMRMI) impacting resting state brain activity
Rentala 2015 (score=2.5)										Usual care bias. Not really randomized. Data suggest mind-body intervention group showed improved well-being and quality of life.[58]

[58] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kuyken 2015 (score=6.0)	Mindfulness Based Therapy	RCT	Sponsored by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, and NIHR Collaboration for Leadership in Applied Health Research and Care South West Peninsula. No COI.	N = 424 patients with (DSM-IV) three or more previous major depressive episodes	Mean age: 49.5 years; 99 males, 325 females	MBCT-TS Group: received support to taper or discontinue antidepressant medications by therapists and GPs (n=212) vs m-ADM Group: received maintenance antidepressant treatment (n=212)	12, 24 weeks 9, 12, 18, 24 months	There was no significant difference between MBCT-TS group and the m-ADM group (HR=0.89, 95% CI 0.67-1.18, p=0.43). Relapse was observed in 44% of MBCT-TS group compared to 47% in m-ADA group (p=0.41).	"We found no evidence that MBCT-TS is superior to maintenance antidepressant treatment for the prevention of depressive relapse in individuals at risk for depressive relapse or recurrence. Both treatments were associated with enduring positive outcomes in terms of relapse or recurrence, residual depressive symptoms, and quality of life."	Data suggest MBCT-TS is not better than antidepressants for the prevention of depression relapse.
Meadows 2014 (score=5.0)	Mindfulness Based Therapy	DARE Study. 2 year follow-up Shawyer 2012	Sponsored by a grant from National Health and Medical Research Council of Australia. No COI.	N = 204 participant with (DSM-IV) diagnosis of major depressive disorder or bipolar disorder	Mean age: 48.4 years; 38 males, 165 females	MBCT Group: received 8 weekly 2 hour group training sessions of mindfulness practices and cognitive behavioral therapy exercises (n=101) vs Control Group:	1, 2 years	MBCT group showed fewer days with major depression (65 days) compared to control group (112 days) (p=0.03). Fewer patients showed relapse at both follow-ups in MBCT group compared to control group	"This work in a pragmatic design with an active control condition supports the effectiveness of MBCT in something closer to implementation in routine practice than has been studied	Data suggest significant reductions in numbers of MD days in MBCT group occurred vs controls (65 vs 112) suggesting long-term effectiveness of MBCT.

						received depression relapse active monitoring (n=102)		(OR=0.45, p<0.05).	hitherto. As expected in this translational research design, observed effects were less strong than in some previous efficacy studies but appreciable and significant differences in outcome were detected. MBCT is most clearly demonstrated as effective for people receiving specialist care and seems to work well combined with antidepressants."	
Kearns 2016 (score= N/A)	Mindfulness Based Therapy	Post-hoc analysis of Shawyer et al 2012 and Meadows et al 2014	Sponsored by the National Health and Medical Research Council of Australian. No mention of COI.	N = 204 participant with (DSM-IV) diagnosis of major depressive disorder or bipolar disorder	Mean age: 48.4 years; 38 males, 165 females	MBCT Group: received 8 weekly 2 hour group training sessions of mindfulness practices and cognitive behavioral therapy exercises (n=101) vs Control Group: received depression relapse active monitoring (n=102)	12, 24 months	Standard linear regressions showed relationships between mindfulness and rumination (p<0.001, for all). No other significant relationships between relapse and rumination were observed.	"Our results strengthen the argument that mindfulness may be important in preventing relapse but that rumination is not a significant mediator of its effects. The study was adequately powered to detect medium mediation effects, but it is possible that smaller effects	Data suggest mindfulness may be important in the prevention of depression relapse, but rumination is not a significant mediator of its effects.

									were present but not detected."	
Pots 2014 (score=5.0)	Mindfulness Based Therapy	RCT	Sponsored by University of Twente. No COI.	N = 151 participants with depressive symptoms (MINI)	Mean age: 48±11.29 years; 33 males, 118 females	MBCT Group: received mindfulness based cognitive therapy consisting of meditation (15 min/day) and 11 sessions of awareness, acceptance, and disengaging from thoughts (n=76) vs Wait List Group: received MBCT training after 3 months (m=75)	3, 6 months	Depressive symptoms were reduced in the intervention group [t (75) =-3.46, p<0.01]. Control group also showed reduced depressive symptoms after they received the intervention [t (74) =-3.03, p<0.01].	"This study shows that MBCT as a public mental health intervention for adults with mild to moderate depressive symptomatology is effective by not only reducing depressive symptoms and anxiety symptoms, but also enhancing positive mental health and psychological flexibility. Furthermore, this study shows that the intervention is applicable and effective in a natural setting."	Waitlist control bias. Data suggest MBCT significantly reduced depression, anxiety, and avoidance and gains were sustained at 3 months.
Michalak 2015 (score=5.0)	Mindfulness Based Therapy	RCT	Sponsored by the German Science Foundation. No mention of COI.	N = 106 patients with current major depressive episode and persistent depressive symptoms (DSM-IV)	Mean age: 50.8 years; 40 males, 66 females	MBCT Group: received mindfulness based therapy consisting of 8 weekly 2.5 hour groups sessions (body scan, sitting meditation, yoga) (n=36) vs CBASP	8 weeks	HAM-D scores reduced from 23.03 to 17.86 in the MBCT group, compared to 24.71 to 14.64 in the CBASP group and from 23.87 to 21.16 in the TAU group. No significant differences	"In conclusion, the results of the present study demonstrate the efficacy of CBASP in a group format for the treatment of chronically depressed patients. MBCT was effective in	TAU bias. Data suggest CBASP better than MBCT and TAU.

						Group: received cognitive behavioral analysis system of psychotherapy consisting of 2 individual treatment sessions and 8 weekly 2.5 hour group sessions (social problem solving skills, empathy, interpersonal discrimination exercises) (n=35) vs TAU Group: received treatment as usual of individual treatment by psychiatrist or licensed psycho-therapist (n=35)		observed between MBCT group and TAU group. CBASP group showed greater improvement in depressive symptoms compared to TAU group. CBASP group was favored over MBCT group (p=0.06).	one of the study centers but not in the other."	
Chiesa 2015 (score=4.5)	Education/ Mindfulness	RCT	No sponsorship or COI	N = 43 patients with diagnosis of major depression via DSM-IV-TR diagnosis criteria.	Mean age: 50.9 years; 12 males, 31 females.	Patients received eight sessions of either mindfulness-based cognitive therapy (MBCT) according to	Follow-up at baseline 4th, 8th, 17th, and 26th week.	Significant improvement of depressive symptoms as measured by Hamilton Rating Scale for Depression (HAM-D) for MBCT group	"[T]he results of the present study suggest the superiority of MBCT over psycho-education for patients with MD who did not achieve remission	Small sample. Data suggest MBT group showed long-term improvement in anxiety & mindfulness.

						manualized procedures (N = 20) vs: psycho-education (N = 20) carried out by a clinical psychologist and structured to be similar to MBCT.		compared with psycho-education group in both short term and long term periods (short term: p=0.002);(long term: p=0.002).	following antidepressant treatment."	
Shallcross 2015 (score=4.5)	Mindfulness Based Therapy	RCT	Sponsored by NIH-NCCIH, National Center for Complementary and Integrative Health. No mention of COI.	N = 92 participants with residual depressive symptoms (DSM-IV)	Mean age: 34.9 years; 21 males, 71 females	MBCT Group: received mindfulness based cognitive therapy (recognize and disengage from ruminative thinking and to process information to prevent depression relapse) (n=46) vs ACC Group: received therapeutic active control condition weekly classes each 2.5 hours for 8 weeks (n=46)	8 weeks, 6, 12 months	Depression symptoms relapse in the ITT sample was observed in 32.6% of MBCT group compared to 30.4% in the ACC group (OR=1.10, 95% CI .419-2.92, p=1). Depression symptoms relapse in the PP sample was observed in 23.5% of MBCT group compared to 29.2% in the ACC group (OR=1.34, 95% CI .264-7.02, p=0.736).	"Our findings indicate that MBCT and HEP are equally effective for preventing depression relapse, reducing depressive symptoms, and improving life satisfaction at a 60-week follow up."	Data suggest comparable efficacy between MBCT and ACC.
Eisendrath 2016 (score=4.5)	Mindfulness Based Therapy	RCT	Sponsored by NIH/NCCAM. No COI.	N = 173 participants with unipolar major depressive	Mean age: 46.1 years; 41 males, 132 females	MBCT Group: received 2 hour 15 minute weekly session for 8 weeks of mindfulness	4, 8, 24, 36, 52 weeks	Mean reduction of depression severity was 36.6% in the MBCT group compared to	"MBCT significantly decreased depression severity and improved	Data suggest MBCT showed greater reduction in $HAM\text{-}D_{17}$ scores

				disorder (DSM-IV)		based cognitive therapy (recognize and disengage from ruminative thinking and to process information to prevent depression relapse) (n=87) vs HEP Group: received health enhancement program consisting of group support and morale; reduction in stigma, facilitator attention; treatment duration, and time spent on at home practice (n=86)		25.3% in the HEP group (p=0.01). Remission rates were higher in MBCT group with 22.4% compared to 13.9% in the HEP group (p=0.15).	treatment response rates at 8 weeks but not remission rates. MBCT appears to be a viable adjunct in the management of TRD."	compared to HEP group.
Ma 2004 (score=4.5)	Mindfulness Based Therapy	RCT	No mention of sponsorship or COI.	N = 75 patients with major depressive disorder (DSM-IV)	Mean age: 44.5±8.9 years; 38 males, 37 females	MBCT Group: received mindfulness based cognitive therapy (a manualized group skills-training program) consisting of 8 weekly 2 hour sessions focusing on	1, 6 months	Relapse was reduced from 78% to 36% in 55 patients of MBCT group compared to TAU group (HR=0.278, 95% CI 0.130-0.597, p=0.001) for patients with 3+ depression episodes. In patients with 2 episodes of	"MBCT is an effective and efficient way to prevent relapse/recurrence in recovered depressed patients with 3 or more previous episodes."	TAU bias. Data suggest MBCT may be effective for prevention of relapse in depressed patients with 3 or more previous episodes.

						bodily sensations, thoughts, and feelings to prevent relapse in depression (n=37) vs TAU Group: patients received treatment as usual encourage to seek help from family doctor or other sources that would normally be used (n=38)		depression, MBCT showed relapse of 50% in MBCT group compared to 20% of TAU group (p=0.321).		
Teasdale 2000 (score=4.5)	Mindfulness Based Therapy	RCT	Sponsored by grant from the Wales Office of Research and Development for Health and Social Care and by the National Institute of Mental Health. No mention of COI.	N = 145 patients with major depression (DSM-III)	Mean age: 43.3 years; 35 males, 110 females	MBCT Group: received mindfulness based cognitive therapy (a manualized group skills-training program) consisting of 8 weekly 2 hour sessions focusing on bodily sensations, thoughts, and feelings to prevent relapse in depression (n=76) vs TAU Group: patients received	10, 20, 30, 40, 50, 60 weeks	Patients with 3+ previous episodes of depression showed a reduced risk of relapse in the MBCT group. Patients with only 2 previous episodes of depression, MBCT group did not reduce relapse. In the PP sample, relapse was lower in MBCT group compared to TAU group (HR=0.419, 95% CI 0.229-0.766, p<.005). Relapse was observed in 56% of MBCT group compared to 31%	"MBCT offers a promising cost-efficient psychological approach to preventing relapse/recurrence in recovered recurrently depressed patients."	TAU bias. Data suggest MBCT may benefit patients with 3 or more episodes of depression.

						treatment as usual encourage to seek help from family doctor or other sources that would normally be used (n=69)		in the TAU group (p>0.10).		
Forkmann 2014 (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by the Dutch Organization for Scientific Research. No COI.	N = 130 patients with residual depressive symptoms, determined by a scale of ≥7 oh the HAM-D17 scale	Mean age: 44 years; 31 males, 99 females	Group 1: received 8 weekly classes on Mindfulness-based cognitive therapy (MBCT) for 2.5 hours, with 30-60 min of individual homework daily (n=64) vs Group 2: participants were put on a waiting list to receive the MBCT treatment after the duration of the study (n=66)	No mention of follow-up past the duration of 8 week treatment	Mean suicidal ideation score decreased from 0.31 to 0.11 in MBCT group and increased from 0.20 to 0.25 in the control group (p=0.008). Mean depression score changed from 10.27 to 7.14 in MBCT group and 10.21 to 9.68 in the control group. (p=0.52). Mean mindfulness score increased from 119.98 to 134.80 in MBCT group and 121.21 to 124.62 in the control group (p=0.77). Mean rumination decreased from 42.16 to 34.38 in MBCT group and 40.77 to 37.92 in the control group (p=0.77).	"The results suggest that MBCT may affect suicidal ideation in patients with residual depressive symptoms and that this effect may be mediated, in part, by participants' enhanced capacity to distance themselves from worrying thoughts."	"Waitlist control bias. Data suggest MBCT may reduce suicidal ideation in depressed patients."

Teismann 2014 (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by the German Research Society. No mention of COI.	N = 60 patients meeting the DSM-IV criteria for Major Depressive Disorder, recurrent, in partial remission	Mean age: 47 years; 17 males, 43 females	Group 1: received 11 sessions of Cognitive-behavioral group treatment for depressive rumination (CBT-DR) (n=31) vs Group 2: participants were put on a wait list to receive CBT-DR after duration of study (n=29)	Follow-up period of 1 year post treatment	Mean BDI-II score changed from 22.93 to 10.23 in the CBT-DR group ($p<0.001$) and 21 to 18.14 in the control group ($p<0.05$). Mean PTQ score decreased from 41.32 to 32.58 in the CBT-DR group ($p<0.001$) and from 43.11 to 40.92 in the control group ($p<0.05$).	"The results indicate that cognitive behavioral group therapy for depressive rumination is effected and well accepted by patients suffering from residual depression."	Waitlist Control Bias. Data suggest CBT-DR seems effective in improving residual depression and patients were satisfied with the treatment.
Huijbers 2015 (score=4.0)	Mindfulness Based Therapy	RCT	No mention of sponsorship or COI.	N = 68 patients with a history of depressive episodes due to major depressive disorder (DSM-IV)	Mean age: 51.7 years; 19 males, 49 females	MBCT+mADM Group: received 8 weekly sessions of 2.5 hours of meditation exercise (body scan, sitting meditation, walking and mindful movement), informal exercises (awareness during every day activity), and cognitive behavioral techniques (education, monitoring,	3, 6, 9, 12, 15 months	Relapse was observed in 36% of MBCT+mADM group compared to 37% in the mADM group ($p=0.95$). Relapse was 39% in MBCT+mADM group compared to 48% in mADM group ($p=0.57$) in the PP sample.	"For this selection of recurrently depressed patients in remission and using mADM for 6 months or longer, MBCT did not further reduce their risk for relapse/recurrence or their (residual) depressive symptoms."	Data suggest MBCT did not further reduce the risk of relapse for patients using m/ADM for 6 months or longer.

						identification of negative thoughts, and devising a relapse prevention plan) sessions and continue taking mADM medication using normal dose (n=33) vs m-ADM Group: received 1 visit with study psychiatrists to review antidepressant medication, and instructed to maintain or reinstate adequate dose of mADM (n=35)				
Huijbers 2016,a (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by ZonMW, The Netherlands Organization for Health Research and Development. No COI.	N = 249 patients with major depressive disorder (DSM-IV)	Mean age: 50.3 years; 81 males, 168 females	MBCT+Discontinuation Group: received 8 weekly sessions of 2.5 hours of meditation exercise (body scan, sitting meditation, walking and mindful movement), informal exercises	3, 6, 12, 15 months	Relapse was observed in 54% of MBCT+discontinuation group compared to 39% in MBCT+mADM group (RR=1.38, 95% 1.05-1.83, p=0.005).	"Our findings suggest an increased risk of relapse/recurrence in patients withdrawing from mADM after MBCT."	Data suggest an increased risk of depression relapse if withdrawing from mADM after MBCT.

						(awareness during every day activity), and cognitive behavioral techniques (education, monitoring, identification of negative thoughts, and devising a relapse prevention plan) sessions and were asked to taper off antidepressants over 5 weeks (n=128) vs MBCT+mADM Group: received same treatment as other group except was asked to maintain or reinstate an adequate dose of antidepressant followed by antidepressant (n=121)				
Huijbers 2016,b (score= N/A)	Mindfulness Based Therapy	Post-hoc analysis of Huijbers 2015 and 2016.	No mention of sponsorship or COI.	N = 317 patients with a history of at least 3 previous depressive	Mean age: 50.6 years; 77 males, 240 females	MBCT + Discontinuation Group: received 8 weekly sessions of 2.5 hours of	3, 6, 9, 12 and 15 months	Relapse rate was 39% in the MBCT preference group compared to 36% in the mADM preference group (p=0.8). Relapse	"The fact that patients with a preference for medication did equally well as those with a preference for	Data suggest no preference between relapse rates of either MBCT or medications.

				episodes (DSM-IV)		meditation exercise (body scan, sitting meditation, walking and mindful movement), informal exercises (awareness during every day activity), and cognitive behavioral techniques (education, monitoring, identification of negative thoughts, and devising a relapse prevention plan) sessions and were asked to taper off antidepressants over 5 weeks (n=249) vs MBCT + mADM Group: received same treatment as other group except was asked to maintain or reinstate an adequate dose of antidepressant followed by		time was not predicted by treatment preference, depression severity, or number of previous episodes or mindfulness skills (HR=1.32, 95% CI 0.70-2.51, p=0.41).	mindfulness supports the applicability of MBCT for recurrent depression. Future studies of MBCT should include measures of preferences to increase knowledge in this area."	

						antidepressant (n=68)				
Geschwind 2012 (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by Dutch Organisation for Scientific Research and Servier. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 130 participants with major depressive disorder (DSM-IV and HRSD scale)	Mean age: 43.9 years; 32 males, 98 females	MBCT Group: received weekly (2.5 hour) meetings for 8 weeks of mindfulness based cognitive therapy including meditation, exercises, and discussions (n=64) vs Control Group: (n=66)	6, 12 months	Reduction in depression symptoms was observed in MBCT group (HRSD: β=0.45, 95% CI -0.18-1.07, p=0.16) compared to control group. $HRSD_{17}$ scale also showed a reduction in depressive symptoms for the MBCT group compared to control (β=-0.56, 95% CI -0.87 - -0.25, p<0.001).	"In summary, the main benefit of the current study is that it suggests that MBCT is also efficacious in individuals with only one or two prior episodes of major depression given current residual depressive symptoms."	Waitlist control bias. Data suggest significant reduction of depressive symptoms with MBCT.
Godfrin 2010 (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by the Flemish Ministry of Welfare, Health, and Family, Belgium. No COI.	N = 106 recovered depressed patients with a history of at least 3 depressive episodes according to the DSM-III-R criteria	Mean age: 45.5 years; 20 males, 86 females	Group 1: Mindfulness Based Cognitive Therapy (MBCT) in group sessions for 2.75 hours/week for 8 weeks in addition daily homework for 45min/day 6 days/week. Participants also had treatment as usual (TAU) (n=52) vs	Follow up at 2, 8, and 14 months	30% of Group 1 and 68.1% of patients in Group 2 experienced at least 1 relapse during the course of treatment (p<0.0005). In both groups, participants with a baseline HRSD score greater than 7 had much shorter time to relapse in depression (p<0.05).	"For patients with a history of at least three depressive episodes who are not acutely depressed, MBCT, added to TAU, may play an important role in the domain of relapse prevention in depression.	Treatment as usual bias. Waitlist control bias. Baseline differences in-group ages. Data suggest MBCT may benefit depressed patients who are not severely depressed by preventing relapse recurrence.

						Group 2: Wait-listed for MBCT while receiving TAU (n=54)				
Ly 2014 (score=4.0)	Mindfulness Based Therapy	RCT	Sponsored by the Regional Ethics Board of Linkoping, Sweden. One or more of the authors have received or will receive benefits for personal or professional use.	N = 81 participants diagnosed with major depressive disorder with an episode in partial remission according to the DSM-IV criteria	Mean age: 36.0 years; 24 males, 57 females	Group 1: Received behavioral activation (BA) therapy for 8 weeks, administered via smartphone application. Participants were given daily activities to do in order to add structure to their routines, along with access to a therapist and reading assignments (n=40) vs Group 2: received mindfulness treatment for 8 weeks, administered via smartphone application. Participants given a many guided and unguided mindfulness exercises lasting either 3	6 month follow-up	Mean BDI-II and PHQ scores were similar between the groups post-treatment ($p=0.60$). BA treatment was more effective than the mindfulness treatment among participants with higher severity depression ($p<0.05$). Mindfulness treatment was more effective than BA treatment among participants with low and moderate depression ($p<0.05$).	"The two interventions did not differ significantly from one another. For participants with higher severity of depression, the treatment based on BA was superior to the treatment based on mindfulness. For participants with lower initial severity, the treatment based on mindfulness worked significantly better than the treatment based on BA."	6-month follow-up. Similar efficacy between interventions. Data suggest severely depressed patients responded best to BA while moderately depressed patients did best with mindfulness.

						or 30 minutes. Participants received motivational and educational emails from therapists (n=41)				
Falsafi 2016 (score=3.5)										Figure 1 does not show completers. Data suggest improvement in both groups for anxiety, depressive symptoms, and stress. The mindfulness group reported increase self-compassion.[59]
Wetherell 2017 (score=3.5)										Antidepressant type and utilization different between groups. Data suggest best improvement in mindfulness group in terms of depression, excessive worry and perhaps some

[59] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										memory function.
Williams 2014 (score=3.5)										TAU bias. Data suggest lack of efficacy of MBCT for the prevention of relapse in depression but some benefit to those with a history of childhood trauma.
Barnhofer 2015 (score= N/A)		Secondary Analysis of Williams 2013.								TAU bias. Data suggest mindfulness training is associated with reductions in suicidal thinking in individuals with histories of suicidal depression.
Gallegos 2013 (score=3.5)										Waitlist control bias. Data suggest increased age and less severe depression symptoms likely respond better to MBSR.[60]

[60] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Jain 2007 (score=3.0)										Waitlist control bias. Data suggest both intervention groups resulted in improved mood and decreased stress. Mindfulness appears to decrease rumination.
Sundquist 2015 (score=2.5)										Usual care bias. Data suggest comparable efficacy for both groups.
Manicavasagar 2012 (score=2.0)										Sparse methods. Data suggest both groups showed similar efficacy in terms of depression and rumination scores.[61]

[61] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Unutzer, 2002 (score=7.0)	Disease Management Programs	RCT	Sponsored by the John A. Hartford Foundation, the California Healthcare Foundation, the Hoog Foundation, and the Robert Wood Johnson Foundation. Dr Williams served on the Primary Care Advisory board for Pfizer, received funding from GlaxoSmithKline, serves as associate director the Depression and Primary Care Initiative. Dr Lin has served as a consultant for Innovative Medical Education.	N = 1801 patients 60 years or older with major depression, dysthymic disorder, or both.	Mean age: 71.2 years; 633 males, 1168 females	IMPACT intervention: access to a depression care manager who provided them extensive education and support for depression (n=906) vs Usual care: use of any primary care or specialty mental health care services available to them in usual care (n=895).	Follow-up 3, 6, and 12 months.	45% of the intervention group patients and 19% of usual care patients had 50%< reduction in depressive symptoms (CI 2.71-4.38, P<.001). Greater quality of life, lower depression severity more satisfaction with depression care, and less functional impairment was seen in the intervention group to the usual care group.	"The IMPACT collaborative care model appears to be feasible and significantly more effective than usual care for depression in a wide range of primary care practices."	Usual Care Bias. Data suggest the IMPACT collaborative care model was better than usual care group.
Smit, 2006 (score=6.0)	Disease Management Programs	RCT	Sponsored by the Dutch Organization for Scientific Research, Medical Sciences Program and Chronic Diseases Program, the Research Foundations of the Health Insurance Company. No COI.	N = 267 adult patients meeting criteria for DSM-IV major depressive disorder.	Mean age: 42.6 years; 96 males, 171 females.	Depression Recurrence Prevention (DRP): structured psychoeducational intervention (n=112) vs DRP and psychiatric consultation (PC+DRP): 1-hour visit with a psychiatrist (n=39) vs DRP and cognitive behavior therapy (CBT+DRP): 10-	Follow-up at 3 and 6 months.	BDI scores on depression severity improved during the first 6 months (6.81 point average). No noteworthy statistical differences were found in between treatment groups, no evidence was found that enhanced care was more effective than care as usual.	"Enhanced care did not result in better short-term outcomes. We found no evidence that the DRP program was more effective than CAU and no indications for added beneficial effects of either the psychiatric evaluation of the CBT treatment	Care as usual bias. Data suggest lack of superiority of enhanced treatment for depression short term effects.

						12 individual weekly 1-hour session of CBT (n=44) vs Care as Usual (CAU): referred back to their PCP and received care that the PCP deemed appropriate (n=72)			to the basic format of the DRP program. Observed depression treatment rates in CAU were high."	
Kroenke, 2009 (score=6.0)	Disease Management Programs	RCT	Sponsored by The National Institute of Mental Health. No COI.	N = 250 patients with low back, hip or knee pain for 3< months on the Stepped Care for Affective Disorder and Musculoskeletal Pain (SCAMP) scale and moderate depression severity (score of 9 or less out of 10 on the Patient Health Questionnaire).	Mean age: 55.5 years; 118 males, 132 females.	Intervention group: 12 weeks of optimized antidepressant therapy followed by 6 sessions of a pain self-management program over 12 weeks and continuation phase of therapy for 6 months (n=123) vs Usual care group: patients informed they had depressive symptoms and that they should seek advice for treatment, no other attempts taken to influence management by study personnel (n=127)	Follow-up at 6 and 12 months.	37.4% of intervention patients and 16.5% of usual care patients had a 50%< reduction in depression severity (RR, 0.6; 95% CI, 1.5-3.2). Reduction in pain, global improvement of pain, and benefits in terms of the primary outcome was seen in intervention patients (RR, 3.3; 95% CI 1.8-5.4).	"Optimized antidepressant therapy followed by a pain self-management program resulted in substantial improvement in depression as well as moderate reductions in pain severity and disability."	Usual care bias. Data suggest optimized antidepressant therapy couples with a self-management pain program improved depression as well as decreased pain severity and disability.
Katzelnick, 2000 (score=5.5)	Disease Management Programs	RCT	Sponsored by Pfizer Pharmaceuticals Inc. No mention of COI.	N = 407 depressed patients (DSM-IV)	Mean age: 45.5 years; 152 males,	Depression management program (DMP): patient education	Follow-up at 6 weeks; 3,	Improvements in Ham-D scores were greater in the intervention group vs the usual care group	"In depressed high utilizers not already in active treatment, a	Usual care bias. Data suggest for high utilizers not already in an

					252 females.	materials, physician education programs, telephone-based treatment, antidepressant pharmacotherapy managed by patients PCP; blinded telephone assessments at 1.5, 3, 6, and 12 months (n=218) vs Usual care (UC): usual care with a primary care physician; blinded telephone assessments at 1.5, 3, 6, and 12 months (n=189)	6, and 12 months.	at 6 weeks, 3 months, 6 months, and 12 months (P=.04; P=.02; P<.001; P<.001); DMP patients were overall more improved than UC patients at 12 months.	systematic primary care-based treatment program can substantially increase adequate antidepressant treatment, decrease depression severity, and improve general health status compared with usual care."	active treatment and a systematic depression management program can improve anti-depressant treatment and decrease severity of depression.
Hansen, 2012 (score=5.5)	Disease Management Programs	RCT	Sponsored by the Lundbeck Foundation and the Research Foundation of the Hovedstadens Syghufaellesskab. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 268 patients with an ICD-10 diagnosis of unipolar depression.	Mean age: 38.6 years; 99 males, 169 females.	Intervention: treated in a specialized outpatient mood disorder clinic; 1 ½ hours of group sessions every week for 12 weeks (n=131) vs Control: offered standard care consisting of the standard mental health with a local general practitioner, private psychiatrist, or the local community	Follow-up at 12 months.	No significant differences were demonstrated in the time of readmission (p=0.6). There was no significant difference in the total score of the MDI (p=0.7) and the prevalence of hypomanic episodes did not differ at the one year follow up on MDQ scale (p=0.6). Treatment satisfaction at the one year follow up had significant differences between the two treatment groups (p<0.001).	"Centralised and specialised secondary care intervention in the early course of severe unipolar depression resulted in no significant effects on time to prehospitalisation, severity of symptoms, or us of antidepressants, but increased patient satisfaction."	Data suggest no difference between groups except improved patient satisfaction.

						health center for 12 weeks (n=137)				
Aragones, 2012 (score=5.5)	Disease Management Programs	RCT	Sponsored by the Carlos III Health Institute of the Spanish Ministry for Health and Consumption. COI: Aragones received honorarium as research advisor and meeting expenses from Lilly.	N = 338 patients 18+ years with DSM-IV criteria of major depressive disorder.	Mean age: 47.65 years; 70 males, 268 females.	Intervention: multi-component chronic care program to manage depression (no specific duration or time) (n=189) vs Control: doctors use their own criteria to attend to patients and use all available resources (no specific duration) (n=149)	Follow-up at 3, 6, and 12 months.	Severity of depression was lower in the intervention group when compared to the control group at 12 months (1.76 points), treatment response rates were also higher (p=0.011).	"The programme for managing depression leads to better clinical outcomes in patients with major depression in primary care settings."	Usual care bias. Data suggest both the treatment response rate and remission rate was improved in intervention group.
Simon, 2004 (score=5.0)	Disease Management Programs	RCT	Sponsored by the National Institute of Mental Health. No COI.	N = 600 primary care patients beginning antidepressant treatment for depression.	Mean age: 44.8 years; 154 males, 446 females.	Usual Care: primary care available to patients (n=195) vs Telephone Management Care: self-management workbook + a structured, scripted telephone program with 3 outreach calls (n=207) vs Telephone Management Care + Telephone Psychotherapy: all aspects of the telephone management care program + structured 8-session cognitive behavioral psychotherapy, 8	Follow-up at 6 months.	Telephone psychotherapy intervention had lower depression scores on the Hopkins Symptom Checklist Depression Scale (SCL) (P=.02) during follow up and a higher rate of patients reporting that depression was improved (P<.001). Difference between telephone care management group and usual care group was no significant (p=.40). Telephone care management had patient reporting's of improvement (P=.004).	"For primary care patients beginning antidepressant treatment, a telephone program integrating care management and structured cognitive-behavioral psychotherapy can significantly improve satisfaction and clinical outcomes. These findings suggest a new public health model of psychotherapy for depression including active outreach and	Usual care bias. Data suggest primary care patients starting antidepressant treatment a telephone program connecting care management and structured CB psychotherapy can improve depression.

						30-40 minutes sessions (n=198)			vigorous efforts to improve access to and motivation for treatment."	
Ludman, 2007 (score=5.0)	Disease Management Programs	RCT	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 393 patients beginning antidepressant treatment in primary care.	Mean age: 44.4 years; 100 males, 293 females.	Usual care: routine care received by patients with no intervention (n=195) vs Telephone Psychotherapy: 8 core sessions of a structured cognitive-behavioral 30-40 minute telephone call with 2-4, 15-minute booster sessions over the year (n=198)	Follow-up 18 months.	When compared to usual care at 6-18 months, the telephone psychotherapy group demonstrated lower mean HSCL depression scores (p<.001). Average depression scores from months 6-18 in the telephone psychotherapy and usual-care groups were .68 (SD=0.55) and .85 (SD=0.65).	"We conclude that the addition of a brief, structured CBT program can significantly improve clinical outcomes for the large number of patients beginning antidepressant drug treatment in primary care."	Usual care bias. Data suggest the addition of a brief CBT program to usual care that
Murray 2010 (score=4.5)	Integrative Program Intervention	RCT	Sponsored by grant from VGH and UBC Hospital Foundation. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 64 patients with a DSM-IV diagnosis of chronic MDD, dysthymic disorder with superimposed MDD, or MDD in partial remission.	Mean age: 45.0 years; 18 males, 46 females	Re-CHORD Group: received 4 month outpatient program with of medication management, group-based interpersonal psychotherapy (16 90- minute sessions, and group occupational therapy (10-12 sessions once a week) (n=34) vs TAU Group: received treatment as usual consisting of physician consultation and using available	4 months	Re-CHORD group showed greater remission rates of depression compared to TAU group in HAM-D 17 scores (p=0.021). Greater improvement in BDI2 and HSCL scores was observed in Re-CHORD group compared to TAU group (p=0.26, p=0.20; respectively).	"Consistent with growing evidence that integrative treatments are necessary for chronic depressive disorders, Re-ChORD was demonstrated in this pilot study to produce significantly greater rates of remission than treatment as usual."	TAU bias. Data suggest Re-CHORD was associated with greater numbers of remission rates than TAU.

						resources with medication or psycho-therapeutic management for 4 months (n=30)				
Damush 2016 (score=4.5)	Pain Self-Management Program	RCT	Sponsored by grant from National Institute of Mental Health. No COI.	N = 250 patients with chronic musculoskeletal pain and comorbid depression (PHQ-9 scale)	Mean age: 55.5 years; 118 males, 132 females	PSM Group: pain self-management program treatment with 6 sessions of self-management (medication management, setting goals, peer discussion, behavior assessment, and other self-management strategies) (n=123) vs Usual Care Control: usual care, diagnosis of depression and told to seek advice from primary care provider about treatment (n=127)	12 months	Pain self-efficacy was improved in PSM group greater than the control group (1.33 vs 0.61, $p<0.05$). Depression self-efficacy was improved more in the PSM group compared to control group (6.69 vs 5.9, p=0.03).	"A combined intervention increased patient self-management behaviors and self-efficacy to manage symptoms among primary care patients with chronic musculoskeletal pain and depression. Receipt of the full dose of the entire PSM program was related to improvements in pain interference and depression severity. "	Usual care bias. Data suggest interventional group resulted in improved self-efficacy and self-management behaviors.
Bartels 2014 (score=4.5)	Integrated Skills Training	RCT	Sponsored by a grant from the National Institute of Mental Health. No mention of COI.	N = 183 participants with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or major	Mean age: 60.2±7.9 years; 77 males, 106 females	HOPES Group: psychosocial functioning and preventive healthcare intervention with weekly skills training classes for 1 year, and 1 year maintenance phase with monthly booster sessions, social skills	1, 2, 3 years	HOPES group showed greater improvement in living skills, functioning, self-efficacy, and psychiatric and negative symptoms ($F(2, 151) = 5.10$, $p = 0.007$).	"Skills training and nurse facilitated preventive healthcare for older adults with serious mental illness was associated with sustained long-term improvement in functioning,	TAU bias. Data suggest improved overall functioning in the integrated skills training and preventive healthcare group.

				depression (DSM-IV)		training, communication, healthy living sessions (2 daily sessions, 2 monthly community trips) and monthly meetings with nurse (n=90) vs TAU Group: same services received prior to study (n=93)			symptoms, self-efficacy, preventive healthcare screening, and advance care planning.“	
Berger 2011 (score=4.5)	Internet-based treatment	RCT	Sponsored by grant from Swiss National Science Foundation, Swedish Research Council. No mention of COI.	N = 76 individuals with diagnosis of major depression or dysthymia (DSM-IV)	Mean age: 38.8±14.0 years; 23 males, 53 females	Pure Self-Help: web-based self-help program (psychoeducation, mindfulness exercises, lifestyle modification, and other behavioral and psychological therapies), 10-60 minute sessions each without support from therapist for 10 weeks (n=25) vs Guided Self-Help: web-based self-help program (described above) plus scheduled email contact with therapist for 10 weeks (n=25) vs Waitlist Control (n=26)	10 weeks, 6 months	Reduction of depression symptoms measured by BDI-2 showed greater improvement in treatment groups compared to control ($p<0.009$), but not between the intervention groups ($p=0.88$) ($F(2.72) = 9.21$, $p<0.001$).	“The findings provide evidence that internet-delivered treatments for depression can be effective whether support is added or not. However, all participants were interviewed in a structured diagnostic telephone interview before inclusion, which prohibits conclusions regarding unguided treatments that are without any human contact.”	Waitlist control bias. Data suggest both the guided as well as the unguided group improved and maintained treatment gains at 6 months.

Katon 1996 (score=4.5)	Structured Depression Treatment Program	RCT	Sponsored by National Institute of Mental Health. No mention of COI.	N = 153 patients with current major or minor depression (DSM-III-R)	Mean age: 46.4±13.6 years; 40 males, 113 females	Intervention Group: targeted CBT skills teaching (4 sessions involving education, skills training, homework, or behavior experiments), counseling to improve medication adherence, 4-6 contacts with a psychologist (total of 2.5-3.5 hours) (n=77) vs Usual Care by primary care physician (n=76)	1, 4, 7 months	Improvement in SCL-20 depression of 50% or more was observed in 70.4% of intervention group compared to 42.3% of usual care group (p=0.04). Similarly, 74.1% of intervention group showed improved IDS score compared to 42.3% of usual care group (p=0.02).	"A multifaceted primary care intervention improved adherence to antidepressant regimens and satisfaction with care in patients with major and minor depression. The intervention consistently resulted in more favorable depression outcomes among patients with major depression, while outcome effects were ambiguous among patients with minor depression."	Usual care bias. At 4 months, data suggest more patients in the intervention group adhered to medication and reported improvement in depression severity.
Lin 1999 (score=N/A)	Disease Management Programs	19 month follow-up of Katon 1995 and 1996	No mention of COI. Sponsored by the NIMH.	N = 156 with a 20-item Symptom Checklist (SCL) depression screening score of 0.75+	Mean age: 44.1 years; 62 males, 94 females	Enhanced Intervention – including education, a booklet on simple cognitive behavioral techniques for managing depression, alternating visits with primary care physician and psychiatrist over 4-6 weeks with 7-10	Follow-up at 19 months	Data only available for 116 patients. Hopkins Symptom Checklist (HSCL) score at 16 months: intervention = 16.4, control = 16.3 (F=0.001, p=0.97). Inventory of Depressive Symptomatology score at 16 months: intervention = 17.6, control = 15.9 (F=001, p=0.98)	"Even though enhanced acute-phase treatment of depression in primary care resulted in better treatment adherence and better clinical outcomes at 4 and 7 months, these improvements failed to persist over the	Usual care bias. Data suggest improvement of treatment adherence and better clinical outcomes did not persist at 19 months post-intervention.

						days between appointments (n=63) vs. Non-Enhanced Intervention – received no altered care (n=53)			following year. Continued enhancement of depression treatment may be needed to ensure better long-term results."	
Perini 2009 (score=4.5)	Internet-based treatment	RCT	No mention of sponsorship or COI.	N = 48 participants with depression (DSM-IV)	Mean age: 49.29±12.06 years; 10 males, 35 females	Sadness Program: online lessons (CBT including behavioral activation, cognitive restructuring), homework assignments, online discussion forum, and regular email contact with mental health clinician for 8 weeks (do 1 lesson every 7-10 days and complete 6 lessons within 8 weeks) (n=27) vs Waitlist Control (n=18)	8 weeks	Sadness program showed greater improvement in PHQ-9 ($F(1, 42) = 8.97$, $p<0.01$) and BDI-2 ($F(1, 42) = 6.01$, $p<0.02$) scores compared to control group.	"In conclusion, these encouraging results provide further support for larger scale trials to determine the clinical efficacy and effectiveness of CCBT programmes for the common mental disorders."	Waitlist control bias. Data suggest an internet-based treatment for depression and other mental health disorders coupled with clinical guidance can improve symptoms of depression.
Simon 2000 (score=4.0)	Feedback and Care Management	RCT	Sponsored by US National Institute of Mental Health. COI: All authors are employees of Group Health Cooperative of Puget Sound.	N = 613 patients with depression (DSM-IV)	Mean age: 46.5 years; 174 males, 439 females	Care Management: phone call from care manager and two 10-15 minute calls at 8 and 16 weeks after initial prescription of antidepressant, feedback report, 15 minutes weekly supervision from psychiatrist	3, 6 months	Depression score was lower in the care management group compared to the usual care group ($t=2.59$, $p=0.008$). Depression score in feedback only group did not differ compared to the usual care group ($t=0.22$, $p=0.82$).	"Monitoring and feedback to doctors yielded no significant benefits for patients in primary care starting antidepressant treatment. A programme of systematic	Usual care bias. Data suggest a program of monitoring, feedback, and care management improved outcomes at some cost. It is unclear if improvements

						(n=196) vs Doctors received a detailed report on each patient 8 and 16 weeks after initial prescription of antidepressant (n=221) vs Usual Care from primary care physician (n=196)			follow up and care management by telephone, however, significantly improved outcomes at modest cost."	were due to intensive pharmacotherapy effects of contact with the case manager or more appropriate follow-up care.
Wang 2007 (score=4.0)	Care Management Group	RCT	Sponsored by grant from National Institute of Mental Health, Robert Wood Johnson Foundation, and the John D. and Catherine T. MacArthur Foundation. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 604 depressed workers (K-6)	Mean age: 41.5 years; 158 males, 446 females	Intervention Group: received telephone outreach and care management program (psychotherapy and/or antidepressant medication), monitored treatment quality continuity, (also offered 8 sessions of CBT after 2 months of severe continued depression) (n=304) vs Usual Care Group: (n=300)	6, 12 months	QIDS-SR scores were lower in the intervention group compared to the usual care group at 12 months (30.9% vs 21.6%, OR=1.7; 95% CI 1.1-2.5).	"A systematic program to identify depression and promote effective treatment significantly improves not only clinical outcomes but also workplace outcomes. The financial value of the latter to employers in terms of recovered hiring, training, and salary costs suggests that many employers would experience a positive return on investment from outreach and enhanced treatment of	Usual care bias. Data suggest a systematic program, which identifies depression and improves clinical outcomes also improves workplace outcomes.

									depressed workers."	
Simon 2006 (score=4.0)	Disease Management Programs	RCT	Sponsored by the National Institute of Mental Health and Lilly Research Laboratories. No mention of COI.	N = 207 patients with depressive disorder. No mention of diagnostic criteria	Mean age: 43.01 years; 73 males, 134 females	Care managers contacted participants within 2 weeks of randomization, then again 4 and 12 weeks later, sessions included assessment of depressive symptoms, medication adherence and side effects, as well as feedback to treating psychiatrists (n=103) vs. Usual care – no contact until first assessment at 3 months (n=104)	Follow-up at 3 and 6 months	Hopkins Symptom Checklist (SCL) depression scale scores 6 month: care management group = 0.95, usual care bias = 1.08 (difference = 0.13, $p > 0.05$).	"This study found that a low-intensity telephone care management program did not appear to significantly improve clinical outcomes for patients starting antidepressant treatment. Compared with findings from earlier primary care studies, this study found that patients receiving care from a psychiatrist received more intensive treatment, although many still experienced poor outcomes."	Usual care bias. Data suggest no benefit in a telephone care management program over usual care.
Katon 2001 (score=4.0)	Disease Management Programs	RCT	Sponsored by the National Institute of Mental Health Services Division, Bethesda. No mention of COI.	N = 386 with DSM-IV major depressive symptoms and history of 3+ residual	Mean age: 46 years; 102 males, 284 females	Received usual care involved prescription of antidepressant medications and an offer to refer to mental health services (n=192) vs. Relapse prevention program – patient	Follow-up at 3, 6, 9, and 12 months	Those in relapse prevention program significantly more likely to refill antidepressant prescriptions (adjusted OR: 1.91, $p<0.001$), also more likely to receive adequate dosage (adjusted OR: 2.08, $p<0.001$).	"A relapse prevention program targeted to primary care patients with a high risk of relapse/recurrence who had largely recovered after	Usual care bias. Data suggest the relapse prevention program was associated with greater adherence to medications and improved

				depressive symptoms		education, 2 visits with depression specialist (one 90 minute session, one 60 minute session), and 3 telephone monitoring sessions (n=194)			antidepressant treatment significantly improved antidepressant adherence and depressive symptom outcomes."	depressive symptoms.
Katon 1999 (score=4.0)	Disease Management Programs	RCT	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 228 with depressive symptoms via DSM-III-R criteria and score of 1.0 of greater on 20 depression items of Hopkins Symptom Checklist (SCL-20) or depressive symptoms via DSM-IV major depressive symptoms with score of 1.5+ on SCL-20	Mean age: 46.95 years; 58 males, 170 females	Usual care – including care provided by family physicians, antidepressant medication, and an option to be referred to a mental health services (n=114) vs. Collaborative Care Intervention – including psychiatric visits about every 2 weeks, medication adjustments, education (n=114)	Follow-up at 1, 3, and 6 months	Significant group x time interaction for SCL-20 (z = -2.06, p = 0.04). Significant differences in rate of change in severity from baseline to 3 months (F=12.38, p = 0.001), not significant difference from 3 to 6 months (F=3.09, p = 0.08).	"A multifaceted program targeted to patients whose depressive symptoms persisted 6 to 8 weeks after initiation of antidepressant medication by their primary care physician was found to significantly improve adherence to antidepressants, satisfaction with care, and depressive outcomes compared with usual care."	Usual care bias. Data suggest improvement in adherence to antidepressant and depression in intervention group compared to control.
Wells 2004 (score=4.0)	Education/ Disease Management Program	RCT	No mention of sponsorship or COI.	N = 991 participants with current depressive symptoms	Mean age: 43.6 years; 285 males, 706 females.	Intervention groups: patients randomized to 2 quality improvement (QI) intervention	Follow-up every 6 months for 24 months with	Patients randomized to quality improvement interventions showed lowering of the rate of probable depressive order when compared	"Programs for QI for depressed primary care patients implemented by managed care	Usual care bias. Data suggest at 5 years, results show managed care practice implemented QI

				via WHO's CIDI screening criteria.		groups where they received either medication management support (QI-meds) (n = 322) or cognitive behavioral therapy (QI-therapy) (n = 357) vs. Control group: patients received usual care (n = 312).	final follow-up at 57 months.	with patients receiving usual care (p=.04).	practices can improve health outcomes 5 years after implementation and reduce health outcome disparities by markedly improving health outcomes and unmet need for appropriate care among Latinos and African Americans relative to whites; thus, equity was improved in the long run."	programs may improve health outcomes. Multiple co-interventions.
Wells 2005 (score=N/A)										Usual care bias. Data suggest quality improvement interventions improved 57-month outcomes for patients with both subthreshold depression and depressive disorder. Same as Wells 2004.
Simon 2011 (score=3.5)										Usual care bias. Data suggest online follow-up care improved adherence to antidepressant

										over usual care.[62]
Dwight-Johnson 2001 (score=3.5)										Usual care bias. Data suggest quality improvement programs that accommodate patient and provider treatment choice may improve the probability of patients enrolling in a treatment for depression.
Rost 2001 (score=3.5)										Data suggest that in facilities without onsite mental health professionals, brief interventions can improve depressive symptoms.[63]
Clarke 2002 (score=3.5)										Usual care bias. Data suggest a trend towards efficacy in intervention group in lower

[62] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

[63] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										acuity (less severely) depressed patients.
Berghöfer 2012 (score=3.5)										Treatment as usual bias. Significant age differences in groups. Data suggest that the systematic treatment program shower superiority to the usual care group via patient's perspective not per physicians. At 12 months, the groups were similar.
Hunkeler 2012 (score=3.5)										Usual care bias. Data suggest web-delivered care management and patient self-management programs like eCare may help patients with chronic and/or recurrent depression.[64]
Kordy 2013										Data suggest potential value in internet

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(score=3.5)										delivered interventions for recurrent depression.
Kordy 2016 (score=N/A)										Post-hoc analysis of Kordy 2013. Data suggest the SUMMIT strategy has the potential to reduce the lifelong burden of recurrent depression.
Goracci 2016 (score=3.0)										Usual care bias. Low retention rate. Data suggest the healthy lifestyle intervention help to prevent relapse.[65]
Zanjani 2010 (score=3.0)										Usual care bias. Data suggest lack of efficacy of intervention group compared to control.
Mavandadi 2015 (score=3.0)										Data suggest symptom monitoring plus care management was associated with better outcomes.

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Aburizik 2013 (score=3.0)										Usual care bias. Data suggest a telephone-based intervention was effective in reducing symptoms of depression in veterans with chronic illness.
Ludman 2007 (score=3.0)										Usual care bias. Pilot study did not detect any clinical outcome differences.[66]
Oslin 2003 (score=2.5)										Usual care bias. Data suggest the use of a telephone disease management program for depression may improve patient outcomes.
Katon 1995 (score=2.5)										Usual care bias. Data suggest a multi-pronged collaborative program improved adherence to antidepressant regimens in patients with major and minor depression. However, over

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										time there were no significant differences between depressive symptoms in groups.
Datto 2003 (score=2.5)										Usual care bias. Data suggest telephone disease management for depressive improves guideline adherence and patient outcomes.[67]

[67] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Emotional Freedom Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Chatwin 2016 (score=4.0)	Cognitive Behavioral Therapy/Emotional Freedom Techniques	RCT	No mention of sponsorship. No COI.	N = 17 participants screened positive for major depressive disorder (MDD) determined by MINI-international neuropsychiatric interview (MINI) 6.0 compared with N=57 controls	No mention of mean age; 14 males, 53 females	EFT Intervention: received emotional freedom techniques program with 2 EFT therapists and standard protocols (n=11) vs CBT Intervention: received cognitive behavior therapy program (n=6) vs Controls: (n=57)	8 weeks, 3, 6 months	No differences in depression scores were observed between intervention groups (p=0.994); however, CBT group compared to the community control group showed lower depression scores (p=0.018), and also lower depression scores for EFT groups compared to community control group (p=0.003). At 8 week follow-up depression scores were higher in EFT groups compared to CBT group (p=0.003) and the community group (p<0.001), and the CBT group had higher depression scores than the control group	"The findings of the present study have indicated that EFT may be an effective treatment strategy worthy of further investigation."	Data suggest comparable efficacy between CBT and EFT on reducing depressive symptoms but CBT group gains not maintained over time.

								(p=0.042). At 3-month follow-up depression scores were higher only when comparing EFT groups compared to community group (p=0.03). At 6-month follow-up similar results were observed for only higher depression scores comparing EFT group to community group (p=0.022).		
Church 2014 (score=3.5)										Waitlist control bias. Data suggest pain ratings decreased in EFT group but data collection performed by individuals having allegiance to EFT which could have biased results.[68]

[68] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Antidepressants

Placebo Controlled RCTs Medication	Superior to Placebo	Not Different From Placebo	Inferior to Placebo
Selective Serotonin Reuptake Inhibitors (SSRI)			
Citalopram		Lepola 2003 (6.5) Feighner 1999 (5.5) Montgomery 1993 (5.0) Mendels 1999 (4.5)	
Escitalopram	Lepola 2003 (6.5) Wade 2002 (6.5) Kornstein 2006 (5.5) Lyketsos 2011 (5.5) Nierenberg 2007 (5.5) Kim 2015 (5.0)	Hellerstein 2010 (4.0)	
Fluoxetine	Silverstone 1999 (6.5) Nemeroff 2007 (5.5) Feighner 1989 (5.0) Byerley 1988 (4.5) Goldstein 2002 (4.5)	Rudolph 1999 (6.0) Fava 1998 (4.5)	
Fluvoxamine	Ottevanger 1994 (6.0) Fabre 1996 (5.5) Conti 1988 (4.5) March 1990 (4.5) Norton 1984 (4.5) Roth 1990 (4.5)		
Paroxetine	Trivedi 2004 (7.0) Detke 2004 (6.5) Claghorn 1993 (4.5) Feighner 1992 (4.5) Feighner 1993 (4.5) Higuchi 2011 (4.5) Kiev 1992 (4.0)	Goldstein 2004 (7.5) Smith 1992 (5.0) Baune 2018 (4.5) Fava 1998 (4.5) Perahia 2006 (4.5)	
Sertraline	Lydiard 1997 (7.0) Keller 1998 (4.5)	Wilson 2003 (6.0)	

	Kocsis 1997 (4.5) Lépine 2004 (4.5) Reimherr 1990 (4.5) Sheikh 2004 (4.5) Doogan 1994 (4.0) Kamijima 2006 (4.0)		
Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)			
Desvenlafaxine	Iwata 2013 (7.0) Dunlop 2011 (6.5) Endicott 2014 (6.5) Boyer 2008 (5.5) Clayton 2015 (5.5) Septien-Velez 2007 (5.5) DeMartinis 2007 (5.0) Liebowitz 2008 (5.0) Tourian 2009 (5.0) Boyer 2015 (4.0) Rosenthal 2013 (4.0)	Feiger 2009 (6.0) Liebowitz 2007 (5.0)	
Duloxetine	Goldstein 2004 (7.5) Detke 2004 (6.5) Brannan 2005 (6.0) Detke 2002a (5.5) Detke 2002b (5.5) Nierenberg 2007 (5.5) Arnold 2004 (4.5) Goldstein 2002 (4.5) Hellerstein 2012 (4.5) Mahableshwarkar 2013 (4.5) Perahia 2006a (4.5) Perahia 2006b (4.5) Perahia 2009 (4.5)	Christensen 2018 (5.5) Mahableshwarkar 2015 (5.5)	
Milnacipran	Macher 1989 (6.0) Rouillon 2000 (4.0)		

Reboxetine	Ban 1998 (5.5) Versiani 1999 (4.5)		
Venlafaxine	Alvarez 2012 (7.5) Cunningham 1994 (6.5) Hewett 2009 (6.5) Silverstone 1999 (6.5) Rudolph 1999 (6.0) Guelfi 1995 (5.5) Kornstein 2008 (5.5) Lecrubier 1997 (5.5) Nemeroff 2007 (5.5) Thase 1997 (5.5) Kocsis 2007 (5.0) Simon 2004 (4.0)		
Tricyclic Antidepressants (TCAs)			
Amitriptyline	Lydiard 1997 (7.0) Bakish 1992 (6.0) Wilcox 1994 (5.5) Bremner 1995 (5.0) Carman 1991 (5.0) Glen 1984 (5.0) Rickels 1982 (5.0) Smith 1975 (5.0) Reimherr 1990 (4.5) Rickels 1974 (4.0) Rickels 1979 (4.0)		
Amoxapine	Smith 1975 (5.0) Rickels 1975 (4.0)		
Clomipramine	Larsen 1989 (5.5) Lecrubier 1990 (4.0)		
Desipramine	Kocsis 1996 (6.5) Miller 2001 (6.0)		

	Ban 1998 (5.5) Roth 1990 (4.5)		
Dothiepin	Ferguson 1994 (4.5)	Doogan 1994 (4.0)	
Doxepin	Ferguson 1994 (4.5)		
Imipramine	Ottevanger 1994 (6.0) Cohn 1996 (5.5) Fabre 1996 (5.5) Fontaine 1994 (5.5) Feighner 1989 (5.0) Liebowitz 1988 (5.0) Quitkin 1988 (5.0) Rickels 1994 (5.0) Byerley 1988 (4.5) Claghorn 1993 (4.5) Feighner 1992 (4.5) Feighner 1993 (4.5) Gerner 1980 (4.5) Gershon 1981 (4.5) Hayes 1983 (4.5) Kocsis 1997 (4.5) March 1990 (4.5) McGarth 1996 (4.5) Norton 1984 (4.5) Versiani 1989 (4.5) Versiani 1990 (4.5) Udabe 1990 (4.5) Ball 1959 (4.0) Kiloh 1961 (4.0) Lecrubier 1990 (4.0) Stewart 1993 (4.0)	Lecrubier 1997 (5.5) Kasper 1995 (4.5)	
Maprotiline		Edwards 1983 (4.0)	
Mianserin	Wilcox 1994 (5.5) Carman 1991 (5.0)	Edwards 1983 (4.0)	

Mirtazapine	Halikas 1995 (7.0) Thase 2001 (6.0) Khan 1995 (5.5) Bremner 1995 (5.0) Claghorn 1995 (4.5) Vartiainen 1994 (4.5)		
Nortriptyline	Sullivan 1993 (5.5) Georgotas 1987 (4.0)		
Monoamine Oxidase Inhibitors			
Isocarboxazide	Zisook 1983 (4.5)		
Moclobemide	Bakish 1992 (6.0) Larsen 1989 (5.5) Lingjærde 1993 (5.0) Casacchia 1984 (4.5) Versiani 1989 (4.5) Versiani 1990 (4.5) Udabe 1990 (4.5) Lecrubier 1990 (4.0)		
Phenelzine	Liebowitz 1988 (5.0) Quitkin 1988 (5.0) Robinson 1973 (4.5) Georgotas 1987 (4.0) Stewart 1993 (4.0)		
Pirlindole	De Wilde 1996 (6.5)		
Selegiline	Bodkin 2002 (7.0) Amsterdam 2003 (6.5) Feiger 2006 (6.0) Amsterdam 2006 (5.0) Jang 2013 (5.0) Mann 1989 (5.0)		
Tranylcypromine	Himmelhoch 1982 (4.5)		
Atypical Antidepressants			

Agomelatine	Olié 2007 (6.5) Kasper 2013 (5.5)		
Amineptine	Ferreri 1997 (4.0)		
Bupropion	Hewett 2009 (6.5) Jefferson 2006 (6.5) Pitts 1983 (5.0) Zung 1983 (5.0)	Koshino 2013 (5.5)	
Nefazodone	Cohn 1996 (5.5) Feighner 1998 (5.5) Fontaine 1994 (5.5) Rickels 1994 (5.0) Feiger 1999 (4.5)		
Trazodone	Zhang 2014 (7.5) Halikas 1995 (7.0) Sheehan 2009 (7.0) Sheehan 2010 (7.0) Cunningham 1994 (6.5) Rickels 1982 (5.0) Gerner 1980 (4.5) Gershon 1981 (4.5) Hayes 1983 (4.5)		
Vortioxetine	Wang 2017 (9.0) Alvarez 2012 (7.5) McIntyre 2014 (7.5) McIntyre 2017 (7.5) Christensen 2018 (5.5) Henigsberg 2012 (5.5) Mahableshwarkar 2015 (5.5)	Jain 2013 (6.0) Liebowitz 2017 (6.0) Inoue 2018 (5.5) Nishimura 2018 (5.5) Baune 2018 (4.5) Mahableshwarkar 2013 (4.5)	
Antidepressant versus Antidepressant RCTs			
Reference Medication	Superior to Other Antidepressant	Not Different From Other Antidepressant	Inferior to Other Antidepressant
Selective Serotonin Reuptake Inhibitors (SSRI)			

Citalopram	Sertraline	Matreja 2007 (4.5)	Escitalopram	Ou 2011 (7.0) Colonna 2005 (6.5)	Escitalopram	Lepola 2003 (6.5) Yevtushenko 2007 (6.5)
			Fluvoxamine	Haffmans 1996 (6.5)		
			Maprotiline	Bouchard 1987 (4.0)		
			Mianserin	De Wilde 1985 (5.0) Guy 1983 (5.0)		
			Mirtazapine	Leinonen 1999 (6.5)		
			Sertraline	Ekselius 1997 (6.0) Hsu 2011 (6.0) Stahl 2000 (5.5) Ekselius 1998 (5.0)		
			Venlafaxine	Hosseini 2015 (4.5)		
Escitalopram	Agomelatine	Urade 2015 (5.0)	Agomelatine	Udristoiu 2016 (6.5) Corruble 2013 (6.0)	Nortriptyline	Martiny 2015 (6.0)
	Citalopram	Lepola 2003 (6.5) Yevtushenko 2007 (6.5)	Citalopram	Ou 2011 (7.0) Colonna 2005 (6.5)		
	Duloxetine	Khan 2007 (5.5)	Duloxetine	Pigott 2007 (6.0) Raskin 2012 (6.0) Nierenberg 2007 (5.5)		
	Paroxetine	Boulenger 2006 (7.0)	Paroxetine	Baldwin 2006 (6.0) Kishi 2017 (4.5)		
			Sertraline	Ventura 2007 (5.5)		
			Vortioxetine	Vieta 2018 (4.0)		
			Venlafaxine	Montgomery 2004 (7.5) Bielski 2004 (5.5)		
Fluoxetine	Milnacipran	Ansseau 1994 (5.5)	Amitriptyline	Beasley 1993 (5.0) Chouinard 1985 (5.0) Judd 1993 (5.0)	Duloxetine	Goldstein 2002 (4.5)
					Nortriptyline	Akhondzadeh 2003 (5.0)

			Marchesi 1998 (5.0) Feighner 1985 (4.5) Versiani 1999 (4.0)	Venlafaxine	Silverstone 1999 (6.5) Rudolph 1999 (6.0) Clerc 1994 (5.5) De Nayer 2002 (4.5)
		Bupropion	Feighner 1991 (4.0)		
		Desipramine	Bowden 1993 (5.5) Remick 1993 (5.5) Simon 1999 (4.0)		
		Doxepin	Remick 1989 (4.5)		
		Fluvoxamine	Dalery 2003 (6.0)		
		Imipramine	Feighner 1989 (5.0) Serrano-Blanco 2006 (5.0) Byerley 1988 (4.5) Simon 1999 (4.0)		
		Maprotiline	Martényi 2001 (5.5) Poelinger 1989 (5.5)		
		Mirtazapine	Versiani 2005 (6.0) Amini 2005 (5.5) Hong 2003 (5.5) Wheatley 1998 (4.5)		
		Moclobemide	Lapierre 1997 (6.5) Lonnqvist 1994a (6.0) Reynaert 1995 (6.0) Gattaz 1995 (5.5) Duarte 1996 (5.5) Williams 1993 (5.5) Larsen 1989 (5.5) Partonen 1996 (5.0) Geerts 1994 (4.5) Lonnqvist 1995 (4.5) Lonnqvist 1994b (4.0)		

			Nefazodone	Gillin 1997 (6.5) Rush 1998 (6.0)		
			Nortriptyline	Joyce 2002 (5.0)		
			Paroxetine	Chouinard 1999 (4.5) De Wilde 1992 (4.5) Fava 1998 (4.5) Fava 2000 (4.5) Tignol 1993 (4.5) Kroenke 2001 (4.0)		
			Phenelzine	Pande 1996 (5.5)		
			Reboxetine	Taner 2006 (4.5)		
			Sertraline	Boyer 1998 (5.5) Sechter 1999 (5.5) Fava 2000 (4.5) Van Moffaert 1995 (4.5) Kroenke 2001 (4.0)		
			Tianeptine	Novotny 2002 (5.5)		
			Trazodone	Fudge 1990 (5.5) Perry 1989 (5.5) Beasley 1991 (4.5) Debus 1988 (4.0)		
			Venlafaxine	Costa e Silva 1998 (6.5) Keller 2007 (5.5) Nemeroff 2007 (5.5) Tzanakaki 2000 (5.5) Dierick 1996 (5.0)		
Fluvoxamine	Imipramine	Ottevanger 1994 (6.0) Fabre 1996 (5.5) Kasper 1995 (4.5)	Amitriptyline	Gasperini 1992 (5.5)	Imipramine	Clerc 2001 (4.0)
			Citalopram	Haffmans 1996 (6.5)	Milnacipran	van der Broek 2004 (7.0)
			Clomipramine	Zohar 2003 (6.0)		
			Desipramine	Roth 1990 (4.5)		
			Dothiepin	Mullin 1988 (5.5)		

			Fluoxetine	Dalery 2003 (6.0)		
			Imipramine	Heijnen 2010 (6.0) Guy 1984 (4.5) March 1990 (4.5) Norton 1984 (4.5) Guelfi 1983 (4.0) Guelfi 1987 (4.0)		
			Maprotiline	Kasper 1993 (5.0) Kasper 1991 (4.5)		
			Mianserin	Perez 1990 (4.5)		
			Milnacipran	Ansseau 1991 (5.0)		
			Moclobemide	Bougerol 1992 (5.5)		
			Paroxetine	Kiev 1997 (5.5) Ushiroyama 2004 (5.0)		
			Sertraline	Franchini 1997 (5.5) Franchini 1998 (4.0)		
Paroxetine	Amitriptyline	Freed 1999 (6.0)	Amitriptyline	Sacchetti 2002 (4.5) Bascara 1989 (4.0)	Duloxetine	Goldstein 2004 (7.5) Perahia 2006 (4.5)
			Bupropion	Gorlyn 2015 (6.0) Grunebaum 2012 (5.0) Grunebaum 2013 (5.0)	Escitalopram	Boulenger 2006 (7.0)
					Venlafaxine	Poirier 1999 (6.5) Ballús 2000 (4.5)
			Clomipramine	Ravindran 1997 (5.0)		
			Duloxetine	Detke 2004 (6.5) Lee 2007 (6.5) Wang 2015 (6.5)		
			Escitalopram	Baldwin 2006 (6.0) Kishi 2017 (4.5)		
			Fluoxetine	Chouinard 1999 (4.5) De Wilde 1992 (4.5) Fava 1998 (4.5) Fava 2000 (4.5)		

				Tignol 1993 (4.5) Kroenke 2001 (4.0)		
			Fluvoxamine	Kiev 1997 (5.5) Ushiroyama 2004 (5.0)		
			Imipramine	Claghorn 1993 (4.5) Cohn 1992 (4.5) Feighner 1992 (4.5) Feighner 1993 (4.5)		
			Maprotiline	Benkert 1997 (5.0) Szegedi 1997 (4.0)		
			Milnacipran	Kamijima 2013 (5.0) Sechter 2004 (4.5)		
			Mirtazapine	Benkert 2000 (6.0) Wade 2003 (5.5) Kim 2011 (4.0)		
			Nefazodone	Baldwin 1996 (4.5) Baldwin 2001 (4.5)		
			Nortriptyline	Mulsant 1999 (4.5)		
			Sertraline	Åberg-Wistedt 2000 (4.5) Fava 2000 (4.5) Kroenke 2001 (4.0)		
			Trazodone	Kasper 2005 (8.0)		
			Vortioxetine	Baune 2018 (4.5)		
Sertraline	Desipramine	Hoehn-Saric 2000 (5.0)	Amitriptyline	Lydiard 1997 (7.0) Möller 2000 (5.5) Reimherr 1990 (4.5)	Citalopram	Matreja 2007 (4.5)
	Dothiepin	Doogan 1994 (4.0)			Venlafaxine	Mehtonen 2000 (4.5)
			Bupropion	Kavoussi 1997 (4.5)		
			Citalopram	Ekselius 1997 (6.0) Hsu 2011 (6.0) Stahl 2000 (5.5) Ekselius 1998 (5.0)		

			Clomipramine	Moon 1994 (5.5) Lépine 2000 (5.0)			
			Duloxetine	Mowla 2016 (6.0)			
			Escitalopram	Ventura 2007 (5.5)			
			Fluoxetine	Boyer 1998 (5.5) Sechter 1999 (5.5) Fava 2000 (4.5) Van Moffaert 1995 (4.5) Kroenke 2001 (4.0)			
			Fluvoxamine	Franchini 1997 (5.5) Franchini 1998 (4.0)			
			Imipramine	Hirschfeld 1998 (5.0) Keller 1998 (4.5) Kocsis 1997 (4.5) Kornstein 2000 (4.5) Lepola 2003 (4.5) Miller 1998 (4.5)			
			Mirtazapine	Behnke 2003 (4.5)			
			Moclobemide	Søgaard 1999 (6.5) Türkçapar 1998 (4.5)			
			Paroxetine	Åberg-Wistedt 2000 (4.5) Fava 2000 (4.5) Kroenke 2001 (4.0)			
			Trazodone	Munizza 2006 (8.0)			
			Venlafaxine	Shelton 2006 (7.0) Sir 2005 (6.0)			
Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)							
Duloxetine	Fluoxetine	Goldstein 2002 (4.5)	Bupropion	Rosso 2012 (5.5)	Escitalopram	Khan 2007 (5.5)	
	Paroxetine	Goldstein 2004 (7.5) Perahia 2006 (4.5)	Escitalopram	Pigott 2007 (6.0) Raskin 2012 (6.0) Nierenberg 2007 (5.5)	Vortioxetine	Christensen 2018 (5.5) Mahableshwarkar 2015 (5.5)	

	Vortioxetine	Mahableshwarkar 2013 (4.5)	Paroxetine	Detke 2004 (6.5) Lee 2007 (6.5) Wang 2015 (6.5)		
			Sertraline	Mowla 2016 (6.0)		
Milnacipran	Fluvoxamine	Clerc 2001 (4.0)	Amitriptyline	Ansseau 1989 (4.0)	Fluoxetine	Ansseau 1994 (5.5)
			Clomipramine	Steen 1997 (5.0)		
			Fluvoxamine	Ansseau 1991 (5.0)		
			Imipramine	Amerongen 2002 (6.0) Tignol 1998 (5.0)		
			Paroxetine	Kamijima 2013 (5.0) Sechter 2004 (4.5)		
Reboxetine	Desipramine	Ban 1998 (5.5)	Fluoxetine	Taner 2006 (4.5)		
			Imipramine	Berzewski 1997 (5.5)		
Venlafaxine	Fluoxetine	Silverstone 1999 (6.5) Rudolph 1999 (6.0) Clerc 1994 (5.5) De Nayer 2002 (4.5)	Amitriptyline	Gentil 2000 (6.0) Sauer 2003 (5.5)	Imipramine	Vermeiden 2017 (7.5)
			Bupropion	Hewett 2009 (6.5)		
			Citalopram	Hosseini 2015 (4.5)		
	Imipramine	Lecrubier 1997 (5.5)	Clomipramine	Samuelian 1998 (5.5)		
	Paroxetine	Poirier 1999 (6.5) Ballús 2000 (4.5)	Escitalopram	Montgomery 2004 (7.5) Bielski 2004 (5.5)		
	Sertraline	Mehtonen 2000 (4.5)	Fluoxetine	Costa e Silva 1998 (6.5) Keller 2007 (5.5) Nemeroff 2007 (5.5) Tzanakaki 2000 (5.5) Dierick 1996 (5.0)		
			Imipramine	Vermeiden 2013 (7.0) Shrivastava 1994 (5.0) Schweizer 1994 (4.5)		
			Mirtazapine	Benkert 2006 (4.5)		

			Sertraline	Shelton 2006 (7.0) Sir 2005 (6.0)		
			Trazodone	Cunningham 1994 (6.5)		
Tricyclic Antidepressants (TCAs)						
Amitriptyline	Amoxapine	Åberg 1977 (4.0)	Amoxapine	McNair 1984 (5.5) Sethi 1979 (5.5) Mason 1990 (4.5) Fruensgaard 1979 (4.0)	Paroxetine	Freed 1999 (6.0)
	Trazodone	Moises 1981 (4.5)			Maprotiline	Montgomery 1980 (5.0)
			Dothiepin	Blacker 1988 (6.5) Lipsedge 1971 (5.0) Deering 1974 (4.5)		
			Doxepin	Bianchi 1971 (5.0)		
			Fluoxetine	Beasley 1993 (5.0) Chouinard 1985 (5.0) Judd 1993 (5.0) Marchesi 1998 (5.0) Feighner 1985 (4.5) Versiani 1999 (4.0)		
			Fluvoxamine	Gasperini 1992 (5.5)		
			Imipramine	Goldberg 1977 (4.0)		
			Maprotiline	Sims 1980 (5.0) Watanabe 1978 (5.0) Weissman 1975 (4.0)		
			Mianserin	Blacker 1988 (6.5) Wilcox 1994 (5.5) Carman 1991 (5.0) Guy 1983 (5.0) Möller 1995 (4.5)		
			Milnacipran	Ansseau 1989 (4.0)		
			Mirtazapine	Bremner 1995 (5.0) Mullin 1996 (4.5)		

		Moclobemide	Bakish 1992 (6.0) Evans 1992 (4.5)	
		Nortriptyline	Mendels 1968 (5.0)	
		Paroxetine	Sacchetti 2002 (4.5) Bascara 1989 (4.0)	
		Pirlindole	Schäpperle 1985 (5.5)	
		Sertraline	Lydiard 1997 (7.0) Möller 2000 (5.5) Reimherr 1990 (4.5)	
		Tranylcypromine	Razani 1983 (4.0)	
		Trazodone	Blacker 1988 (6.5) De Wilde (6.5) Rickels 1982 (5.0)	
		Venlafaxine	Gentil 2000 (6.0) Sauer 2003 (5.5)	
Amoxapine	Imipramine Takahashi 1979 (5.0)	Amitriptyline	McNair 1984 (5.5) Sethi 1979 (5.5) Mason 1990 (4.5) Fruensgaard 1979 (4.0)	Amitriptyline Åberg 1977 (4.0)
		Imipramine	Smith 1975 (5.0) Rickels 1979 (4.0)	
		Maprotiline	Robinson 1984 (6.0)	
		Trazodone	Robinson 1984 (6.0)	
Clomipramine		Dothiepin	Welch 1997 (5.5)	
		Fluvoxamine	Zohar 2003 (6.0)	
		Imipramine	Lecrubier 1990 (4.0)	
		Isocarboxazide	Larsen 1991 (5.5)	
		Maprotiline	Drago 1983 (5.0)	
		Milnacipran	Steen 1997 (5.0)	

		Mianserin	Dunbar 1985 (4.0) Levin 1982 (4.0)		
		Moclobemide	Kragh-Sorensen 1995 (6.0) Koczkas 1989 (5.5) Larsen 1991 (5.5) Guelfi 1992 (4.5) Lecrubier 1995 (4.5) Lecrubier 1990 (4.0)		
		Paroxetine	Ravindran 1997 (5.0)		
		Sertraline	Moon 1994 (5.5) Lépine 2000 (5.0)		
		Venlafaxine	Samuelian 1998 (5.5)		
Desipramine		Doxepin	Amsterdam 1982 (5.5)	Reboxetine	Ban 1998 (5.5)
		Imipramine	Rose 1967 (5.0) Simon 1999 (4.0)	Sertraline	Hoehn-Saric 2000 (5.0)
		Fluoxetine	Bowden 1993 (5.5) Remick 1993 (5.5) Simon 1999 (4.0)		
		Fluvoxamine	Roth 1990 (4.5)		
Dothiepin		Amitriptyline	Blacker 1988 (6.5) Lipsedge 1971 (5.0) Deering 1974 (4.5)	Sertraline	Doogan 1994 (4.0)
		Clomipramine	Welch 1997 (5.5)		
		Doxepin	Ferguson 1994 (4.5)		
		Fluvoxamine	Mullin 1988 (5.5)		
		Mianserin	Blacker 1988 (6.5)		
		Moclobemide	Beaumont 1993 (4.0)		
		Trazodone	Blacker 1988 (6.5)		
Doxepin		Amitriptyline	Bianchi 1971 (5.0)		

			Desipramine	Amsterdam 1982 (5.5)		
			Dothiepin	Ferguson 1994 (4.5)		
			Fluoxetine	Remick 1989 (4.5)		
			Mianserin	Khan 1983 (5.0)		
			Moclobemide	Lingjærde 1995 (6.5)		
Imipramine	Fluvoxamine	van der Broek 2004 (7.0)	Amineptine	Mendis 1989 (4.5)	Amoxapine	Takahashi 1979 (5.0)
	Mirtazapine	Bruijn 1996 (4.5)	Amitriptyline	Goldberg 1977 (4.0)	Fluvoxamine	Ottevanger 1994 (6.0) Fabre 1996 (5.5) Kasper 1995 (4.5)
	Venlafaxine	Vermeiden 2017 (7.5)	Amoxapine	Smith 1975 (5.0) Rickels 1979 (4.0)		
			Clomipramine	Lecrubier 1990 (4.0)	Phenelzine	Liebowitz 1988 (5.0) Quitkin 1988 (5.0) McGrath 1993 (4.0) Stewart 1993 (4.0)
			Desipramine	Rose 1967 (5.0) Simon 1999 (4.0)		
			Fluoxetine	Feighner 1989 (5.0) Serrano-Blanco 2006 (5.0) Byerley 1988 (4.5) Simon 1999 (4.0)	Venlafaxine	Lecrubier 1997 (5.5)
			Fluvoxamine	Heijnen 2010 (6.0) Guy 1984 (4.5) March 1990 (4.5) Norton 1984 (4.5) Guelfi 1983 (4.0) Guelfi 1987 (4.0)		
			Maprotiline	Lehmann 1976 (4.5) Logue 1978 (4.5)		
			Milnacipran	Amerongen 2002 (6.0) Tignol 1998 (5.0)		
			Moclobemide	Baumhackl 1989 (5.0) Rimón 1993 (5.0) Kok 1995 (4.5)		

			Rimón 1993 (4.5) Versiani 1989 (4.5) Versiani 1990 (4.5) Udabe 1990 (4.5) Lecrubier 1990 (4.0)		
		Nefazodone	Cohn 1996 (5.5) Fontaine 1994 (5.5) Rickels 1994 (5.0)		
		Paroxetine	Claghorn 1993 (4.5) Cohn 1992 (4.5) Feighner 1992 (4.5) Feighner 1993 (4.5)		
		Phenelzine	Quitkin 1991 (5.0) Imlah 1964 (4.0)		
		Reboxetine	Berzewski 1997 (5.5)		
		Sertraline	Hirschfeld 1998 (5.0) Keller 1998 (4.5) Kocsis 1997 (4.5) Kornstein 2000 (4.5) Lepola 2003 (4.5) Miller 1998 (4.5)		
		Trazodone	Fabre 1983 (5.0) Gerner 1980 (4.5) Gershon 1981 (4.5) Hayes 1983 (4.5)		
		Trimipramine	Rifkin 1980 (4.0)		
		Venlafaxine	Vermeiden 2013 (7.0) Shrivastava 1994 (5.0) Schweizer 1994 (4.5)		
Maprotiline		Amineptine	Bornstein 1979 (4.5)	Amitriptyline	Montgomery 1980 (5.0)
		Amitriptyline	Sims 1980 (5.0) Watanabe 1978 (5.0) Weissman 1975 (4.0)		

		Amoxapine	Robinson 1984 (6.0)	
		Citalopram	Bouchard 1987 (4.0)	
		Clomipramine	Drago 1983 (5.0)	
		Fluoxetine	Marténvi 2001 (5.5) Poelinger 1989 (5.5)	
		Fluvoxamine	Kasper 1993 (5.0) Kasper 1991 (4.5)	
		Imipramine	Lehmann 1976 (4.5) Logue 1978 (4.5)	
		Mianserin	Möller 1991 (5.0) Edwards 1983 (4.0)	
		Moclobemide	Gachoud 1994 (5.5) Laux 1989 (4.5) Vaz-Serra 1994 (4.5) Steinmeyer 1993 (4.0)	
		Paroxetine	Benkert 1997 (5.0) Szegedi 1997 (4.0)	
		Pirlindole	Pöldinger 1985 (4.5)	
		Trazodone	Robinson 1984 (6.0)	
Mianserin		Amitriptyline	Blacker 1988 (6.5) Wilcox 1994 (5.5) Carman 1991 (5.0) Guy 1983 (5.0) Möller 1995 (4.5)	
		Citalopram	De Wilde 1985 (5.0) Guy 1983 (5.0)	
		Clomipramine	Dunbar 1985 (4.0) Levin 1982 (4.0)	
		Dothiepin	Blacker 1988 (6.5)	
		Doxepin	Khan 1983 (5.0)	
		Fluvoxamine	Perez 1990 (4.5)	

			Maprotiline	Möller 1991 (5.0) Edwards 1983 (4.0)		
			Nortriptyline	Hoc 1982 (4.0)		
			Pirlindole	De Wilde 1997 (5.5)		
			Trazodone	Richards 1982 (7.0) Blacker 1988 (6.5) Moon 1988 (4.0)		
Mirtazapine			Amitriptyline	Bremner 1995 (5.0) Mullin 1996 (4.5)	Imipramine	Bruijn 1996 (4.5)
			Citalopram	Leinonen 1999 (6.5)		
			Fluoxetine	Versiani 2005 (6.0) Amini 2005 (5.5) Hong 2003 (5.5) Wheatley 1998 (4.5)		
			Paroxetine	Benkert 2000 (6.0) Wade 2003 (5.5) Kim 2011 (4.0)		
			Trazodone	Halikas 1995 (7.0) van Moffaert 1995 (5.5)		
			Sertraline	Behnke 2003 (4.5)		
			Venlafaxine	Benkert 2006 (4.5)		
Nortriptyline	Escitalopram	Martiny 2015 (6.0)	Amitriptyline	Mendels 1968 (5.0)		
	Fluoxetine	Akhondzadeh 2003 (5.0)	Fluoxetine	Joyce 2002 (5.0)		
	Phenelzine	Georgotas 1987 (4.0)	Mianserin	Hoc 1982 (4.0)		
			Paroxetine	Mulsant 1999 (4.5)		
			Protriptyline	Priest 1976 (4.5)		
Protriptyline			Nortriptyline	Priest 1976 (4.5)		
Trimipramine			Amineptine	Vauterin 1979 (4.5)		
			Imipramine	Rifkin 1980 (4.0)		

Monoamine Oxidase Inhibitors				
Isocarboxazid		Clomipramine	Larsen 1991 (5.5)	
		Moclobemide	Larsen 1991 (5.5)	
Moclobemide		Amitriptyline	Bakish 1992 (6.0) Evans 1992 (4.5)	
		Clomipramine	Kragh-Sorensen 1995 (6.0) Koczkas 1989 (5.5) Larsen 1991 (5.5) Guelfi 1992 (4.5) Lecrubier 1995 (4.5) Lecrubier 1990 (4.0)	
		Dothiepin	Beaumont 1993 (4.0)	
		Doxepin	Lingjærde 1995 (6.5)	
		Fluoxetine	Lapierre 1997 (6.5) Lonnqvist 1994a (6.0) Reynaert 1995 (6.0) Gattaz 1995 (5.5) Duarte 1996 (5.5) Williams 1993 (5.5) Larsen 1989 (5.5) Partonen 1996 (5.0) Geerts 1994 (4.5) Lonnqvist 1995 (4.5) Lonnqvist 1994b (4.0)	
		Fluvoxamine	Bougerol 1992 (5.5)	
		Imipramine	Baumhackl 1989 (5.0) Rimón 1993 (5.0) Kok 1995 (4.5) Rimón 1993 (4.5) Versiani 1989 (4.5)	

				Versiani 1990 (4.5) Udabe 1990 (4.5) Lecrubier 1990 (4.0)		
			Isocarboxazide	Larsen 1991 (5.5)		
			Maprotiline	Gachoud 1994 (5.5) Laux 1989 (4.5) Vaz-Serra 1994 (4.5) Steinmeyer 1993 (4.0)		
			Pirlindole	Tanghe 1997 (5.0)		
			Sertraline	Søgaard 1999 (6.5) Türkçapar 1998 (4.5)		
			Tranylcypromine	Heinze 1993 (5.5)		
Phenelzine	Imipramine	Liebowitz 1988 (5.0) Quitkin 1988 (5.0) McGrath 1993 (4.0) Stewart 1993 (4.0)	Fluoxetine	Pande 1996 (5.5)	Nortriptyline	Georgotas 1987 (4.0)
			Imipramine	Quitkin 1991 (5.0) Imlah 1964 (4.0)		
			Tranylcypromine	Birkenhäger 2004 (6.5)		
Pirlindole			Amitriptyline	Schäpperle 1985 (5.5)		
			Maprotiline	Pöldinger 1985 (4.5)		
			Mianserin	De Wilde 1997 (5.5)		
			Moclobemide	Tanghe 1997 (5.0)		
Tranylcypromine			Amitriptyline	Razani 1983 (4.0)		
			Moclobemide	Heinze 1993 (5.5)		
			Phenelzine	Birkenhäger 2004 (6.5)		
Atypical Antidepressants						
Agomelatine	Sertraline	Kasper 2010 (5.5) Kasper 2013 (5.5)	Escitalopram	Udristoiu 2016 (6.5) Corruble 2013 (6.0)	Escitalopram	Urade 2015 (5.0)

				Vortioxetine	Montgomery 2014 (4.5) Papakostas 2018 (4.5)
Amineptine		Imipramine	Mendis 1989 (4.5)		
		Maprotiline	Bornstein 1979 (4.5)		
		Trimipramine	Vauterin 1979 (4.5)		
Bupropion		Duloxetine	Rosso 2012 (5.5)		
		Fluoxetine	Feighner 1991 (4.0)		
		Paroxetine	Gorlyn 2015 (6.0) Grunebaum 2012 (5.0) Grunebaum 2013 (5.0)		
		Sertraline	Kavoussi 1997 (4.5)		
		Venlafaxine	Hewett 2009 (6.5)		
Nefazodone		Fluoxetine	Gillin 1997 (6.5) Rush 1998 (6.0)		
		Imipramine	Cohn 1996 (5.5) Fontaine 1994 (5.5) Rickels 1994 (5.0)		
		Paroxetine	Baldwin 1996 (4.5) Baldwin 2001 (4.5)		
Tianeptine		Fluoxetine	Novotny 2002 (5.5)		
Trazodone		Amitriptyline	Blacker 1988 (6.5) De Wilde 1987 (6.5) Rickels 1982 (5.0)	Amitriptyline	Moises 1981 (4.5)
		Amoxapine	Robinson 1984 (6.0)		
		Dothiepin	Blacker 1988 (6.5)		
		Fluoxetine	Fudge 1990 (5.5) Perry 1989 (5.5) Beasley 1991 (4.5) Debus 1988 (4.0)		

			Imipramine	Fabre 1983 (5.0) Gerner 1980 (4.5) Gershon 1981 (4.5) Hayes 1983 (4.5)		
			Maprotiline	Robinson 1984 (6.0)		
			Mianserin	Richards 1982 (7.0) Blacker 1988 (6.5) Moon 1988 (4.0)		
			Mirtazapine	Halikas 1995 (7.0) van Moffaert 1995 (5.5)		
			Paroxetine	Kasper 2005 (8.0)		
			Sertraline	Munizza 2006 (8.0)		
			Venlafaxine	Cunningham 1994 (6.5)		
Vortioxetine	Agomelatine	Montgomery 2014 (4.5) Papakostas 2018 (4.5)	Escitalopram	Vieta 2018 (4.0)	Duloxetine	Mahableshwarkar 2013 (4.5)
	Duloxetine	Christensen 2018 (5.5) Mahableshwarkar 2015 (5.5)	Paroxetine	Baune 2018 (4.5)		

Antidepressants Comparing Doses										
SSRIs										
Citalopram										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Almeida 2014 (score=7.0)	B Vitamins	RCT	No COI. Sponsored by the National Health and Medical	N = 153 participants with a major depressive episode	No mention of mean age, all participants were	Citalopram plus 0.5mg of vitamin B12, 2mg of folic acid and 25mg of	Follow-up at 12, 26, and 52 weeks	At 12 weeks remission of depressive episode symptoms reached by	"B vitamins did not increase the 12-week	Data suggest 12 weeks of added B-vitamins did not enhance antidepressant response but

			Council of Australia.	in the context of a major depressive disorder (single episode or recurrent) per DSM-IV-TR.	aged ≥50 with a majority of participants being between 50 and 69 years; 67 males, 86 females	vitamin B6 (n=77) vs. Citalopram plus placebo (n=76). Citalopram daily dosages were 10 mg, and then 2 weeks later increased to 20 mg and could be maximized to 40 mg between 4 and 8 weeks. Vitamins and placebos were in capsules and were taken daily.		78.1% of those treated by placebo and 79.4% of those treated with vitamins (p = 0.84). At 26 weeks remission reached by 76.5% and 85.3%. At 52 weeks remission reached by 75.8% and 85.5% (effect of intervention over 52 weeks, odds ratio OR = 2.49).	efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Replication of these findings would mandate that treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to manage major depression in middle-aged and older adults."	maintained antidepressant response over one-year.

Gastpar 2005 (score=5.5)	St. John's Wort/Citalopram	RCT	No mention of sponsorship or COI.	N = 388 patients with major depressive episode and recurrent major depression (DSM-IV and ICD-10)	Mean age: 49.8 years; 125 males, 263 females	Hypericum Group: received 900 mg of hypericum perforatum extract/tablet (n=131) vs Citalopram Group: received 20 mg of citalopram (n=127) vs Placebo group: (n=130)	7, 21, 42 days	HAM-D scores decreased by 11.6 points in hypericum group compared to 11.5 points in citalopram group and 9.0 points in the placebo group. Superiority of citalopram to placebo ($p<0.0001$) as well as the comparison of hypericum group compared to placebo.	"The non-inferiority of hypericum extract as compared to citalopram and the superiority of both active compounds to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in comparison to citalopram. These results revealed that hypericum extract STW2-VI is a good alternative	Data suggest comparable efficacy of hypericum extract STW3-C1 and citalopram and both are only slightly better than placebo group.

									to chemically defined antidepressants in the treatment of outpatients with moderate depression.”	
Adamson 2015 (score=5.0)	Citalopram/Naltrexone	RCT	No COI. Sponsored by the Health Research Council of New Zealand grant.	N = 138 participants with alcohol dependence and major depressive episode with both meeting DSM-IV criteria	Mean age: 43.6 years; 56 males, 82 females	20 mg citalopram during week 1, increased to 2 capsules during weeks 2-5, increased to 3 capsules at week 6, medication administered for 12 weeks (n=73) vs. Placebo – at same dosages as citalopram group (n=65). Naltrexone	Follow-up at 3, 6, 9, and 12 weeks	Naltrexone adherence for citalopram group (percent consuming ≥ 80% of days) = 71.8%, placebo = 77.8% (p = 0.430).	“In conclusion, we found no evidence that citalopram improves mood or drinking behavior in nonabstinent outpatients with co-occurring alcohol dependence and major depression who are also being treated	Data suggest lack of efficacy of adding citalopram to naltrexone for major depressive patients with co-existing alcohol dependence.

						given to all 25 mg daily, increased to 50 mg then to 75-100 mg after 6 weeks			with naltrexone. ”	
Menchetti 2014 (score=4.0)	Sertraline/ Citalopram/Counseling	RCT	No COI. Sponsored by the Italian Ministry for University and Research as Research Program of National Interest in 2005.	N = 287 participants meetings DSM-IV criteria for major depression	Mean age: 44.9 years, 76 males, 211 females	Interpersonal counseling – six 30-minute sessions (initial session being 60-minutes) (n=143) vs. SSRI treatment – given either sertraline or citalopram, patients met with psychiatrist every 2 to 3 week intervals, dosages not specified (n=144). Treatments given over a 2-month period	No long-term follow-up	At 2 months significantly higher percentage of patients who reached remission in interpersonal group compared to SSRI group (58.7%, 45.1%, p = 0.021)	“We identified some patient characteristics predicting a differential outcome with pharmacological and psychological interventions. Should our results be confirmed in future studies, these characteristics will help clinicians to define	Data suggest a significantly greater number of patients reached remission (58.7%) in the interpersonal counseling group compared to the SSRI group (45.1%), suggesting IP counseling better than either sertraline or citalopram.

									criteria for first-line treatment of depression targeted to patients' characteristics."	
Trivedi 2006 (score=4.0)	Bupropion/ Citalopram/ Buspirone	RCT	Sponsored by the National Institute of Mental Health, National Institutes of Health. COI, one or more authors have received or will received benefits for personal or professional use.	N = 565 patients with nonpsychotic major depressive disorder without remission who had received 12 weeks of citalopram therapy, no mention of diagnostic criteria	Mean age: 41.1 years; 233 males, 332 females	Augmentation of citalopram with sustained-release bupropion. Initial dose of sustained-release bupropion = 200 mg daily for 2 weeks, 300 mg daily at week 4, 400 mg daily at week 6 (n=279) vs. Augmentation of citalopram with buspirone. Initial dose of buspirone	Follow-up at 2, 4, 6, 9, and 12 weeks	Both treatments had similar rates for Hamilton Rating Scale for Depression remission (HRSD-17) (29.7% vs. 30.1%) and for 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR-16) remission (39.0% vs. 32.9%). Sustained-release bupropion had greater reduction QIDS-SR-16 scores (25.3% vs. 17.1%, p<0.04)	"Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings."	Data suggest similar efficacy between bupropion SR and buspirone for prevention of depression relapse.

						= 15 mg daily for 1 week, 30 mg daily for 1 week, 45 mg daily for weeks 3 to 5, 60 mg daily during week 6 (n=286). All medications taken twice daily				
Escitalopram										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Rossini 2005 (score=7.5)	rTMS/Escitalopram	RCT	No sponsorship or COI.	N = 99 patients with major depressive episode (DSM-IV)	Mean age:47.4 ±12.9 years; 20 males, 79 females	Active Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225 mg venlafaxine (n=17 and 10 consecutive days of active	5 weeks	Active group showed greater favor in HAM-D score reduction compared to sham group (F=7.6, p=0.0073). Response rates were greater in active group (p=0.002). HAM-D score reduction was not significant among medications in	"These findings support the efficacy of rTMS in hastening the response to antidepressant drugs in patients with major depressive disorder. The effect of rTMS seems to be	Data suggest rTMS accelerates patient response to escitalopram, sertraline or venlafaxine in patients with MDD.

						repetitive transcranial magnetic stimulation (15 hz, 30 trains of 30 pulses 2 seconds each with 28 second inter-train interval (n=50) vs Sham Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225mg venlafaxine (n=16) and sham rTMS (n=49)		either the active or sham group.	unaffected by the specific concomitantly administered drug."	
Papakostas 2015 (score=7.5)	Ziprasidone, Escitalopram	RCT	Sponsored by the NIMH, Pfizer and Forest Laboratories. COI, one	N = 139 participants who had 8 weeks of open-label	Mean age: 44.46 years; 41 males,	Escitalopram 10-30 mg/day plus Ziprasidone dosage range of 20–80 mg twice	Follow-up at weeks 1, 2, 3, 4, 5, 6, 7 and 8	Mean improvement in Hamilton Depression Rating Scale scores at 8 weeks:	"Ziprasidone as an adjunct to escitalopram demonstrated	Data suggest ziprasidone as adjunctive therapy to escitalopram shows efficacy in patients with MDD who have persistent

			or more of the authors have received or will receive benefits for personal or professional use	escitalopram and still met DSM-IV criteria for major depressive disorder	98 females	daily (n=71) vs. Escitalopram 10-30 mg/day plus placebo of 20–80 mg twice daily (n=68). All treatments were given for 8 weeks		ziprasidone group = -6.4, placebo group = -3.3 (p=0.04)	antidepressant efficacy in adult patients with major depressive disorder experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram."	symptoms after 8 weeks of escitalopram monotherapy.
Lavretsky 2011 (score=7.5)	Tai Chi/Escitalopram	RCT	Supported by NIH, General Clinical Research Centers Program, the UCLA Cousins Center at the Semel Institute for Neurosciences; and the UCLA Older Americans Independenc	N = 112 older adults (60+ years old) with a current MDD episode, a 16 or higher on the Hamilton Depression Rating Scale (HAMD), and a 26	Mean age: 40.6±7.3; 28 males, 45 females.	TCC (n = 36) 4 weeks of escitalopram drug dosing then participated 2 hours of Tai Chi a week for 10 weeks vs. HE (n = 37) 4 weeks of escitalopram drug dosing and weekly health education	Follow-up at baseline, 4, 6, and 14 weeks.	Final HAMD scores, TCC vs HE groups, percentage: 94% achieved HAMD score less than 10, 65% achieved remission (HAMD <6) vs. 77% HAMD of 10 or less and 51% achieving remission (HAMD <6) (x2=3.68, p<0.06). Both groups	"Complementary use of a mind–body exercise, such as TCC, may provide additional improvements of clinical outcomes in the pharmacologic treatment of geriatric	Both groups experienced improvement in symptoms. Data suggest TCC and escitalopram group trended to show reduction in depressive symptoms with remission than the HE and escitalopram group.

			e Center Inflammatory Biology Core. No mention of COI.	or higher on the Mini-Mental State Exam		sessions for 10 weeks		demonstrated improvement in depression, but TCC group showed greater reductions (group*time interaction: F[5, 285]=2.26; p<0.05).	depression. ”	
Brunoni 2017 (score=6.0)	Escitalopram/tDCS	RCT	Sponsored by a grant from Fundacão de Ampara à Pesquisa do Estado de São Paulo, NARSAD Young Investigator from the Brain and Behavior Research Foundation, FAPESP Young Researcher from the São Paulo State Foundation, and the National	N = 245 patients with unipolar depression (DSM-5)	Mean age: 42.7 years; 79 males, 166 females	Escitalopram: received 10 mg escitalopram for 3 weeks and 20 mg thereafter (n=94) vs tDCS: received transcranial direct-current stimulation (tDCS) with 22 sessions each 30-min per day (2 mA of 15 sessions each day during the week then 7 sessions once a week	10 weeks	Mean HRDS-17 scores decreased by 11.3±6.5 points in escitalopram group compared to 9.0±7.1 points in tDCS group, and 5.8±7.9 points in the placebo group. Escitalopram was superior to placebo (p<0.001) and tDCS was superior to placebo (p=0.01).	“In conclusion, tDCS did not show noninferiority to escitalopram in this placebo-controlled trial involving patients with unipolar major depressive disorder.”	Data suggest escitalopram superior to tDCS which was better than placebo but tDCS was associated with increased new onset mania (escitalopram> tDCS> placebo).

			Council for Scientific and Technological Development Associacão Beneficente Alzira Denise Hertzog da Silva, and scholarships from Brazillian Coordination, and FAPESP. No mention of COI.			until week 10) (n=94) vs Placebo: received same dosing as escitalopram group of a placebo pill (n=60)				
Wang 2014 (score=5.5)	Quetiapine/ Escitalopram	RCT	Sponsored by AstaZeneca Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 471 patients with mild depressive disorder (DSM-IV)	Mean age: 40.0 years; 131 males, 328 females	Quetiapine XR: received 150 mg/day of quetiapine XR (50 mg for 2 days, then increased to 150 mg on days 3-14) if no response, increased to 300 mg/day for	1, 3, 5, 7, 14 days, 8 weeks	Reduction in MADRS total score was -17.21 (p=0.174) in quetiapine XR, -16.73 (p=0.346) in escitalopram, compared to -15.61 in placebo. Response rate was 44.8% (p=0.376) in quetiapine XR, 48.0% (p=0.157)	"In this study, neither quetiapine XR (150/300 mg/day) nor escitalopram (10/20 mg/day) showed significant separation from	Data suggest lack of efficacy as neither quetiapine XR at 150 mg/d or 300 mg/d nor escitalopram 10 mg/d were significantly better than placebo in treating patients with MDD.

						remainder of study (n=154) vs Escitalopram: received 10 mg/day of escitalopram (n=152) vs Placebo: (n=153)		in escitalopram, compared to 40.5% in placebo.	placebo. Both compounds have been shown previously to be effective in the treatment of MDD; possible reasons for this failed study are discussed. Quetiapine XR was generally well tolerated, with a profile similar to that reported previously. "	
Burke 2002 (score=5.5)	Escitalopram	RCT	Sponsored by grant from Forest Pharmaceuticals, Inc. No mention of COI.	N = 485 patients with a diagnosis of major depressive disorder	Mean age: 40.1 years; 169 males,	Group 1: received 40 mg/day of citalopram for 8 weeks (n=125) vs Group 2:	1, 2, 4, 6, 8 weeks	Mean MADRS score reduction was 9.4 in group 4, 12.8 in group 2, 13.9 in group 3, and 12.0 in group 1. Mean	"Escitalopram, a single isomer SSRI, is well-tolerated	Data suggest escitalopram at both doses (10 mg/d and 20 mg/d) and citalopram 40 mg/d were comparable in efficacy and all

				(DSM-IV)	316 females	received 10 mg/day escitalopram for 8 weeks (n=118) vs Group 3: received 20 mg/day escitalopram for 8 weeks (n=123) vs Group 4: received 1 capsule of placebo for 8 weeks (n=119)		HAM-D total score were reduced by 7.6 in group 4, 10.2 in group 2, 11.7 in group 3, and 9.9 in group 1. Escitalopram groups and citalopram improved greater compared to placebo.	and has demonstrated antidepressant efficacy at a dose of 10 mg/day."	active drugs were superior to placebo.
Stewart 2014 (score=5.0)	Escitalopram/Bupropion	RCT	Sponsored by grants from NIMH. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 245 outpatients with non-bipolar major depression (DSM-IV-TR)	Mean age: 40.3 years; 82 males, 163 females	Bupropion+ Placebo: received 150 mg/day bupropion for first week, increased to 300 mg/day for next 2 weeks, then to 450 mg/day for remaining 12 weeks and a placebo matching	1, 2, 3, 4, 6, 8, 10, 12 weeks	Remission was not achieved earlier for dual group compared to bupropion or escitalopram alone groups (p=0.258, p=0.960, respectively). Dual group showed highest rate of remission compared to both monotherapy groups, until final follow up	"These results do not support initial use of bupropion plus escitalopram to speed or enhance antidepressant response."	Data suggest comparable efficacy between bupropion, escitalopram, and combination bupropion-escitalopram suggesting no benefit is achieved with combination therapy for prevention of remission.

						escitalopram dosing (n=83) vs Bupropion+ Escitalopram: received 150 mg/day bupropion for first week, increased to 300 mg/day for next 2 weeks, then to 450 mg/day for remaining 12 weeks and received 10 mg escitalopram for first week, and 10 mg increase weekly to 40 mg/day at week 4 and beyond (n=78) vs Escitalopram+Placebo: received 10 mg escitalopram		where escitalopram group showed same remission rate in HAM-D scores.		

						for first week, and 10 mg increase weekly to 40 mg/day at week 4 and beyond (n=84)				
Lam 2013 (score=5.0)	CBT/Escitalopram	RCT	Sponsored by grant from Lundbeck Canada. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 99 patients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 43.3 years; 45 males, 54 females	CBT Group: received 10 mg/day escitalopram (increased to 20 mg/day at week 2) and telephone-based cognitive behavioral therapy consisting of 8 sessions (each 30-40 min) over 8-10 weeks including motivation-exercises, identify, challenge and distance negative thoughts	2, 4, 8, 12 weeks	Decrease in MADRS score was 63% in CBT group compared to 61% in control group (p=0.86). Remission rates were 56% in CBT group compared to 53% in control group (p=0.74). Work functioning LEAP total score and LEAPS productivity scale showed greater improvement in CBT group compared to control group (p=0.046,	"Combined treatment with escitalopram and telephone-administered CBT significantly improved some self-reported work functioning outcomes, but not symptom-based outcomes, compared with escitalopram alone."	Data suggest depression scores were most improved via escitalopram compared to telephone-delivered CBT although self-reported work functions showed improvement with telephone delivered CBT.

						training, and personal care and self-management skills (n=48) vs Control Group: received 10-minute structured phone call weekly for 8 weeks and received 10 mg/day escitalopram (increased to 20 mg/day at week 2) (n=51)		p=0.036, respectively).		
Schramm 2015 (score=5.0)	CBT/Escitalopram	RCT	Sponsored by Lundbeck GmbH, Hamburg, Germany. No mention of COI.	N = 60 patients with chronic major depression (DSM-IV)	Mean age: 43.63±10.56 years; 28 males, 32 females	CBASP Group: received 22 sessions of cognitive behavioral analysis system of psychotherapy (n=29) vs ESC/CM Group: received 18 session over	8, 28 weeks	Improvement in MADRS scores was observed for both groups at 8 weeks ($p<0.001$) and at 28 weeks ($p<0.001$). Response rate was 68.4% in CBASP and 60.0% in ESC/CM group with neither	"CABSP and ESC/CM appear to be equally effective treatment options for chronically depressed outpatients. For nonimprovers to the	Small sample size. Data suggest both CBT and escitalopram were effective in the treatment of chronic major depression.

						28 weeks of escitalopram 10 mg/day for first week then increased to 20 mg/day for rest of study and clinical management consisting of psychoeducation, support and empathy intervention (n=30)		group being superior.	initial treatment, it is efficacious to augment with medication in the case of nonresponse to CBASP and vice versa."	
Han 2013 (score=4.5)	Aripiprazole, Escitalopram	RCT	Sponsored by Korea Otsuka Pharmaceuticals. No COI.	N = 35 patients with comorbid major depression and alcohol dependence according to DSM-IV criteria	Mean age: 39.6 years; 23 male, 12 female	Group 1: Given flexible dose of aripiprazole (5-15 mg) and escitalopram (10-20 mg) daily for 6 weeks (n=17) vs Group 2: Given 10-20 mg of escitalopram	Follow up at baseline, and 6 weeks	Mean Beck Depression Index (BDI) scores for Group 1 was 32.1 at baseline and 16.0 at week 6 (p=0.01). Mean BDI score for Group 2 was 29.6 at baseline and 16.9 (p<0.01). There were 4 non-responders in Group 1 and 6 non-responders	"The change of brain activity within the left anterior cingulate gyrus in all patients with co-morbid alcohol dependence and major depressive disorder was	Small sample. Data suggest escitalopram plus aripiprazole decreased alcohol craving and depression scores.

						daily (n=18).		in Group 2 (p=0.15).	negatively correlated with the change in craving for alcohol. These findings suggest that the effects of aripiprazole on anterior cingulate cortex might mediate the successful treatment of alcohol dependence in patients with major depressive disorder."	
Muhonen 2008 (score=4.5)	Escitalopram/Memantine	RCT	Sponsored by the National Public Health Institute, the Finnish Foundation for Alcohol	N = 80 alcohol-dependent outpatient with major depressive disorder	Mean age: 47.7 years; 44 males, 36 males	Memantine: received 20 mg/day of memantine (starting at 5 mg/day and increased by 5 mg weekly until	1, 2, 4, 12, 26 weeks	MADRS score decreased in both memantine group and the escitalopram group ($p<0.001$); however, there were no differences	"These data provide new evidence for the safety and potential efficacy of	Relatively small sample size. Data suggest comparable efficacy between memantine and escitalopram.

			Research, and the Helsinki Health Center Research Fund. No COI.	(DSM-IV)		20 mg/day) (n=40) vs Escitalopram: received 20 mg/day of escitalopram (starting at 5 mg/day and increased by 5 mg weekly until 20 mg/day) (n=40) After 4 weeks, physician could decrease dosing if intolerance		between groups (p=0.94).	memantine and escitalopram for major depressive disorder in patients with comorbid alcohol dependence."	
Romera 2012 (score=4.5)	Duloxetine/Escitalopram	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will received benefits for personal or professional use.	N = 291 patients with single or recurrent episodes of MDD (DSM-IV-TR)	Mean age:48.7 years; 69 males, 222 females	All patients received 4 weeks of 10 mg/day escitalopram then randomized to Group 1: received 60-120 mg/day from week 4 to week 16 (n=138) vs Group 2: received 10-	4, 6, 8, 10, 12, 14, 16 weeks	Reduced HAM-D score was achieved in 61.6% of group 1 compared to 64.1% in group 2 (p=0.652). Group 1 showed earlier time to achieve SDS score <6 compared to group 2 (p=0.042).	"In MDD patients with moderate to severe painful physical symptoms not improving after 4 weeks of treatment with escitalopra	Data suggest duloxetine switching may benefit patients with moderate to severe pain and MDD.

						20 mg/day of escitalopram during weeks 4-8 then switched to 60-120 mg/day duloxetine from week 8 to 16 if did not achieve <50% HAM-D score reduction (n=153)			m, an earlier switch to duloxetine may lead to better pain and functional outcomes."	
Dunlop 2017 (score=4.5)	CBT/Duloxetine/Escitalopram	RCT	Sponsored by NIH grants. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 344 patients with current major depressive disorder (DSM-IV)	Mean age: 40.0±11.7 years; 148 males, 196 females	CBT Group: received 16 individual sessions of cognitive behavioral therapy consisting of 50 min sessions (n=115) vs Escitalopram Group: received 10-20 mg/day escitalopram (n=114) vs	2, 4, 6, 8, 10, 12 weeks	Mean HAM-D score reduction was 10.9 points, but did not differ across the groups (F=0.53, p=0.589). Remission rates were 41.9% for CBT group, 46.7% in escitalopram group, and 54.7% in duloxetine group (p=0.170).	"Treatment guidelines that recommend either an evidence-based psychotherapy or antidepressant medication for nonpsychotic major depression can be	Data suggest patient preference towards CBT or pharmacotherapy did not significantly impact treatment outcomes in patients not receiving prior treatment.

						Duloxetine Group: received 30-60 mg/day duloxetine (n=115)			extended to treatment-naïve patients. Treatment preferences among patients without prior treatment exposure do not significantly moderate symptomatic outcomes."	
Fluoxetine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lam 2006 (score=9.0)	Light Therapy	RCT	One or more of the authors is a consultant or on the Speaker/Advisory Boards or has received research funds from: AstraZeneca,	N = 96 patients with a DSM–IV criteria for major depressive disorder with a seasonal (winter)	Mean age: 43.5 years; 32 males, 64 females.	Light group: Exposure to white fluorescent light box (Model Daylight 10000, ultraviolet filter, rated at 10,000 lux at	Follow up at weeks 1, 2, 4, and 8 or at unexpected termination.	No significant differences between light and fluoxetine group for clinical response rate ($\chi 2=0$, df=1, p=1.00) and CGI improvement since last visit	"Light treatment showed earlier response onset and lower rate of some adverse events relative to fluoxetine,	Data suggest light treatment resulted in an earlier response rate compared to fluoxetine but otherwise comparable efficacy

			Canadian Institutes of Health Research, Eli Lilly, GlaxoSmith Kline, Janssen, Lundbock, Merck, Roche, Servier, Vancouver Hospital Foundation, and Wyeth.	pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.		distance of 14 in from screen to cornea),with 20mg placebo pill 30 minutes after waking up (n=48) vs Fluoxetine group: Identical light box fitted with a neutral density gel filter to reduce light exposure to 100 lux, with 20mg of fluoxetine 30 minutes after waking up (n=48)		(mean=1.90 [SD=1.15] versus 1.92 [SD=1.09], respectively) (t=0.09, df=94, p=0.93). Light group had greater improvement at only week 1. Fluoxetine group had greater treatment emergent adverse events.	but there were no other significant differences in outcome between light therapy and antidepressant medication."	
Michalak 2007 (score=NA)	Light Therapy	CAN-SAD study/ secondary analyses	Sponsored by the Canadian Institutes of Health Research. No COI.	N = 96 patients with a DSM–IV criteria for major depressive disorder with a	Mean age: 66.7 years; 32 males, 64 females	Light group: 10,000 lux light treatment (Uplift Technologies Inc., Model Daylight) and a	Follow up at 1, 2, 3, 4, 5, 6, 7, and 8 weeks	Q-LES-Q measures in the light group had average improvements (20.56; SD=13.11) compared with fluoxetine group (21.77;	"Patients with SAD report markedly impaired QoL during the winter months. Treatment with light	Data suggest quality of life markedly improved with light therapy suggesting it has similar benefits as antidepressant therapy.

				seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.		placebo (n=48) vs Fluoxetine group: 100 lux light and 20mg of fluoxetine. (n=48) Light treatment was done asap after waking up between 07:00 and 08:00 hours. Medication treatment was taken daily after light treatment. Treatments lasted for 8 weeks.		SD=17.04) [F(1,79=0.13, N.S.]. SF-20 scores in the light group was 7.82 (SD=15.49) vs 9.38 (SD=14.39) in the fluoxetine group [F(1,79=0.22, N.S.]	therapy or antidepressant medication is associated with equivalent marked improvement in perceived QoL. Studies of treatment interventions for SAD should routinely include broader indices of patient outcome, such as the assessment of psychosocial functioning or life quality."	
Enns 2006 (score=NA)	Light Therapy	CAN-SAD post hoc analyses	Sponsored by the Canadian Institutes of Health Research.	N = 95 patients with a DSM–IV criteria for major depressi	Mean age: 43.8 years; 32 males,	Light group: Received light therapy (10,000 lux) for 30 min in the morning and	Follow up at 8 weeks and during summer (July	Mean BDI-II score of SAD was 23.8 while non-SAD was 23.7. Sad group had lower neuroticism	"The personality profile of SAD patients differs from both non-seasonal	Data suggest personality profile of SAD patients different from non-seasonal depressed patients as SAD

			No mention of COI.	ve disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.	63 females	a placebo pill daily for 8 weeks. (n=48) vs Fluoxetine group: Received fluoxetine (20mg) and morning dim light exposure (200 lux) daily for 8 weeks. (n=48)	or August)	scores but higher openness scores than non-SAD group.	depressed patients and norms. Elevated openness scores appear to be a unique feature of patients with SAD. Since mood state has a significant impact on personality scores, assessment of personality in SAD patients should ideally be conducted when they are in remission."	patients tend to be more open
Lam 2016 (score=8.0)	Light Therapy	RCT	Sponsored by grant MCT-94832 from the Canadian Institutes of Health	N = 122 adults with MDD (DSM-IV-TR) of at	Mean age: 36.8 years; 46 males,	10,000-lux fluorescent white light box for 30 min/d in morning plus 20mg	Follow up at weeks 0, 1, 2, 4, 6, and 8 or at	Mean (SD) changes in MADRS score for the light was 13.4 (7.5), fluoxetine was 8.8 (9.9),	"Bright light treatment, both as monotherapy and in combination with	Data suggest all treatment groups improved but that combination bright light and fluoxetine therapy was most efficacious

			Research. One or more of the authors have received research funds, grants, honoraria, or have served on the advisory boards.	least moderate severity in outpatient psychiatry clinics in academic medical centers, MDD diagnosis confirmed with Mini International Neuropsychiatric Interview (MINI), also had Hamilton Depression Rating Scale score of	76 females.	placebo (n=32) vs Inactive negative ion generator for 30 min/d plus fluoxetine hydrochloride, 20mg/d) (n=31) vs Receiving light therapy and fluoxetine (n=29) vs Sham light therapy and placebo. (n=30). All patients took the pill every morning	unexpected termination	combination was 16.9 (9.2), and placebo was 6.5 (9.6). Combination therapy was better than placebo in MADRS response (β = 1.70; df = 1; P = .005)	fluoxetine, was efficacious and well tolerated in the treatment of adults with non-seasonal MDD. The combination treatment had the most consistent effects."	

				20 or above						
Ruhrmann 1998 (score=7.5)	Light Therapy	RCT	Sponsored by a grant from Eli Lilly, Germany. No mention of COI.	N=42 patients with a total score of at least 16 on the 21-items Hamilton Depression Rating Scale (HDRS) at entry and after the placebo phase (1st week)	Mean age: 41.1 years; 9 males, 33 females.	Fluoxetine group: Placebo during the 1st week then 5 weeks placebo light condition and 20mg of fluoxetine per day (n=20) vs Bright light group: placebo during the 1st week then 5 weeks of bright light (2 hr a day, 3,000 lux and a placebo pill)	Follow up weekly	Remission rate in bright light (50%) was better than fluoxetine (25%), P=0.10. HDRS scores improved faster in Light therapy than fluoxetine. However, atypical symptoms in fluoxetine had a quicker effect.	"Both treatments produced a good antidepressant effect and were well tolerated. An apparently better response to bright light requires confirmation in a larger sample."	Data suggest comparable efficacy between fluoxetine and bright light for the treatment of SAD
Ferreri 2001 (score=6.5)	Mianserin /Fluoxetine	RCT	No mention of sponsorship or COI.	N=104 patients with major depression	Mean age: 46.6 years; 27 males,	Mianserin: received placebo identical to fluoxetine and 60	7, 14, 42 days	Mean HAM-D score was decreased by -16.1±7.0 points in fluoxetine+mia	"Mianserin augmentation of fluoxetine in patients non-responders to	Data suggest augmenting fluoxetine with mianserin in major depressive fluoxetine non-

				(DSM-III-R)	77 females	mg/day of mianserin (n=34) vs Fluoxetine: received placebo identical to mianserin and 20 mg of fluoxetine (n=38) vs Fluoxetine+ Mianserin: received 20 mg of fluoxetine and 60 mg of mianserin (n=32) All patients received medication for 6 weeks.		nserin group compared to -11.3±7.4 points in fluoxetine group ($p \leq 0.03$).	fluoxetine 20 mg/day increases response to treatment and is well tolerated."	responders resulted in an increased therapeutic response.
Khoraminya 2012 (score=6.5)	Vitamin D	RCT	No COI or sponsorship.	N = 42 patients (minus 2 dropouts) with diagnosis of major depressive disorder via	Mean age: 38.88 years; 6 males, 34 females	1500 IU vitamin D3 plus 20 mg fluoxetine daily for 8 weeks (n=20) vs. 20 mg fluoxetine daily for 8 weeks (n=20)	Follow-up at 2, 4, 6 and 8 weeks during treatment	Hamilton Depression Rating Scale (HDRS) scores at base, week 2, week 4, week 6, and week 8, respectively: Fluoxetine only – 30.2, 25.23, 21.35, 19.00, 17.2, Vitamin	"In the present 8-week trial, the vitamin D + fluoxetine combination was superior to fluoxetine alone in controlling	Data suggest vitamin D plus fluoxetine was better than fluoxetine alone for decreasing symptoms of depression.

				DSM-IV.				D and Fluoxetine – 29.4, 23.94, 18.5, 14.6, 11.7 (Repeated measure analysis of variance on time: F = 9.29, p = 0.004, Analysis of covariance adjusted for baseline values: F = 8.54, p = 0.006)	depressive symptoms."	
Abolfazli 2011 (score=6.0)	Fluoxetine/ Modafinil	RCT	Sponsored by a grant from Tehran University of Medical Sciences. Authors Abolfazli, Tabrizi, and Raznahan associated with Tehran University. Akhondzadeh received the grant from Tehran University.	N = 46 participants meeting DSM-IV-TR criteria for major depression	Mean age: 33.20 years; 23 males, 23 females	Fluoxetine 40 mg/day with Modafinil 400 mg/day (n=23) vs. Fluoxetine 40 mg/day with Placebo (n=23). Medications were given for 6 weeks	Follow-up at 1, 2, 4, and 6 weeks	Significant difference in Hamilton Depression Rating Scale scores for both groups from baseline to six weeks (t(42) = 5.10, p = 0.001). Significant difference in response rates between two groups (at least 50% reduction in the Hamilton Depression	"These findings suggest modafinil as a well-tolerated and potentially effective agent in combination with fluoxetine in the management of patients with major depression."	Data suggest modafinil added to fluoxetine was better than fluoxetine alone in decreasing symptoms of major depression.

								Rating Scale score): modafinil group = 95.45%, placebo group = 54.54% (p = 0.003))		
Fava 2002 (score=5.5)	Fluoxetine/Desipramine/Lithium	RCT	No mention of COI. Sponsored by the National Institute of Mental Health.	N = 101 participants who met DSM-III-R criteria for major depressive disorder	Mean age: 41.6 years; 52 males, 49 females	High dose Fluoxetine 40-60 mg/day (n=33) vs. Fluoxetine 20 mg/day and Desipramine 25-50 mg/day (n=34) vs. Fluoxetine 20 mg/day and lithium 300-600 mg/day (n=34). All treatments administered daily for four weeks	Follow-up at 1, 2, 3 and 4 weeks	Mean change in Hamilton Depression Rating Scale scores from baseline to posttreatment: high-dose fluoxetine = 5.1, fluoxetine and desipramine = 3.5, fluoxetine and lithium = 3.6 (F = 0.9, p = 0.4)	"We found not significant differences in efficacy among these three treatment strategies among patients who had failed to respond adequately to 8 weeks of treatment of fluoxetine 20 mg/day, although the high-fluoxetine group was associated with nonsignificantly higher response	Data suggest similar efficacy in all 3 groups with a trend towards higher response rates in the high fluoxetine group for both non-responders and partial responders. Limited information on baseline group details.

									rates in both partial responders and nonresponders."	
Smeraldi 1998 (score=5.5)	Amisulpride/ Fluoxetine	RCT	No mention of sponsorship or COI.	N = 268 patients with dysthymia or a single episode of major depression (DSM-III-R)	Mean age: 49.4 years; 86 males, 182 females	Amisulpride: received 50 mg/day of amisulpride for 3 months (n=139) vs Fluoxetine: received 20 mg/day of fluoxetine for 3 months (n=129)	3 months	MADRES score reduction of ≥50% was achieved in 74% in amisulpride and in 67% in fluoxetine group (p=0.23). Response rate was 73% in amisulpride compared to 67% in fluoxetine (p=0.316).	"No statistically significant differences were found between the two drugs for MADRS, ERD, Sheehan Disability Scale, and CGI."	Data suggest a similar response rate as measured by a decrease in MADRS score of at least 50% but the fluoxetine group was slightly (non-statistically significantly) better than amisulpride group in partial depressive remission.
De Jonghe 2001 (score=5.0)	Insight-Oriented Psychotherapy/Fluoxetine	RCT	Sponsored by grant from Eli Lilly Nederland. No mention of COI.	N = 167 patients with major depression (DSM-III)	Mean age: 34 years; 49 males, 80 females	Pharmacotherapy Group: received fluoxetine 20 mg/d, if intolerance or inefficacy, received 50 mg/day amitriptyline—if	8, 16, 24 weeks	Reduction in depressive symptoms was achieved at each follow-up time favoring combined therapy group in 23% at 8 weeks, 31% at 16 weeks, and 62% of patients at 24 weeks.	"Patients found combined treatment significantly more acceptable, they were significantly less likely to drop out of combined therapy and,	6-month efficacy evaluation. Data suggest combination psychotherapy with anti-depressants for treating depression best as patient adherence to treatment is better as well as statistically better than pharmacotherapy

						intolerance or inefficacy, received 300 mg/day moclobemide (n=57) vs Combined Therapy: received both medication same as pharmacotherapy group and short psychodynamic supportive psychotherapy (16 45-minute sessions) consisting of focused behavioral and cognitive aspects of actual relationships (n=72)		Reduction of depressive symptoms was achieved in 40.7% of pharmacotherapy group and 59.2% in combined therapy group.	ultimately, significantly more likely to recover. Combined therapy is preferable to pharmacotherapy in the treatment of ambulatory patients with major depression."	alone (59.2% vs 40.7%).
Bastos 2015 (score=5.0)	Fluoxetine/	RCT	No mention of COI or sponsorship.	N = 272 participants	Mean age: 29.61	Long-term psychotherapy – one	Follow-up at 6, 12,	Mean Beck Depression Inventory	"These findings have	Data suggest long-term psychodynamic psychotherapy

	Psychotherapy			meeting DSM-IV-TR criteria for major depressive disorder or depressive disorder not otherwise specified	years; 104 males, 168 females	weekly session (LTPP) (n=90) vs. Fluoxetine – 20-60 mg/day (n=91) vs. Combination of both treatments (n=91). All groups received treatment for 24 months.	18, and 24 months	(BDI) scores at the end of 24 months: LTPP = 22.08, Combination = 22.04, Fluoxetine = 12.53). Mixed analysis showed significant decrease in BDI scores among all groups(F8; 479 = 45, 96, p < 0.001)	implications for patients with depression who may benefit from long-term psychodynamic psychotherapy or combined treatment, or for depression patients who do not wish to take medication such as fluoxetine."	(LTPP) and combination LTPP plus fluoxetine are better than fluoxetine alone.
Harrer 1999 (score=5.0)	St. John's Wort/Fluoxetine	RCT	No mention of sponsorship or COI.	N = 149 patients with mild to moderate depressive episodes (ICD-10)	Mean age: 68.8 years; 20 males, 129 females	SJW Group: received 2 coated tablets twice daily of 200 mg St John's Wort extract LoHyp-57 (Ze 117) (n=69) vs Fluoxetine Group: received 2	1, 2, 4, 6 weeks	HAM-D score reduced for both groups; however, neither were statistically significant. Response rate was 71.4% in SJW group and 72.2% in fluoxetine group.	"There was a trend towards somewhat better results with Hypericum in mild depressive episodes, and with fluoxetine in moderate depressive	Data suggest comparable efficacy but there was a trend for St. John's Wort to be better in mild depression and fluoxetine better for moderate depression.

						coated tablets twice daily of 5.6 mg fluoxetine-HCl (n=68)			episodes, but these differences were not statistically significant."	
Schrader 2000 (score=5.0)	St. John's Wort/Fluoxetine	RCT	No mention of sponsorship or COI.	N = 252 patients with depressive episode or recurrent depressive disorder (ICD-10)	Mean age: 46.5 years; 83 males, 157 females	Fluoxetine: received 20 mg once daily of fluoxetine (n=114) vs Hypericum: received 250 mg 2 times daily of hypericum (n=126)	6 weeks	Overall HAM-D scores were decreased for both groups ($p<0.09$). Mean CGI score was superior in hypericum compared to fluoxetine ($p<0.03$).	"We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is	Data suggest comparable efficacy but fewer adverse events with Ze 117.

									safety. Hypericum was superior to fluoxetine in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported."	
Jazayeri, 2008 (score=4.5)	Omega 3 fatty-acids	RCT	Sponsored by Vice-Chancellor for Research, Tehran University of Medical Sciences, Tehran, Iran. No mention of COI.	N = 60 outpatients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 34.8 years; 15 males, 45 females	Depressed patients given 1000 mg Eicosapentaenoic acid (EPA) daily for 8 weeks (n=16) vs 20 mg Fluoxetine daily for 8 weeks (n=16) vs 20 mg Fluoxetine + 1000 mg EPA daily for 8 weeks (n=16)	Follow up at 4, 6, and 8 weeks	The fluoxetine and EPA combination is significantly better than fluoxetine or EPA alone. Fluoxetine and EPA appear to be equally effective in controlling depressive symptoms. Response rates were 50%, 56% and 81% in the fluoxetine, EPA and combination groups, respectively.	"In the present 8 week trial EPA and fluoxetine had equal therapeutic effects in major depressive disorder. EPA and fluoxetine combination was superior to either of them alone."	Data suggest EPA + fluoxetine better than either fluoxetine or EPA alone.

Reimherr 1998 (score=4.5)	Fluoxetine	RCT	Sponsored by Lilly Research Laboratories. No mention of COI.	N = 395 participations who met the DSM-III-R criteria for major depression and met criteria for remission (no longer meeting DSM-III-R criteria) after 12 or 14 weeks of open-label fluoxetine therapy (20 mg/day)	Mean age: 40.30 years; 121 males, 274 females	Placebo (no continuation therapy) for 50 weeks (n=96) vs. 14 weeks of Fluoxetine 20 mg/day and then placebo (n=97) vs. 38 weeks of Fluoxetine 20 mg/day and then placebo (n=100) vs. 50 weeks of Fluoxetine 20 md/day	Follow-up at weeks 12, 14, 26, 38, and 50	Kaplan-Meier estimates of relapse rates after 24 weeks of treatment (fluoxetine = 26.4%, placebo = 48.6%, $p < 0.001$), after 38 weeks of treatment (fluoxetine = 9.0%, placebo = 23.2%, $p < 0.04$), and after 62 weeks of treatment (fluoxetine = 10.7%, placebo = 16.2%, $p = 0.54$)	"Patients treated with fluoxetine for 12 weeks whose depressive symptoms remit should continue treatment with fluoxetine for at least an additional 26 weeks to minimize the risk of relapse."	Data suggest fluoxetine treated patients whose symptoms of depression remit should be on fluoxetine therapy for at least an additional 26 weeks of therapy to prevent and/or limit relapse."
Blier 2010 (score=4.5)	Fluoxetine/Mirtazapine	RCT	Sponsored by Organon Pharmaceuticals. COI, one or more	N = 105 patients meeting DSM-IV criteria	Mean age: 43.81 years; gender	Fluoxetine 20 mg daily (n=28) vs. Mirtazapine 30 mg and	Follow-up at days 4, 7, 10, 14, 21,	Statistically significant difference in mean changes in	"The combination treatments were as well tolerated as	Data suggest all 3 combination therapies were superior to fluoxetine

			of the authors have received or will receive benefits for personal or professional use.	for major depressive disorder	distribution not mentioned	Fluoxetine 20 mg daily (n=25) vs. Mirtazapine 30 mg and Venlafaxine 225 mg daily titrated in 2 weeks (n=26) vs. Mirtazapine 30 mg and Bupropion 150 mg daily (n=26). All treatments given for 6 weeks.	28, 35, and 42	Montgomery–Åsberg Depression Rating Scale (MADRS) between monotherapy and 3 combination treatments (p = 0.09).	fluoxetine monotherapy and more clinically effective. The study results, which add to a growing body of evidence, suggest that use of antidepressant combinations from treatment initiation may double the likelihood of remission compared with use of a single medication."	monotherapy [mirtazapine + fluoxetine, mirtazapine + venlafaxine, mirtazapine + bupropion].
Shelton 2005 (score=4.5)	Nortriptyline/Fluoxetine/Olanzapine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or	N = 500 subjects with unipolar, nonpsychotic MDD	Mean age: 42.4 years; 160 males, 340 females	OFC: received either 6 mg/day olanzapine and 25 mg/day fluoxetine or	0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks	OFC group showed a greater decrease in MADRS scores than OLZ group (p=0.005).	"The olanzapine/fluoxetine combination did not differ significantly from the other	Data suggest comparability of all 4 treatment groups but combo olanzapine/fluoxetine resulted in a quicker response.

			will receive benefits for personal or professional use.	(DSM-IV)		12 mg/day olanzapine and 50 mg/day fluoxetine (n=146) vs OLZ: received 6 mg/day of olanzapine (ranged from 6-12 mg/day (n=144) vs FLX: received 25 mg/day fluoxetine (ranged from 25-50 mg/day) (n=142) vs NRT: received 25 mg/day nortriptyline (increased to 50 mg/day on day 2, and 75 mg/day by day 4) (n=68)		Remission rates were 16.9% for OFC group, 12.9% for OLZ group, 13.3% for FLX, and 18.2% for NRT group (p=0.62).	therapies at endpoint, although it demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization."	

Dam 1998 (score=4.5)	Mianserin / Fluoxetine	RCT	Sponsored by Organon and Eli Lilly. No mention of COI.	N = 34 patients with major depression (DSM-III-R)	No mention of mean age, range from 18-70 years; no mention of sex.	Fluoxetine Alone: received 20 mg of fluoxetine (n=18) vs Mianserin+ Fluoxetine: received 30 mg of mianserin and 20 mg of fluoxetine (n=16)	1, 2, 3, 4, 5, 6 weeks	Combination group showed an effect change of 0.69 in HAM-D scores ($p<0.05$) with the greater change in HAM-D scores compared to fluoxetine group.	"In conclusion, we found in the efficacy analysis, though not in the intention-to-treat analysis, that the combination of fluoxetine and mianserin was superior to fluoxetine alone."	Data suggest combo mianserin plus fluoxetine better than fluoxetine alone.
Salminen 2008 (score=4.0)	Insight-Oriented Therapy	RCT	Sponsored by the Social Insurance Institution of Finland, and the Signe and Ane Gyllenberg Foundation. No mention of COI.	N = 51 patients with major depressive disorder of mild or moderate severity (DSM-IV)	Mean age: 42.4 years; 16 males, 35 females	PSY Group: received 16 weekly psychodynamic psychotherapy sessions (n=26) vs Fluoxetine Group: received 20 mg/day of fluoxetine for 3-4 weeks then increased to 40 mg/day of fluoxetine	4 months	Both groups achieved reduction in HDRS score ($p<0.0001$), but no between group differences were found. Fluoxetine group showed 68% remission compared to 71% in the PSY group ($p=0.84$).	"Both STPP and pharmacological treatment with fluoxetine are effective in reducing symptoms and in improving functional ability of primary care patients with mild or moderate	Data suggest comparable efficacy.

						if no response was achieved (total16 weeks) (n=25)			depression. This study suggests no marked differences in the therapeutic effects of these two treatment forms in a primary care setting."	
Corya 2006 (score=4.0)	Olanzapine/Fluoxetine/Venlafaxine	RCT	Sponsored by Lilly Research Laboratories. No mention of COI.	N = 483 subjects with major depressive disorder (DSM-IV)	Mean age: 45.7±10.8 years; 133 males, 350 females	All groups received medications for 12 weeks. Group 1: received 1 mg/day of olanzapine and 5 mg/day of fluoxetine (n=59) vs Group 2: received 6 mg/day of olanzapine and 25 mg/day fluoxetine (n=63) vs Group 3:	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks	For analysis, group 1-5 were combined. Group 1-5 showed a greater improvement in MADRS mean score (-7.2) compared to group 6 (-4.8, p=0.03), group 7 (-4.7, p=0.03), and group 8 (-3.7, p=0.002). Groups 1-5 showed greater advantage to group 6 overall (-14.1 vs -7.7, p<0.001).	"In conclusion, the OFC showed a rapid and robust antidepressant effect in this sample of TRD patients, along with a safety profile comparable to its component monotherapies."	No baseline data stratified by group. Data suggest similar efficacy between olanzapine, fluoxetine, venlafaxine, and combination olanzapine/fluoxetine for the treatment of treatment resistant depression.

						received 6 mg/day of olanzapine and 50 mg/day of fluoxetine (n=63) vs Group 4: received 12 mg/day olanzapine and 25 mg/day of fluoxetine (n=60) vs Group 5: received 12 mg/day olanzapine and 50 mg/day fluoxetine (n=57) vs Group 6: received 6 or 12 mg/day olanzapine (n=62) vs Group 7: received 25 mg/day or 50 mg/day of fluoxetine (n=60) vs				

						Group 8: received 75-375 mg/day of venlafaxine (n=59)				
Brunner 2014 (score=4.0)	Olanzapine/Fluoxetine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 444 patients with single or recurrent unipolar mild depressive disorder (DSM-IV-TR)	Mean age: 44.4 years; 513 males, 1034 females	OFC Group: received an initial dose of 3 mg/day olanzapine and increased up to 18 mg/day and an initial dose of 25 mg/day fluoxetine and increased up to 50 mg/day (n=221) vs Fluoxetine Group: received 25-50 mg/day of fluoxetine (n=223) for 27 weeks	12 weeks, then weekly thereafter until week 47	Relapse time was longer in OFC group compared with fluoxetine group ($p<0.001$). Mean MADRS score change was 30.4 to 9.3.	"We believe this is the first controlled relapse-prevention study in subjects with TRD that supports continued use of a second-generation antipsychotic beyond stabilization."	High dropout rates. Data suggest time to relapse was significantly longer in the combo olanzapine/fluoxetine group.

Fluvoxamine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Zanardi 1998 (score=4.5)	Fluvoxamine/Pindolol	RCT	Sponsored by Instituto Scientifico Ospedale San Raffaele. No mention of COI.	N = 72 patients with major depressive episode (DSM-III-R)	Mean age: 47.4±10.1 years; 16 males, 56 females	Group 1: received 300 mg/day fluvoxamine and 7.5 mg/day placebo (n=36) vs Group 2: received 300 mg/day fluvoxamine and 7.5 mg/day pindolol (n=36)	1, 2, 3, 4, 5, 6 weeks	Reduction in HAM-D scale to an 8 or less was achieved in 80% of group 1 compared to 80.5% in group 2. Response rates were greater in group 2 compared to group 1 (p=0.0001, p=0.023, respectively).	"[t]he combination of fluvoxamine with pindolol may be a useful pharmacologic strategy in the treatment of this disorder. A rapid clinical response in such patients is of relevance in clinical practice as well as in economic fields, given the direct and indirect costs of depression."	Data suggest comparable efficacy between fluvoxamine plus pindolol and fluvoxamine plus placebo suggesting lack of efficacy of pindolol addition.
Maina 2010 (score=4.5)	BDT/Fluvoxamine/ Sertraline	RCT	No mention of sponsorship or COI.	N = 57 patients with OCD	Mean age: 31.5 years;	PT-alone Group received either 100	16 weeks, 12 months	HAM-D-17 remission was not significant between groups	"Supplemental BDT in the treatment of patients	Lack of efficacy of BDT. Data suggest combining BDT with either

				concurrent with MDD (DSM-IV)	24 males, 30 females	mg/day of fluvoxamine increased to a daily dose of 300 mg/day or 50 mg/day sertraline increased to a daily dose of 200 mg/day: (n=30) vs PT+BDT Group: received weekly 45 min sessions of brief dynamic therapy (10-16 sessions) (n=27)		(p=0.463). Mean HAM-D-score improved from 17.56±4.9 to 13.40±5.3 in BDT group compared to 20.48±5.1 to 15.10±5.5 in PT alone group.	with OCD with concurrent MDD who are receiving effective medication has no significant clinical effect on both obsessive and depressive symptoms."	fluvoxamine or sertraline is no better than administration of either medication alone in patients with MDD and concurrent OCD.
Paroxetine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Szegedi 2005 (score=6.5)	St. John's Wort/Paroxetine	RCT	Sponsored by Dr Willmar Schwabe Pharmaceuticals. COI: AS has	N = 251 patients with acute major depression	Mean age: 47.3 years; 76 males,	Hypericum Group: received hydroalcoholic extract from herba hyperici	7, 14, 28, 42 days	Hamilton depression scores decreased by an average of 14.4±8.8 points for hypericum	"In the treatment of moderate to severe major depression, hypericum extract WS	Data suggest comparable efficacy to paroxetine and may be slightly better.

			received consultancy fees from Dr Willmar Schwabe Pharmaceuticals. RK is head of a contract research organization. AD and MK are employees of Dr. Willmar Schwabe Pharmaceuticals.	(DSM-IV criteria)	168 females	with 3-6% hyperiforin and 0.12-0.28% hypericin (300-600 mg) (n=122) vs Paroxetine Group: received 20 mg tablets of paroxetine (40 mg per day) (n=122)		group compared to 11.4±8.6 points in the paroxetine group. Hypericum group showed better improvement in remission compared to paroxetine group (p=0.02).	5570 is at least as effective as paroxetine and is better tolerated."	
Qu, 2013 (score=6.0)	Acupuncture/Paroxetine	RCT	Sponsored by Key Project of the National Eleventh-Five Year Research Program of China, Key Project of Phase III of Guangdong and General Research Fund of	N = 160 patients with a diagnosis of MDD via the International Classification of Diseases (10th version) (ICD-10)	Mean age: 33.3 years; 75 males, 85 females.	Group 1: Paroxetine (PRX) alone – those not medicated had initial dose of 10 mg/day, escalated to 20 mg/day in one week, PRX taken for 6 weeks (n = 48) vs	Follow-up at 1 month.	Group comparisons through HAMD-17 revealed significant differences between the 3 (PRX— r2= 0.725; MA + PRX -- r2= 0.655; EA + PRX -- r2 = 0.784). MA and EA treatments	"[A]s most antidepressant agents have broad side effects, acupuncture in manual and electrical stimulation modes provides a safe and effective treatment in augmenting the	Contact bias with acupuncture group. Data suggest electrical acupuncture better than manual acupuncture for sustained benefits and may be synergistic with antidepressant effects like those from Paroxetine.

			Research Grant Council of HKSAR. No COI.			Group 2: Manual manipulation acupuncture treatment (MA), 3 30-minute sessions per week for 6 weeks, along with PRX (n = 54) vs Group 3: Manual manipulations with electrical stimulation (EA), 3 30-minutes sessions per week for 6 weeks, along with PRX (n = 58)		produced significantly higher reductions in scores compared to PRX alone (p=0.000), although no noteworthy differences were demonstrated through the two acupuncture groups. Higher response rates were seen through the MA and EA groups compared to PRX (69.8% and 69.6% vs 41.7%, p= 0.004).	antidepressant efficacy and reducing the incidence of exacerbation of depression in the early phase of SSRI treatment."	
Lôo 2002 (score=5.5)	Agomelatine/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 711 participants meeting DSM-IV major	Mean age: 42.3 years; 238 males,	Group 1: received 1 mg/day agomelatine (n=141) vs Group 2:	1, 2, 4, 6, 8 weeks	Groups 1-3 showed reduced mean HAM-D scores compared to placebo	"In conclusion, this placebo-controlled study clearly shows that,	Data suggest 25 mg of agomelatine was comparable to paroxetine and both medications were superior to placebo.

				depressive disorder criteria	473 females	received 5 mg/day agomelatine (n=147) vs Group 3: received 25 mg/day agomelatine (n=137) vs Group 4: received 20 mg paroxetine (n=147) vs Group 5: received 20 mg placebo capsule (n=139)		(p=0.037). Mean HAM-D score was lower in paroxetine group compared to placebo (p=0.03) and a similar observation was made for group 3 (agomelatine 25 mg) compared to placebo (p<0.05).	of the three doses tested, agomelatine 25 mg is effective in the treatment of major depression and is identified as the target dose."	
Appelhof 2004 (score=5.5)	Paroxetine/ Triiodothyronine	RCT	Sponsored by the Academic Medical Center Anton Meelmeijer Fund. No mention of COI.	N = 113 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 46.5 years; 43 males, 70 females	All participants received paroxetine for eight weeks. Doses titrated at 10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day for four weeks. Participants	Follow-up at weeks 1, 2, 4, 6, and 8	Significant improvement in Hamilton Depression Rating Scale (HRSD) scores for all three groups (p < 0.001 for all). HRSD mean score difference from baseline to 8 weeks: placebo = -9.4, 25 µg T3 = -9.8, 50	"In conclusion, these results do not support a role for T3 addition to selective serotonin reuptake inhibitors in the treatment of nonrefractory major depressive	Data suggest lack of efficacy of triiodothyronine to paroxetine and more adverse effects.

						also randomized to receive one of the following: Triiodothyronine (T3) 25 µg/day (n=30) vs. T3 50 µg/day (n=30) vs. Placebo daily (n=53)		µg T3 = -8.3 (F = 0.042, p = 0.66)	disorder. On the contrary, more adverse reactions occurred in T3-treated patients."	
Cassano 2002 (score=5.5)	Amisulpride/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 275 patients with major depressive disorder (DSM-IV)	Mean age: 51.25 years; 63 males, 200 females	Amisulpride: received 50 mg/day amisulpride for 8 weeks (n=136) vs Paroxetine: received 20 mg/day of paroxetine for 8 weeks (n=136)	7, 14, 28, 42, and 56 days	Response rate was 76% in amisulpride compared to 84% in paroxetine. Remission in HAM-D total score was reduced in both groups, but was similar (p=0.37).	"In conclusion, in the present study, paroxetine and amisulpride were highly effective and well tolerated. We believe that statistical results of a non-inferiority trial should be carefully	Data suggest therapeutic equivalence between amisulpride and paroxetine at 8 weeks with tolerability favoring amisulpride.

									evaluated in the light of the overall study findings."	
Franchini 1998 (score=5.0)	Paroxetine	RCT	No mention of COI. Sponsored by Istituto Scientifico Ospedale San Raffaele grants.	N = 68 participants meeting DSM-IV criteria for recurrent, unipolar depression	Mean age: 47.0 years; 24 males, 44 females	Paroxetine 20 mg/day (n=34) vs. Paroxetine 40 mg/day (n=34).	Follow-up at 10, 11, 12, 13, 17, 18, 20, 21, 25, and 28 months	Survival analysis for the 28-month follow-up showed advantage for 40 mg of paroxetine (χ^2 = 5.56, p = 0.180)	"These data suggest that a full dose of paroxetine is recommended in unipolar patients who are at high risk for recurrent depressive episodes."	Data suggest 40 mg of paroxetine is better than 20 mg paroxetine for those at increased risk for recurrence.
Folkerts, 1997 (score=4.5)	Electroconvulsive Therapy/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 39 patients who had a major depressive episode using ICD-10 guidelines	Mean age: 49.8 years; 18 males, 21 females.	Group 1 was given 0.5 atropine sulphate, 0.75-1.38 mg/kg methohexital, and 0.7-1.0 mg/kg succinylcholine via IV with right unilateral ECT 3 times a week (n=21) vs group 2 was given 20 mg	4 weeks	There was a 59% decrease in HAMD score for group 1 vs 29% in group 2 ($p<0.001$). Prior treatment had a significant effect on the outcome ($p<0.05$). Group 2 had better results after the open study phase ($p<0.03$).	"The present study found ECT to be superior to paroxetine in medication-resistant major depression, in terms of both degree and speed of response"	Data suggest ECT better than paroxetine for treatment-resistant depression in terms of magnitude or response.

						paroxetine daily and 40 mg within 7 days. Mean dose was 44 mg daily for 4 weeks (n=18)				
Uchida 2005 (score=4.5)	Sulpiride, Paroxetine	RCT	No mention of COI or sponsorship.	N = 41 participants meeting DSM-IV criteria for major depressive disorder without psychotic features	Mean age: 38.94 years; 25 males, 16 females	Paroxetine 10-40 mg/day plus Sulpiride 100 mg/day (n=20) vs. Paroxetine 10-40 mg/day alone (n=21)	Follow-up at weeks 1, 2, 4, 6, 8, and 12	Mean change in Montgomery-Asberg Depression Rating Scale: Paroxetine + sulpiride group = 34.4 to 5.6, Paroxetine alone group = 32.2 to 10.4 ($p < 0.001$). Combined group had greater reduction in Hamilton Rating Scale for Depression and Zung Depression Scale scores between week 1 and 12 ($p < 0.05$)	"The combination treatment may be a safe and effective strategy for accelerating antidepressant response."	Small study sample. Open label trial. Data suggest addition of sulpiride to paroxetine resulted in significant improved depression scores.

Dimidjian 2006 (score=4.5)	Cognitive Behavioral Therapy/ Paroxetine	RCT	Sponsored by National Institute of Mental Health Grant. COI: Dunner is a consultant or on the advisory board for, and serves on the speaker's bureau of a number of pharmaceutical companies, including GlaxoSmith Kline.	N = 241 subjects with major depression on the scale of DSM-IV.	Mean age: 39.9 years; 82 males, 159 females	Behavioral Activation (BA) group: received max twenty-four 50-minute sessions over 16 weeks, sessions twice weekly for first 8 weeks, and then only weekly after (n=43) vs. Cognitive Therapy (CT) group: same session schedule and frequency as BA group (n=45) vs. Antidepressants (ADM): received 16 weeks of paroxetine, started at 10mg/day,	Follow up at 8 and 16 weeks	Subjects in BA improved significantly greater than participants in CT on both the BDI, t(81)=2.23 (p=.029), and the HRSD, t(188)= 2.09 (p=.038). Participants in ADM improved significantly greater than participants in CT on both the BDI, t(81)= 2.76, (p=.007), and the HRSD, t(188)=2.31, (p=.022). When comparing participants in BA and ADM, were no significant differences in the rates of improvement on the BDI, t(81)= 0.25,	"Among more severely depressed patients, behavioral activation was comparable to antidepressant medication, and both significantly outperformed cognitive therapy."	Data suggest BA comparable to ADM and better than CBT.

						then 20mg/day at week 2, then 30mg/day at week 4, then 40mg/day at week 6, and 50mg/day dosage at week 12 (n=100) vs. Placebo (PLA) group: received 8 for weeks (n=53)		(p= .80), or on the HRSD, t(188)=0.05, (p=.96).		
DeRubeis 2005 (score=4.5)	Paroxetine/CBT	RCT	Sponsored by the National Institute of Mental Health.	N = 240 participants with moderate to severe major depressive disorder meeting DSM-IV major depressive disorder criteria	Mean age: 40 years; 98 males, 142 females	Paroxetine 10-50 mg/day for 16 weeks (n=120) vs. Placebo 10-50 mg/day for 8 weeks (n=60) vs. Cognitive Therapy (CT) for 16 weeks, 50-minute sessions twice weekly for 4 weeks then	Follow-up at weeks 2, 4, 6, 8, 10, 12, 14, and 16	At 8 weeks there was a significant difference in response rates between groups (paroxetine = 50%, placebo = 25%, CT = 43%, p = 0.006). At 16 weeks there was no difference in response rates between groups (paroxetine =	"Cognitive therapy can be as effective as medications for the initial treatment of moderate to severe major depression, but this degree of effectiveness may depend on a high level of therapist experience	Data suggest at 8 weeks the response rates to both paroxetine and CBT were comparable.

						1-2 times weekly for 8 weeks, then weekly for 4 weeks (n=60)		58%, CT = 58%, p = 0.92)	or expertise."	
Hollon 2005 (score=N/A)	Paroxetine/CBT	Secondary Analysis of DeRubeis 2005	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 104 participants with moderate to severe major depressive disorder meeting DSM-IV major depressive disorder criteria, met criteria for continuation phase portion of study	Mean age and gender distribution not reported	Continuation of paroxetine (cAMD) (n=34) vs. Withdrawal onto placebo (n=35) vs. Cognitive Therapy responders – given up to 3 booster sessions during 12-month continuation phase (n=35)	Follow-up at weeks 1, 2, 4, 6, and 8 and months 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12	Patients who withdrew from CT were less likely to relapse during the continuation phase than those who withdrew from medications (30.8%, 76.2%, p = 0.004). Patients who withdrew from CT were no more likely to relapse than those who kept taking medications (30.8%, 47.2%, p = 0.20)	"Cognitive therapy has an enduring effect that extends beyond the end of treatment. It seems to be as effective as keeping patients on medication."	Data suggest CT effects persist after treatment and is as effective as prolonged ADT.
Blier 2009 (score=4.5)	Mirtazapine/ Paroxetine	RCT	Sponsored by Organon Pharmaceuticals. COI: One or more	N = 61 participants with a DSM-IV	Mean age: 43.10 years; 33	Mirtazapine 30 mg/day (n=21) vs. Paroxetine 20 mg/day	Follow-up at days 4, 7, 10, 14, 21,	Statistically greater decrease in Montgomery-Asberg	"These results indicate that the combined	Data suggest combination therapy leads to better results than monotherapy.

			of the authors have received or will receive benefits for personal or professional use.	diagnosis of unipolar depression	males, 28 females	(n=19) vs. Combination Group: received 30 mg/day mirtazapine and 20 mg/day paroxetine (n=21). All medications given for six weeks	28, 35, 42, 49, and 56	Depression Rating Scale (MADRS) scores in combination therapy compared to monotherapies at day 42 (F = 7.17, p = 0.002).	use of two antidepressants was well tolerated and produced a greater improvement than monotherapy."	
Bauer 1999 (score=4.5)	Paroxetine/ Amitriptyline/ Lithium	RCT	Sponsored by SmithKline Beecham Pharma GmbH. No mention of COI.	N = 42 participants on a stable lithium regimen with major depressive episode meeting DSM-III-R criteria	Mean age: 48.59 years; 18 males, 24 females	Paroxetine 20 mg daily, then increased to 40 mg daily after 2 weeks (n=19) vs. Amitriptyline 50 mg daily, then increased to 150 mg daily after 2 weeks (n=23). Medications given for six weeks	Follow-up at weeks 1, 2, 3, 4, 5, and 6	At 4 weeks patients taking paroxetine had higher proportion of 50% reduction in Hamilton Depression Rating Scale scores compared to amitriptyline group (79% vs. 39%, p = 0.04). At 6 weeks the difference was not significant.	"The main finding of this study is that, in a population of patients on long-term lithium prophylaxis, the addition of paroxetine or amitriptyline to treat an episode of major depression seems to be effective and safe."	Small sample size. Data suggest after 4 weeks there were more patients achieving a 50% reduction in HAM-D scores than in the amitriptyline group.
Sertraline										

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Cooper-Kazaz 2007 (score=7.0)	Sertraline /Liothyronine	RCT	Sponsored by the Stanley Medical Research Institute. No COI.	N = 124 adults meeting the DSM-IV criteria for major depressive disorder.	Mean age: 43.1 years; 66 males, 58 females	Sertraline hydrochloride and liothyronine sodium: 50mg/d for one week and 100mg/d thereafter; 20-25ug/d for one week and 40-50ug/d thereafter (n=64) vs. Sertraline and placebo: 50mg/d for one week and placebo; 50mg/d for one week and 100mg/d thereafter (n=60)	Follow-up at 8 weeks.	There was no indication of significant effects with the liothyronine supplements. Remission rates were higher in sertraline/liothyronine when compared to sertraline/placebo (58% vs 38%, p=.02). At baseline, values of patients with sertraline/liothyronine remission were lower than those without remission (p<.002).	"These results demonstrate enhancement of the antidepressant effect of sertraline by concurrent treatment with liothyronine without a significant increase in adverse effects."	Data suggest sertraline enhanced with liothyronine increased antidepressant effect.
Brenes 2007 (score=6.5)	Exercise (Aerobic, Strengthening, Flexibilit	RCT	Sponsored by grant form Wake Forest University	N = 37 adults with minor depressi	Mean age: 74.5 years; 14	Medication Group: received open-label sertraline 25	2, 6, 10, 14 weeks, and 4 months	Depression HRSD scale was reduced in exercise and sertraline group	"Individuals in the exercise condition showed	Pilot study with usual care bias. Data suggest both exercise and sertraline benefit late

	y)/Sertraline		School of Medicine Women's Health Center of Excellence for Research, Leadership, and Education, The Claude D. Pepper Older Adults Independence Center and the Wake Forest University General Clinical Research Center, and National Institute of Mental Health Grant. No mention of COI.	on (DSM-IV criteria)	males, 23 females	mg/day for week 1 and 50 mg/day for week 2 (increasing 25 mg dose increments for a max of 150 mg) (n=11) vs Exercise Group: completed a 3 days a week for 16 weeks exercise program of aerobic and resistance exercise training (60-min sessions) (n=14) vs Usual Care Group: received a phone call by research staff at weeks 2, 6, 10, 14 weeks by research		compared to an increase in usual care condition (p=0.005). All groups showed an improvement in SF-36 scale while the improvement in exercise and sertraline group showed greater improvement compared to the usual care group (p=0.11).	greater improvements in physical functioning than individuals in the usual care condition. Both sertraline and exercise show promise as treatments for late-life minor depression. However, exercise has the added benefit of improving physical functioning as well."	life depression but exercise also improves the individual's physical function.

						staff about patient's general health status (n=12)				
Mao 2015 (score=6.5)	Sertraline / R. Rosea	RCT	Sponsored by the National Institute of Health Center for Complementary and Alternative Medicine (NCCAM) and the Jack Warsaw Fund for Research in Biological Psychiatry. COI, Dr. Mao is supported by NCCAM.	N = 57 subject with a DSM-IV Axis I diagnosis of MDD.	Mean age: 44.9 years; 31 males, 26 females	R. Rosea: 340 mg capsule(n=20) vs. Sertraline: 50 mg capsule (n=19) vs. Placebo: capsule (n=18) 1 capsule during week 1; <50% reduction in HAMD-D after 2 weeks= 2 capsules week 3 and 4; <50% reduction after 4 weeks= 3 capsules weeks 5 and 6; <50% reduction in HAMD-D after 6	Follow-up at 8 and 12 weeks.	There was no significant difference in all treatment groups, R. Rosea, Sertraline, and Placebo (p=0.79, p=0.28, p=0.17). Sertraline had the greatest decline in HAM-D scores when compared to R. Rosea (95% CI). Sertraline also had the greatest decline in HAM-D scores when compared to placebo (95% CI).	"These findings suggest that R. Rosea, although less effective than sertraline, may possess a more favorable risk to benefit ratio for individuals with mild to moderate depression."	Data suggest comparable results for all groups including placebo.

						weeks= 4 capsules weeks 6-12.				
Amore 2001 (score=6.5)	Amisulpride/Sertraline	RCT	No mention of sponsorship or COI.	N = 313 patients with dysthymia with or without a superimposed episode of major depressive disorder (DSM-IV)	Mean age: 47.1 years; 100 males, 213 females	Amisulpride: received 50 mg/day of amisulpride for 12 weeks (n=157) vs Sertraline: received 50-100 mg/day of sertraline for 12 weeks (n=156)	5, 10, 15 days, 4, 8, 12 weeks	Reduction in HAM-D total score was achieved better in the amisulpride group compared to the sertraline group ($p<0.0121$). Response rate at 8 weeks for MADRS scale was 54% in amisulpride compared to 69% in sertraline.	"The tolerability of both drugs was satisfactory. Amisulpride is significantly more effective than sertraline during the first weeks of treatment in dysthymia."	Data suggest faster onset of action of amisulpride than sertraline at 4 weeks and faster time to initial improvement, but at week 12 both drugs showed comparable efficacy.
Hypericum Depression Trial Study Group 2002 (score=6.0)	St. John's Wort/Sertraline	RCT	Sponsored by National Center for Complementary and Alternative Medicine and the National Institute of Mental Health to Duke	N = 340 patients with major depressive disorder (DSM-IV)	Mean age: 42.3 years; 116 males, 224 females	Hypericum Group: received 900 mg/day hypericum (n=113) vs Placebo: received equivalent placebo (n=116) vs Sertraline: received	1, 8, 18 weeks	HAM-D scores were reduced by -9.20 (95% CI-10.51 to -7.89) for placebo compared to -8.68 (95% CI -10.01 to -7.35) for H perforatum ($p=0.59$) and -10.53 (95% CI	"This study fails to support the efficacy of H perforatum in moderately severe major depression. The result may be due to low assay sensitivity of	Data suggest lack of efficacy as Hypericum perforatum not superior to placebo for treatment of major depression.

			University Medical Center. No mention of COI.			50mg/day sertraline (n=111)		–11.94 to -9.12) for sertraline (p=0.18).	the trial, but the complete absence of trends suggestive of efficacy for H perforatum is noteworthy."	
Wang 2015 (score=6.0)	Sertraline /Deanxit	RCT	Sponsored by Guangdong Natural Science Foundation, Science and Technology Planning Project of Guangzhou City, and the fund of West China Psychiatric Association. No COI.	N = 75 patients diagnosed with depression by the HAM-D and anxiety with the HAM-A scales.	Mean age: 62.2 years; 28 males, 47 females.	Deanxit: Sertraline (75 mg/day) and deanxit (a combination medication of 10 mg melitracen and 0.5 mg of flupentixol- a tricyclic antidepressant and an antipsychotic) (one piece/day) (n=38) vs. Placebo: Sertraline (75 mg/day) and placebo (on piece/day) (n=37)	Follow-up at 2 weeks.	Overall, there was no distinct differences between the groups at the end point, with the exception of difference in scores between the deanxit and placebo group on day 8 (p=0.006) and day 15 (p=0.001). HAM-A scores were favoring the deanxit group on day 4, 8, and 15 (p=0.006, p=0.001, p=0.002).	"The rapid onset of sertraline plus short-term deanxit indicated that it might be an inspiring strategy to manage depression and anxiety within the first two weeks in chronic somatic diseases."	Data suggest sertraline plus short term deanxit may benefit patients with depression and anxiety.

Meyers 2009 (score=6.0)	Sertraline /Olanzapine	RCT	Sponsored by United States Public Health Services and the National Institute of Mental Health. No COI.	N = 259 patients with unipolar MDpsy with a score of 2 or less on the Delusional Assessment Scale (DAS) and a score 3 or less on the Schedule of Affective Disorder and Schizophrenia (SADS).	Mean age: 58.0 years; 103 males, 156 females	Sertraline + Olanzapine: 150-200 mg/day of sertraline and 15-20 mg/day of olanzapine (n=129) vs. Olanzapine + Placebo: 15-20 mg/day of olanzapine and : 150-200 mg/day of placebo (n=130)	Follow-up every week until 6 weeks, then every other week until 12 weeks.	Combination therapy was found to be superior in in young adults than older adults (p=.02, p=0.01). Olanzapine/Sertraline was seen to have higher remission rate when compared to Olanzapine/placebo (p<.001).	"Combination pharmacotherapy is efficacious for the treatment of MDpsy. Future research must determine the benefits of continuing atypical antipsychotic medications beyond twelve weeks against the associated metabolic effects."	High attrition rate. Data suggest combination therapy in beneficial for psychotic depression.
Brenner 2000 (score=5.5)	St. John's Wort/Sertraline	RCT	Sponsored by Lichtwer Pharma AG, Berlin, Germany. No mention of COI.	N = 30 patients diagnosed with major depression (recurren	Mean age: 45 years; 11 males, 19 females	Hypericum Group: received LI 160 H. perforatum 600 mg/day during week 1, and 900	2, 4, 7 weeks	HAM-D scores reduced by 40±30% in hypericum group compared to 42±24% in the placebo group.	"In a controlled, randomized comparison of hypericum extract (LI 160) and sertraline in	Small sample. Data suggest comparable efficacy and may be slightly better.

				t, or single episode) (DSM-IV)		mg/day for remainder of trial (n=15) vs Sertraline: received 50 mg/day for week 1, and 75 mg/day for the rest of the trial (n=15)			the treatment of mild to moderate depression, hypericum was found to be at least as efficacious as the SSRI antidepressant. Both drugs were well tolerated."	
Blumenthal 1999 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by the National Institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 156 people with major depressive disorder via DMS-IV criteria, assessed by the Diagnostic Interview Schedule and the Hamilton Rating Scale for	Mean age: 57 years; 43 males, 113 females	Sertraline initiated with 50 mg and titrated until well tolerated group (n = 48) vs three supervised exercise sessions per week group (n = 53) vs both sertraline and exercise as above group (n = 55)	Follow up at 1, 2, 3, 4, 6, 8, and 12 weeks.	Growth curve analysis of HAM-D showed the rate of treatment response differed across the treatment groups (P=0.02). 60.4% of the exercise group, 68.8% of the medication group and 65.5% of the combination group no longer met DSM-IV criteria for	"An exercise training program may be considered an alternative to antidepressants for treatment of depression in older persons. Although antidepressants may facilitate a more rapid initial therapeutic response	Data suggest comparable response between all 3 groups and antidepressant appeared to result in a faster response but at the end of the 16-week intervention, exercise and antidepressant were equally effective for treating MDD symptoms.

				Depression (HAM-D)				MDD post treatment (No statistical difference found)	than exercise, after 16 weeks of treatment exercise was equally effective in reducing depression among patients with MDD.	
Babyak 2000 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary Analysis of Blumenthal 1999	Sponsored by the National institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 133 volunteers who met DSM-IV criteria for MDD and scored at least 13 on the HRSD at study entry.	Mean age and gender information not reported	Group that did three supervised exercise sessions per week for 16 weeks at 70%-85% heart rate reserves with a 10 min warm up, 30 minutes at proper intensity and 5 min cool down (n = 44) vs group that received sertraline initiated at	Follow up at 2, 6, 10, 14, and 16 weeks in original study. Follow up at 4 and 10 months for secondary study.	At 10 months 30% of the exercise group were still considered depressed based on DSM-IV diagnosis or an HRSD score greater than 7 vs 52% in the medication group and 55% in the combination group (p=0.028). Looking at the 83 patients assessed as being in remission at 4	"Among individuals with MDD, exercise therapy is feasible and is associated with significant therapeutic benefit, especially if exercise is continued over time."	Data suggest exercise was associated with lower relapse rates than those associated with the medication group.

						50 mg and titrated until well-tolerated up to 200 mg (n = 42) vs group that did both the exercise and medication interventions (n = 47)		months, at 10 months participants in the exercise group had an odds ratio of 6.10 (p=0.01) of being partially or fully recovered compared to the other two groups.		
Murri 2015 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/Sertraline	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU) grant. No COI.	N = 121 patients with major depression on Hamilton Rating Scale for Depression (HRSD) score ≥ 18	Mean age: 75.2 years; 35 males, 86 females	Sertraline Only: received 50 mg sertraline (n=42) vs Sertraline+ Non-progressive Exercise (S+PAE): received 50 mg sertraline and 3 session per week for 24 weeks of exercise sessions(n= 37) vs Sertraline+P	4, 8, 12, 24 weeks	Remission rates at 4 weeks were 36% for S+PAE group, 40% for S+NPE group, and 7% for sertraline only group (p=0.001). Remission rates at 8 weeks were 60% in S+PAE group, 49% in S+NPE group, and 40% for sertraline only group (p=0.22). Remission rates at 12 weeks were 83% for	"Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression."	Data suggest exercise as adjunct therapy for depression in late life individuals.

						rogressive Aerobic Exercise (S+NPE): received 50 mg sertraline and exercise involving improved cardiopulmonary condition (n=42)		S+PAE group, 54% for S+NPE group, and 45% for sertraline only group (p=0.001). HRSD scores decreases more in the exercise groups compared to the sertraline only group.		
Schweizer 2001 (score=5.5)	Sertraline	RCT	Sponsored by Pfizer, Inc. No mention of COI.	N = 91 participants meeting DSM-IV criteria for major depressive disorder who were had non-response to 3 weeks of 50 mg/day of sertraline	Mean age: 38.96 years; 43 males, 48 females	Sertraline 50 mg/day for 5 weeks (n=37) vs. Sertraline 150 mg/day for 5 weeks (n=38) vs. Sertraline 50 mg non-responders not randomized (n=16)	Follow-up weekly until 8 weeks	At 8 weeks there was not statistical difference in remission rate (Hamilton Depression Rating Scale score ≤ 8) between 50 mg and 150 mg sertraline group (p > 0.10)	"In conclusion, the results of the current study suggest that increasing the dose of sertraline after 3 weeks of partial or non-response offers only modest additional therapeutic benefit compared to continued treatment at the same	Data suggest lack of evidence for a dose-response curve for sertraline in the treatment of depression.

									dose for additional 5 weeks."	
Kolouri 2016 (score=5.5)	Sertraline /Nepeta Menthoides	RCT	No COI. Sponsored by Shiraz University of Medical Sciences.	N = 72 participants meeting DSM-5 criteria for major depression	Mean age: 35.27 years; 49 males, 17 females. Mean age and gender information only available for 66 participants	Nepeta menthoides extract – 500 mg capsule, contained 400 mg of freeze-dried aqueous extract power and 100 mg starch (n=36) vs. Sertraline – 50 mg/day (n=36). Both groups given one capsule for five days and then increased to two capsules. Treatments given for four weeks	Follow-up at 2, 4, and 6 weeks	Repeated measures ANOVA showed difference in Beck Depression Inventory II score in each group ($F=74.02$, $p < 0.001$). There was a significant difference between the two groups ($F = 17.6$, $p < 0.001$)	"Nepeta menthoides may have potential benefits in the control of mood in patients suffering from major depression. Sustention of antidepressant effect and delay in the recurrence of depression could be considered worthwhile using this herb."	Data suggest Nepeta menthoides may have some positive impact on mood.
Malt 1999 (score=5.5)	Mianserin /Sertraline	RCT	Sponsored by Pfizer Norway. COI: One or	N = 372 patients with depressi	Mean age: 48.2 years;	Sertraline: received 50-200 mg/day of sertraline	1,2 3, 4, 6, 8, 12, 16,	Mean change in depression score was -14.9 points in	"The combination of active drug and	Study suggests medication is only slightly better than placebo as data

			more of the sponsors have received or will receive benefits for personal or professional use.	on (DSM-III-R)	101 males, 269 females	over 6 weeks (n=122) vs Mianserin: received 30-120 mg/day of mianserin over 6 weeks (n=121) vs Placebo: receive no specific dose of placebo (n=129) All patients received psychological treatment.	20, 24 weeks	sertraline, -15.5 points in mianserin, and -12.5 in placebo (p=0.034). Efficacy of sertraline versus placebo was OR=0.63 (95% CI 0.36-1.11) compared to mianserin versus placebo OR=0.83 (95% CI 0.47-1.47).	simple psychological treatment (counseling, emotional support, and close follow up over a 24 week period) was more effective than simple psychological treatment alone, in particular for those with recurrent depression."	suggest remission occurred in 47% placebo randomized group 54% mianserin group, and 61% sertraline. Data suggest a combination of either sertraline or mianserin with psychological treatment is more effective than psychological treatment alone especially in those with recurrent depression.
Van Gurp 2002 (Score=5.0)	St. John's Wort/Sertraline/Fluoxetine	RCT	Sponsored by grant from St. Mary's Hospital Centre, grant from Pfizer Canada. No COI.	N = 87 patients diagnosed with major depression (DSM-IV)	Mean age: 40.1 years; 33 males, 52 females	St John's Wort: received 900 mg of st john's wort (3-300 mg tablets daily) (n=44) vs Sertraline: received 50 mg sertraline (16.67 mg tablets 3	2, 4, 8, 12 weeks, 6 months	Mean HAM-D and BDI scores were decreased for both groups (p=0.582, p=0.808, respectively).	"The more benign side effects of SJW make it a good first choice for this patient population."	Data suggest comparable efficacy with less adverse events than SJW.

						times daily) (n=34)				
Sarris 2012 (score=5.0)	St. John's Wort/Sertraline	RCT	No sponsorship or COI.	N = 124 participants with major depressive disorder (DSM-IV)	Mean age: 44.4 years; 43 males, 77 females	SJW Group: received 900 mg/day hypericum (n=35) vs Placebo: received equivalent placebo (n=40) vs Sertraline: received 50mg/day sertraline (n=49)	8, 10, 14, 18, 22, 26 weeks	HAM-D scores were 6.6±4.5 in SJW group, 7.1±5.4 in the sertraline group, and 5.7±5.4 in the placebo group (p=0.036). Remission rates were 58% for sertraline, 63% for SJW group, and 74% for placebo (p=0.20).	"In conclusion, while the results of the continuation phase of this large RCT revealed similar findings to the acute phase, the surprising outcome that a placebo response was maintained, and the questions of why this occurred, are of considerable interest."	Placebo controlled. Data suggest comparable efficacy between all treatments at 26 weeks.
Belvederi, 2015 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU) 2010-12	N = 121 primary care patients with major depression (score	Mean age: 75.2 ± 6.0 years; 35 males,	Sertraline only (S): Prescribed drug 50 mg (2 week titration period, zolpidem	None	45% of participants In Sertraline group, 73% of participants in (S+NPE) group, and 81% (S+PAE) group	"Physical exercise may be a safe and effective augmentation to antidepressant therapy in	Data suggest significant efficacy in the physical exercise group.

			grant, area 2 for clinical Governance. No mention COI	of 18 or higher on the 17-item HRSD) selected by physicians and conditions were compatible with regular exercise	86 females	10mg/day and lorazepam 2mg/day was allowed for insomnia) (n=42) vs Sertraline plus non-progressive exercise (S+NPE): Prescribed 3 supervised group exercise sessions per week (60 min, 24 wks in groups of 3 to 6 participants) in addition to sertraline as in the sertraline group (n=37) vs Sertraline plus progressive aerobic exercise (S+PAE):		achieved remission ($p < 0.001$; 95% CI 1.27 – 3.54)	late-life major depression."	

						Prescribed the same group exercise sessions, but training scheme was programmed to increase over the weeks (n=42)				
Thase 2002 (score=4.5)	Imipramine/ Sertraline	RCT	Sponsored by Pfizer Inc. Multiple authors have served as paid consultants for Pfizer Inc.	N = 168 nonresponses to 12 weeks of medication treatment, all met DSM-III-R criteria for chronic major depressive disorder	Mean age: 40.5; 56 males, 112 females	Imipramine nonresponses received sertraline (mean dosage = 163 mg/day) (n=51) vs. Sertraline nonresponses received imipramine (mean dosage = 221 mg/day) (n=117). Medications given for 12 weeks	Follow-up weekly for 6 weekly, then biweekly for another 6 weeks	Hamilton Depression Rating Scale scores (HAMD) mean end point improvement: Imipramine = 9.3, Sertraline = 12.1 (p = 0.57)	"More than 50% of chronically depressed antidepressant nonresponders benefits from a switch from imipramine to sertraline, or vice versa, despite a high degree of chronicity."	Data suggest a benefit in switching to an antidepressant of a different class after first-line therapy has failed.
Brunoni 2013 (score=4.5)	Sertraline / tDCS	RCT	No COI. Sponsored by the São Paulo	N = 120 participants who were	No mention of age or sex	Placebo medication and sham transcranial	Follow-up at 2, 4,	Significant difference in Montgomery-Asberg	"In MDD, the combination of tDCS and	Data suggest combination sertraline plus ECT is synergistic.

			Research Foundation.	antidepressant-free meeting DSM-IV criteria for unipolar, nonpsychotic major depressive disorder	distribution	direct current stimulation (tDCS) (n=30) vs. Placebo medication and active tDCS (n=30) vs. Sertraline medication and sham tDCS (n=30) vs. Sertraline medication and active tDCS (n=30). All treatments given for six weeks. tDCS included 2-mA anodal left/cathodal right prefrontal tDCS (twelve 30-minute sessions). Sertraline hydrochlori	and 6 weeks	Depression Rating Scale scores between active tDCS and sertraline versus sertraline group (mean difference = 8.5; p = 0.002), versus tDCS group (5.9, p = 0.03), and versus placebo/sham tDCS (11.5, p < 0.001).	sertraline increases the efficacy of each treatment. The efficacy and safety to tDCS and sertraline did not differ."	

						de dosage was 50 mg/day.				
Zilcha-Mano 2014 (score=4.5)	Insight-Oriented Psychotherapy/Sertraline	RCT	Sponsored by a NIMH grant, grant from Pfizer Corp. and from the Fulbright Program. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 156 patients diagnosed with MDD (DSM-IV)	Mean age: 37.5±12.2 years; 64 males, 92 females	SET Group: received 20 sessions of manualized psychodynamic therapy 2 times weekly for 4 weeks, then weekly for rest of treatment (n=51) vs MED Group: received sertraline (unless don't respond then switched to venlafaxine after 8 weeks) no mention of dose (n=55) vs Placebo: received placebo (if no response then switched to	4, 6, 8, 12, 16 weeks	Depressive symptoms were reduced in all groups ($p<0.001$). No between group differences were observed ($ps \geq .09$).	"Current treatments for depression significantly improve patients' QOL and well-being. No significant differences were found between the three conditions examined in this study. The current study highlights the role of well-being in predicting subsequent symptomatic change."	Data suggest comparable efficacy between treatment groups.

						a different placebo after 8 weeks) no mention of dosing (n=50)				
Gastpar 2005 (score=4.5)	Sertraline /St. John's Wort	RCT	No mention of COI or sponsorship.	N = 241 participants meeting ICD-10 criteria for moderate depressive disorder	Mean age: 48.89 years; 61 males, 180 females	Hypericum – ethanolic hypericum extract STW3 (Laif 600), 612 mg/day (n=123) vs. Sertraline – 50 mg/day (n=118). Treatments were given for 24 weeks	Follow-up at weeks 1, 12 and 24	Hamilton Depression Rating Scale scores at 12 weeks: hypericum = 22.0, sertraline = 22.1) and at 24 weeks: hypericum = 5.7, sertraline = 7.1. Covariance analysis with respect to non-inferiority was significant ($p < 0.0001$) – hypericum was not inferior	"The results indicate that hypericum extract STW 3 is not inferior to sertraline and that it is a well-tolerated drug for the treatment of moderate depression. These favorable effects were achieved with a once-daily dose of 612 mg of hypericum extract given for up to 24 weeks."	Data suggest hypericum extract STW3 is not inferior to sertraline and is well tolerated.

Maina 2010 (score=4.5)	BDT /Fluvoxamine/ Sertraline	RCT	No mention of sponsorship or COI.	N = 57 patients with OCD concurrent with MDD (DSM-IV)	Mean age: 31.5 years; 24 males, 30 females	PT-alone Group received either 100 mg/day of fluvoxamine increased to a daily dose of 300 mg/day or 50 mg/day sertraline increased to a daily dose of 200 mg/day: (n=30) vs PT+BDT Group: received weekly 45 min sessions of brief dynamic therapy (10-16 sessions) (n=27)	16 weeks, 12 months	HAM-D-17 remission was not significant between groups (p=0.463). Mean HAM-D-score improved from 17.56±4.9 to 13.40±5.3 in BDT group compared to 20.48±5.1 to 15.10±5.5 in PT alone group.	"Supplemental BDT in the treatment of patients with OCD with concurrent MDD who are receiving effective medication has no significant clinical effect on both obsessive and depressive symptoms."	Lack of efficacy of BDT. Data suggest combining BDT with either fluvoxamine or sertraline is no better than administration of either medication alone in patients with MDD and concurrent OCD.
Menchetti 2014 (score=4.0)	Sertraline /Citalopram/Counseling	RCT	No COI. Sponsored by the Italian Ministry for University and Research as Research	N = 287 participants meetings DSM-IV criteria for major	Mean age: 44.9 years, 76 males, 211 females	Interpersonal counseling – six 30-minute sessions (initial session being 60-	No long-term follow-up	At 2 months significantly higher percentage of patients who reached remission in interpersonal	"We identified some patient characteristics predicting a differential outcome with	Data suggest a significantly greater number of patients reached remission (58.7%) in the interpersonal counseling group compared to the

			Program of National Interest in 2005.	depression		minutes) (n=143) vs. SSRI treatment – given either sertraline or citalopram, patients met with psychiatrist every 2 to 3 week intervals, dosages not specified (n=144). Treatments given over a 2-month period		group compared to SSRI group (58.7%, 45.1%, p = 0.021)	pharmacological and psychological interventions. Should our results be confirmed in future studies, these characteristics will help clinicians to define criteria for first-line treatment of depression targeted to patients' characteristics."	SSRI group (45.1%), suggesting IP counseling better than either sertraline or citalopram.
Hoffman, 2008, (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Grant MH 49679 from National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center	N = 202 sedentary participants who met DSM-IV and Hamilton Depression Rating	Mean age: 51.7 ± 7.6 years; 49 male, 153 female	Supervised Aerobic Exercise: Exercise 3 a week for 16 weeks. Assigned training ranges between 70-85% of HR (n=51) vs Home-	None	Participants in al treatment groups experienced decreased symptoms of depression measured by HAM-D, BDI.	"These findings suggest that exercise does not confer clinically meaningful improvements in neurocognitive function among clinically	Data suggest exercise was no better than sertraline for memory or verbal fluency but better than sertraline for executive function. However individuals in the exercise groups demonstrated higher aerobic capacities

			Program. COI Dr. Doraiswamy received grants and honoraria from serval pharmaceutical companies. Dr. Blumenthal previously received an investigator-initiated research grant from Pfizer/Eisai for an unrelated study.	Scale (HAM-D) criteria for MDD		Based Aerobic Exercise: participants received an initial exercise training session with an exercise physiologist, target HR between 70-85% HR (n=53) vs. Sertraline Group: received Zoloft (50 mg and titrated until 200mg), met with a staff (n=49) vs Placebo Pill group: met with a staff psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=49)			depressed adults. Exercise offered no clear benefit relative to placebo pill on any of the neuropsychological tests we used in this study."	then the non-exercise groups

Hoffman, 2011 (score= 4.0)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary analysis	Sponsored by Grant MH 49679 (J.A.B>) from the National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center Program, National Institutes of Health, own stock NovaDel Pharma, and receives royalties from John Wiley and Sons. No Mention of COI.	N = 172 sedentary adults with MDD (scored 12 or more on Beck Depression Inventory-2) and were not receiving antidepressant medication of psychotherapy and physically inactive	Mean age: 51.79 ± 7.64 years; 46 male, 126 females	Supervised Aerobic Exercise group: participated 3 45 min exercise groups weekly. Each person was assigned individual target rate between 70-85% (n=43) vs Home-Based Aerobic Exercise: participated in initial training session with an exercise physiologist, as well as two follow up sessions after the first and second month (n=48) Sertraline	1 year	46% of MDD remission increase at post treatment for 66% of participants available at follow up	"The effects of aerobic exercise on MDD remission seem to be similar to sertraline after 4 months of treatment; exercise during the follow-up period seems to extend the short-term benefits of exercise and may augment the benefits of antidepressant use."	One-year follow-up of Hoffman 2008. Data suggest at one year there was a 50% chance of relapse to depressive symptoms in the exercise group but there were extended benefits of exercise, which perhaps may augment antidepressant use for 0-180 minutes of exercise per week.

						Group: received Zoloft (50 mg and titrated until 200mg), met with a staff vs. psychiatrist at 2,4,8,12 and 16 weeks (n=41) vs Placebo Pill group: met with a staff psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=40)				
Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)										
Duloxetine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Cutler 2009 (score=6.0)	Quetiapine/ Duloxetine	RCT	Sponsored by AstaZeneca. COI: One or more of the authors have received or will receive	N = 612 patients with mild depressive disorder (DSM-IV)	Mean age: 41.3 years; 233 males, 354 females	Duloxetine: received 60 mg/day of duloxetine (n=141) vs Placebo: (n=152) vs Quetiapine	1, 2, 4, 6 weeks	Mean MADRS score was reduced by 14.81 in quetiapine XR 150 group (p<.001), 15.29 in quetiapine	"Quetiapine XR monotherapy (150 mg/day and 300 mg/day) is effective, with safety	Data suggest at week 6 there were significantly improved MADRS scores with both doses of quetiapine and duloxetine compared to

			benefits for personal or professional use.			XR 150: received 150 mg/day of quetiapine XR (n=147) vs Quetiapine XR 300: received 300 mg/day of quetiapine XR (n=147)		XR 300 group (p<.001), and 14.64 in duloxetine (p<.01), and 11.18 in placebo. Response rates were 54.4% in quetiapine XR 150, 55.1% in quetiapine XR 300, 49.6% in duloxetine, and 36.2% in placebo.	and tolerability consistent with the known profile of quetiapine XR, in the treatment of patients with MDD, with onset of symptom improvement demonstrated at week 1."	placebo. Remission rates were also improved in quetiapine 300 mg and duloxetine but not 150 mg quetiapine improvement with quetiapine occurs as early as week one.
Brecht 2011 (score=6.0)	Duloxetine	RCT	Sponsored by Eli Lilly and Boehringer Ingelheim GmbH. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 338 patients with severe depression (DSM-IV)	Mean age: 44.8 years; 87 males, 251 females	Group 1: received duloxetine 60 mg/day (n=167) vs Group 2: received duloxetine 120 mg/day (n=171)	4, 8 weeks	Mean MADRS score change in group 1 was -20.1±10.6 compared to -19.9±10.0 in group 2 (p=0.88).	"Duloxetine 60-mg and 120-mg doses were equally effective and demonstrated no significant differences in treating severe depressive symptoms in hospitalized patients. The safety and	Unclear if doses were packaged identically. Data suggest no difference between duloxetine 60 mg versus 120 mg from baseline to 4 weeks for treatment of severe depression.

									tolerability profile of duloxetine in both dosages did not differ and was similar to those reported in previous duloxetine studies."	
Mahableshwarkar 2015 (score=5.5)	Vortioxetine/ Duloxetine	RCT	Sponsored by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 614 participants with primary diagnosis of recurrent MDD meeting DSM-IV criteria	Mean age: 42.9 years; 160 males, 454 females	Vortioxetine 15 mg daily (n=147) vs. Vortioxetine 20 mg daily (n=154) vs. Duloxetine 60 mg daily (n=152) vs. Placebo daily (n=161). All medications received for 8 weeks	No long term follow-up	Mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS): placebo = −12.83, vortioxetine 15 mg = −14.30 ($p = 0.224$, compared to placebo), vortioxetine 20 mg = −15.57 ($p = 0.023$), and duloxetine 60 mg = −16.90 ($p < 0.001$)	"Vortioxetine 20 mg significantly reduced MADRS total scores after 8 weeks of treatment. Both vortioxetine doses were well tolerated."	Data suggest 20 mg dose of vortioxetine comparable to duloxetine and both superior to placebo.

Fornaro 2014 (score=5.5)	Duloxetine/Bupropion	RCT	Sponsored by University of Genova. No COI.	N = 46 patients with major depression (DSM-IV)	Mean age: 39.0 years; 16 males, 30 females	Duloxetine +Placebo: received 60-120 mg/day of duloxetine plus one 150-300 mg/day dummy pill of placebo for 6 weeks (n=23) vs Duloxetine+ Bupropion: received 60-120 mg/day of duloxetine plus 1 capsule of bupropion (150-300 mg/day) sustained release for 6 weeks(n=23)	2, 4, 6 weeks	Withdrawal rate of 68% in placebo group compared to 61% in bupropion group. Placebo group showed 18.2% response at week 4 compared to 28.6% in bupropion group. Placebo group showed an additional response in 13.6% at week 6 compared to 1% in bupropion group.	"Additional studies, including an adequate course of duloxetine trial, are nonetheless aimed to allow a firm conclusion about the usefulness of the combination of duloxetine and bupropion for treatment-resistant cases of major depression with atypical features."	Lack of efficacy as data suggest only 21.7% of patients receiving duloxetine-placebo achieved response vs 26.1% receiving duloxetine-bupropion.
Perahia 2008 (score=5.0)	Duloxetine	RCT	Sponsored by Eli Lilly and Co. COI: One or more of the authors have received or	N = 368 adult outpatients with major depressive disorder	Mean age: 49.0 years; 85 males,	Direct Switch: received SSRI with abrupt discontinuation then	10 weeks	Both groups improved from HAM-D17 scores of -10.23 for DS group (95% CI -11.26 – 9.20)	"Switch to duloxetine was associated with significant improvemen	Data suggest direct switching or tapered switching to duloxetine resulted in significant improvements in both emotional and

			will receive benefits for personal or professional use.	(DSM-IV)	283 females	given duloxetine 60 mg/day (n=183) vs Start-Taper Switch: received SSRI then tapered discontinuation of SSR over 2 weeks then given simultaneous administration of duloxetine 60 mg/day resulting in a 2 week overlap of SSRI and duloxetine (n=185)		compared to -10.49 in the STS group (95% CI –11.52 - -9.45) (p≤.001).	ts in both emotional and painful physical symptoms of depression and was well tolerated and safe, regardless of which of the switch methods was used."	physical depression symptoms.
Romera 2012 (score=4.5)	Duloxetine/Escitalopram	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will	N = 291 patients with single or recurrent episodes of MDD (DSM-IV-TR)	Mean age: 48.7 years; 69 males, 222 females	All patients received 4 weeks of 10 mg/day escitalopram then randomized to Group 1: received 60-	4, 6, 8, 10, 12, 14, 16 weeks	Reduced HAM-D score was achieved in 61.6% of group 1 compared to 64.1% in group 2 (p=0.652). Group 1 showed earlier	"In MDD patients with moderate to severe painful physical symptoms not improving	Data suggest duloxetine switching may benefit patients with moderate to severe pain and MDD.

			received benefits for personal or professional use.			120 mg/day from week 4 to week 16 (n=138) vs Group 2: received 10-20 mg/day of escitalopram during weeks 4-8 then switched to 60-120 mg/day duloxetine from week 8 to 16 if did not achieve <50% HAM-D score reduction (n=153)		time to achieve SDS score <6 compared to group 2 (p=0.042).	after 4 weeks of treatment with escitalopram, an earlier switch to duloxetine may lead to better pain and functional outcomes."	
Dunner 2005 (score=4.5)	Duloxetine	RCT	No mention of sponsorship or COI.	N = 137 patients with mild depressive disorder (DSM-IV)	Mean age: 42 years; 55 males, 82 females	Group 1: received 30 mg duloxetine once daily (n=67) vs Group 2: received 60 mg duloxetine	2, 4, 6, 8, 12 weeks	Overall changes in HAMD17 scores were -13.8 for Group 1 compared to -13.3 in Group 2 (p=0.648).	"Results from this open-label study in patients with MDD suggest that starting duloxetine treatment at 30 mg QD	Open label trial. Data suggest initial dosing of 30 mg duloxetine for 1 week and then increasing dose to 60 mg thereafter "may" reduce the risk of treatment emergent nausea.

						once daily (n=70)			for 1 week, followed by escalation to 60 mg QD, might reduce the risk for treatment-emergent nausea in these patients while producing only a transitory impact on effectiveness compared with a starting dose of 60 mg QD."	
Dunlop 2017 (score=4.5)	CBT/Duloxetine/Escitalopram	RCT	Sponsored by NIH grants. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 344 patients with current major depressive disorder (DSM-IV)	Mean age: 40.0±11.7 years; 148 males, 196 females	CBT Group: received 16 individual sessions of cognitive behavioral therapy consisting of 50 min sessions (n=115) vs Escitalopra	2, 4, 6, 8, 10, 12 weeks	Mean HAM-D score reduction was 10.9 points, but did not differ across the groups (F=0.53, p=0.589). Remission rates were 41.9% for CBT group,	"Treatment guidelines that recommend either an evidence-based psychotherapy or antidepressant medication	Data suggest patient preference towards CBT or pharmacotherapy did not significantly impact treatment outcomes in patients not receiving prior treatment.

						m Group: received 10-20 mg/day escitalopram (n=114) vs Duloxetine Group: received 30-60 mg/day duloxetine (n=115)		46.7% in escitalopram group, and 54.7% in duloxetine group (p=0.170).	for nonpsychotic major depression can be extended to treatment-naïve patients. Treatment preferences among patients without prior treatment exposure do not significantly moderate symptomatic outcomes."	
Perahia 2008 (score=4.0)	Duloxetine/Telephone Intervention	RCT	Sponsored by Eli Lilly and Company and Boehringer Ingelheim. COI: One or more of the authors have received or will receive benefits for	N = 962 patients with major depressive disorder (DSM-IV)	Mean age: 46.2 years; 345 males, 617 females	Duloxetine-only group: received 60-120 mg/day of duloxetine (n=485) vs Duloxetine +TI group: received 60-120 mg/day of duloxetine	1, 4, 9, 12 weeks	Remission rate was 42.8% in duloxetine-only group compared to 43.5% in duloxetine-TI group (p=0.873). Response rate was 56.6% in duloxetine-only group	"A telephone intervention in combination with antidepressant medication (duloxetine) did not improve depression	Data suggest lack of efficacy. Data suggest addition of telephone intervention to duloxetine did not improve depressive outcomes compared to treatment with duloxetine alone.

			personal or professional use.			and the telephone intervention consisting of 3 calls over 12 weeks that provide information and modify beliefs about the illness and its treatment (n=477)		compared to 58.4% in duloxetine-TI group (p=0.581).	outcomes compared with antidepressant alone in this clinical trial, perhaps due to high drug adherence in both treatment groups. Addition of a telephone intervention was, however, associated with increased reporting of AEs."	
Fava 2006 (score=4.0)	Duloxetine	RCT	Sponsored by Eli Lilly and Company and Boehringer Ingelheim. No mention of COI.	N = 87 patients with major depressive disorder (DSM-IV)	Mean age: 44.2 years; 18 males, 69 females	QD Group: received duloxetine 60 mg once daily and placebo pill once daily (n=58) vs BID Group: received duloxetine	12 weeks	Response to treated was achieved by 62% in BID group compared to 74% in QD group. Change in HAM-D17 score was from 19.5 to 7.2 (p<.001) in QD	"Patients relapsing on duloxetine 60 mg QD benefited from an increase to 60 mg BID. These duloxetine doses were well	Data suggest a significant proportion of relapsing patients who have been on duloxetine may benefit with an increased dose.

						60 mg twice daily (n=29)		group compared to 19.6 to 9.7 in BID group (p<.001).	tolerated and effective, and appear appropriate for MDD patients requiring treatment of relapse."	
Venlafaxine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Bares 2009 (score=7.5)	TMS/Venlafaxine	RCT	Supported by a grant from Ministry of Education of Czech Republic MSMT 1M0517. No COI.	N = 60 inpatients with DSM-IV criteria depressive disorder who did not respond to at least one antidepressant treatment before	Mean age: 44.7 years; 12 males, 48 females	1Hz rTMS (Magstim Super Rapid stimulator), every weekday at 100% of MT with 600 pulses/session, sessions being 600 s. Coil placed 45° from midline of scalp. Given placebo capsule (n=29) vs Receiving venlafaxine ER (75mg)	Follow up at baseline and weekly up to week 4	Regarding MADRS score, there was no significant difference between the two groups (time x group interaction, F=1.01, df=4,224, p=0.38). Regarding the rating scale BDI-SF, there was no significant differences (F=0.73, df=4,224, p=0.56). Regarding	"The findings of this study suggest that, at least in the acute treatment, the right sided rTMS produces clinically relevant reduction of depressive symptomatology in patients with resistant depression comparable to venlafaxine	Both groups showed significant reduction of depressive symptoms. Data suggest right side rTMS reduces symptoms of depression equivalent efficacy to venlafaxine ER (comparable efficacy).

						on days 1-5 with dose increasing to 150mg/day. Sham treatment of rTMS, but with coil rotated 90° away from scalp. Voltage reduced to 70% (n=31)		rating scale CGI, there was also no significant difference (F=1.73, df=4,224, p=0.17). Response rates also were not statistically significant, as rTMS was 33% and venlafaxine was 39%	ER. Larger sample sizes are required to confirm these results."	
Wijkstra 2010 (score=6.5)	Quetiapine/ Venlafaxine/ Imipramine	RCT	Sponsored by grants from AstraZeneca and Wyeth Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 122 patients with psychotic major depression (DSM-IV-TR)	Mean age: 50.6 years; 60 males, 62 females	Imipramine: received 75-450 mg/day of imipramine (n=42) vs Venlafaxine: received 75-375 mg/day of venlafaxine (n=39) vs Quetiapine: received 75-375 mg/day of venlafaxine and 100-600 mg/day of quetiapine	1, 2, 3, 4, 5, 6, 7 weeks	Quetiapine group showed a better outcome of reduced HAM-D score compared to venlafaxine (OR=3.86, 95% cI 1.53-9.75). Imipramine did not show a greater improvement compared to venlafaxine group (OR=2.20, 95% CI 0.89-5.41) nor did quetiapine	"That unipolar psychotic depression should be treated with a combination of an antidepressant and an antipsychotic and not with an antidepressant alone, can be considered evidence based with	Data suggest the addition of an antipsychotic to an antidepressant is superior to antidepressant therapy alone (venlafaxine-quetiapine).

						(n=41) All patients were treated for 7 weeks.		compared to imipramine (OR=1.75, 95% CI 0.72-4.25).	regard to venlafaxine–quetiapine vs. venlafaxine monotherapy. Whether this is also the case for imipramine monotherapy is likely, but cannot be concluded from the data.“	
McIntyre 2007 (score=5.5)	Quetiapine/ Venlafaxine	RCT	No mention of sponsorship or COI.	N = 58 patients with a diagnosis of major depression (DSM-IV)	Mean age: 44.5 years; 22 males, 36 females	Quetiapine: received 50-200 mg/day (n=29) vs Venlafaxine: no specific dose of venlafaxine (n=29)	1, 2, 4, 6, 8 weeks	Response rates for HAM-D (≥50% reduction) were 48% in quetiapine and 28% in placebo (p=0.008). HAM-A response rate (≥50% reduction) was 62% in quetiapine and 28% in placebo (p=0.002).	“In summary, quetiapine as an adjunct to an SSRI/SNRI was effective in reducing symptoms of major depressive disorder and comorbid anxiety in patients who had residual depressive	Data suggest quetiapine added to SSRI/venlafaxine patients with major depression was significantly better than placebo in improving depressive symptoms.

									symptoms despite having received treatment with an SSRI/SNRI. "	
Martiny 2012 (score=5.5)	Venlafaxine	RCT	Sponsored by Dr. Klaus Martiny and Neuropsykiatrisk Laboratorium for drug analyses. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 31 patients with major depression (DSM-IV)	Mean age: 46.8 years; 17 males, 14 females	Active Group: received active pindolol 20 mg and venlafaxine (75 mg capsule daily for 5 days then 150 mg daily for rest of study) (n=15) vs Placebo Group: received placebo 20 mg and venlafaxine (75 mg capsule daily for 5 days then 150 mg daily for rest	12, 19 days	Response rate in HAM-D17 scale was 52.4% for active group compared to 39.7% in the placebo group. Remission rate was 14.1% in active group compared to 27.8% in placebo group.	"The differential effect of pindolol, on depression outcome, in patients with varying degrees of venlafaxine metabolism into ODV, corresponds to patients being poor or extensive metabolizers of venlafaxine. From this finding, we conclude that only patients who are poor metabolizers of	Small sample size. Data suggest lack of efficacy of pindolol enhancing efficacy of venlafaxine for treatment of major depression.

						of study) (n=16)			venlafaxine might benefit from pindolol augmentation."	
De Jonghe 2004 (score=5.0)	Insight-Oriented Psychotherapy/Venlafaxine	RCT	Sponsored by grant from Wyeth Nederland. No mention of COI.	N = 208 patients with mild or moderate major depressive disorder (DSM-IV)	Mean age: 35.5±10.7 years; 33 males, 67 females	Psychotherapy: received short psychodynamic supportive psychotherapy (SPSP) consisting of 16 sessions within 6 months (n=106) vs Combined Therapy: received psychotherapy and pharmacotherapy consisting of 6 months of venlafaxine unless intolerable then changed to nortriptyline, if	6 months	Psychotherapy group showed a decrease in HRSD score from 18.14 to 11.35 compared to combined therapy group from 17.99 to 9.53 (F=3.04, p=0.083). Success rate was achieved in 32%-69% of psychotherapy group compared to 42%-79% in the combined group. Between group differences were observed for HRSD scores (p<0.046).	"In summary, we investigated the possible advantages of combining antidepressants with psychotherapy in ambulatory patients with mild to moderate major depressive disorder. We found that psychotherapy is more acceptable than combined therapy."	Data suggest comparable efficacy.

						intolerable switched to lithium (SPSP and antidepressant medication) n=85)				
Ozdemir 2015 (score=4.0)	Light Therapy	RCT	Sponsored by Yuzuncu Yil University Scientific Research Projects Office. No COI.	N = 50 patients diagnosed with Major Depressive Disorder for the first time diagnosed using the DSM-IV	Mean age: 35.5 years; 23 males, 27 females	Group 1: Venlafaxine starting at 75mg/day and increased to 150mg/day for 8 weeks (n=25) vs Group 2: Treated with Venlafaxine (same dosages as Group 1) and Bright Light Therapy (7000 lux) for 1 hour in the morning, daily for 8 weeks. (n=25)	Outcomes measured at week 1, 2, 4, and 8 of treatment duration. No mention of follow-up past duration of 8-week treatment	The mean HDRS depression score in decreased in both groups, the decrease in mean scores for Group 1 was 29.28 to 7.40, and the decrease in mean scores for Group 2 was 29.88 to 5.72 after 8 weeks of treatment ($p<0.01$).	"Both venlafaxine and venlafaxine + bright light therapy treatment strategies significantly reversed the depressive mood of patients with severe MDD; however, the latter induced significantly stronger and more rapid beneficial effects."	Data suggest either monotherapy of venlafaxine or combination therapy (venlafaxine and bright light therapy) significantly improved MDD symptoms but combo therapy resulted in stronger and more rapid results.
Corya 2006 (score=4.0)	Olanzapine/Fluoxeti	RCT	Sponsored by Lilly Research	N = 483 subjects with	Mean age: 45.7±10	All groups received medications	1, 2, 3, 4, 5, 6, 7, 8, 9,	For analysis, group 1-5 were combined.	"In conclusion, the OFC	No baseline data stratified by group. Data suggest similar

	ne/Venlafaxine		Laboratories. No mention of COI.	major depressive disorder (DSM-IV)	.8 years; 133 males, 350 females	for 12 weeks. Group 1: received 1 mg/day of olanzapine and 5 mg/day of fluoxetine (n=59) vs Group 2: received 6 mg/day of olanzapine and 25 mg/day fluoxetine (n=63) vs Group 3: received 6 mg/day of olanzapine and 50 mg/day of fluoxetine (n=63) vs Group 4: received 12 mg/day olanzapine and 25 mg/day of fluoxetine (n=60) vs Group 5:	10, 11, 12 weeks	Group 1-5 showed a greater improvement in MADRS mean score (-7.2) compared to group 6 (-4.8, p=0.03), group 7 (-4.7, p=0.03), and group 8 (-3.7, p=0.002). Groups 1-5 showed greater advantage to group 6 overall (-14.1 vs -7.7, p<0.001).	showed a rapid and robust antidepressant effect in this sample of TRD patients, along with a safety profile comparable to its component monotherapies."	efficacy between olanzapine, fluoxetine, venlafaxine, and combination olanzapine/fluoxetine for the treatment of treatment resistant depression.

						received 12 mg/day olanzapine and 50 mg/day fluoxetine (n=57) vs Group 6: received 6 or 12 mg/day olanzapine (n=62) vs Group 7: received 25 mg/day or 50 mg/day of fluoxetine (n=60) vs Group 8: received 75-375 mg/day of venlafaxine (n=59)				
Tricyclic Antidepressants										
Amitriptyline										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Ravizza 1999 (score=6.5)	Antipsychotic/Amisulpride/ Amitriptyline	RCT	No mention of COI or sponsorship.	N = 253 participants with a dysthymia or	Mean age: 47.05 years; 90	Amisulpride 50 mg/day (n=166) vs. Amitriptyline 25-75	Follow-up at days 14 and 28 and	Montgomery and Asberg Rating Scale mean total score at	"Results of the present study in a large patient population	Data suggest comparable drug efficacy in the treatment of dysthymia.

				single episode of major depression in partial remission (DSM-III-R criteria)	males, 163 females	mg/day (n=87). Medications were given for six months	months 2, 4, and 6	baseline and 6-months: amisulpride = 21.0, 10.2, amitriptyline = 21.7, 10.1 (p = 0.495)	further confirm the safe use of amisulpride in dysthymia and support its administration upon a medium-term treatment period."	
Klieser 1989 (score=5.5)	Trazodone/Amitriptyline/Haloperidol	RCT	No mention of COI or sponsorship.	N = 45 patients with major depressive disorder and 75 with acute schizophrenia, no diagnostic criteria listed	Mean age: 42.6 years; 49 males, 71 females	400 mg trazodone daily (n=30) vs. 20 mg haloperidol daily (n=30) vs. 150 mg amitriptyline daily (n=30) vs. Placebo daily (n=30). All treatments given for three weeks	No follow-up	Hamilton Depression Rating Scale (HAM-D) scores decreased in all drug treatments. Mean change in HAM-D scores at 3 weeks: trazodone = -3.1, amitriptyline = -12.1, haloperidol = -4.0, placebo = -4.1	"After only 7 days of trazodone treatment, a relatively reliable decision can be established as to whether a therapeutically success can be expected if treatment is continued."	Mixed population of depression and schizophrenic patients. Data suggest trazodone appears to not have antipsychotic action on schizophrenia but depression patients did respond to trazodone.
Mynors-Wallis 1995 (score=4.5)	Problem Solving Therapy/	RCT	Sponsored by the Wellcome Trust. No	N = 91 patients with major	Mean age: 37.1±11.4 years;	PST Group: received problem solving	6, 12 weeks	Hamilton rating scale improved for all groups (p=0.037). PST	"As a treatment for major depression	At 12 weeks, there was a significant improvement for

	Amitriptyline		mention of COI.	depression (Hamilton rating scale for depression)	21 males, 70 females	treatment for 6 sessions over 3 months (n=29) vs Amitriptyline Group: received 50 mg amitriptyline for 2 nights, then increased 25 mg per night until 150 mg total taken for 6 sessions over 3 months (n=27) vs Placebo Group: received placebo in same dosing as amitriptyline group (n=26)		group was superior to placebo in Ham-D score mean difference=4.69 (95% CI 0.41-8.96) but not superior to amitriptyline (M=0.94, 95% CI -3.28-5.15). Amitriptyline was superior to placebo in HAM-D score (M=3.75, 95% CI -0.59-8.09).	in primary care, problem solving treatment is effective, feasible, and acceptable to patients."	depressive scores in the PST group.
Singh 1988 (score=4.5)	Amitriptyline Hydrochl	RCT	No mention of sponsorship or COI.	N = 130 outpatients with a clinical	Mean age: 38.9 years;	Alprazolam Group: received 0.5 mg	1, 2, 3, 6 weeks	Mean HAM-D score decreased 77% in the alprazolam	"In this study, both alprazolam and	Data suggest comparable efficacy in non-clinically

	oride/Alprazolam			diagnosis of moderate depression (ICD-9)	73 males, 57 females	alprazolam (n=67) vs Amitriptyline Group: received 25 mg amitriptyline hydrochloride (n=63) All patients received a daily maximum of nine capsules (4.5 mg alprazolam, 225 mg amitriptyline hydrochloride)		group compared to 72% in the amitriptyline group (p>0.01).	amitriptyline hydrochloride produced significant improvement in the symptoms of nonpsychotic depression."	depressed outpatients.
Bauer 1999 (score=4.5)	Paroxetine/ Amitriptyline/ Lithium	RCT	Sponsored by SmithKline Beecham Pharma GmbH. No mention of COI.	N = 42 participants on a stable lithium regimen with major depressive episode meeting	Mean age: 48.59 years; 18 males, 24 females	Paroxetine 20 mg daily, then increased to 40 mg daily after 2 weeks (n=19) vs. Amitriptyline 50 mg daily, then increased to	Follow-up at weeks 1, 2, 3, 4, 5, and 6	At 4 weeks patients taking paroxetine had higher proportion of 50% reduction in Hamilton Depression Rating Scale scores compared to amitriptyline	"The main finding of this study is that, in a population of patients on long-term lithium prophylaxis, the addition of paroxetine	Small sample size. Data suggest after 4 weeks there were more patients achieving a 50% reduction in HAM-D scores than in the amitriptyline group.

				DSM-III-R criteria		150 mg daily after 2 weeks (n=23). Medications given for six weeks		group (79% vs. 39%, p = 0.04). At 6 weeks the difference was not significant.	or amitriptyline to treat an episode of major depression seems to be effective and safe."	
Spiker 1985 (score=4.5)	Perphenazine, Amitriptyline	RCT	Sponsored by NIMH grants. No mention of COI.	N = 58 patients with major depressive disorder, primary type, and psychotic subtype, according to the Research Diagnostic Criteria (RDC)	Mean age: 44.1 years; 22 males, 36 females	Amitriptyline at 50 mg 4 times per day (n=19) vs. Perphenazine 16 mg 4 times per day (n=17) vs. amitriptyline at 50 mg + perphenazine at 16 mg 4 times per day (n=22)	Follow-up at days 7, 14, 21, 28 and 35	Mean HAMD score decreased from 26.0 to 13.1 in perphenazine group, from 30.6 to 11.6 in amitriptyline group, and from 28.7 to 5.6 in amitriptyline plus perphenazine group (p=0.01).	"[T]his study demonstrated that although there are clearly some patients who respond to amitriptyline alone, and to perphenazine alone, amitriptyline plus perphenazine is the treatment of choice."	Data suggest combination amitriptyline and perphenazine resulted in a better response than either amitriptyline or perphenazine alone.
Young 1976 (score=4.0)	Flupentixol, Amitriptyline	RCT	No mention of COI or sponsorship.	N = 60 participants with mild to moderately severe depressio	Age and sex data only available for 51 participants.	Amitriptyline 75-225 mg/day (n=30) vs. Flupentixol 1.5-4.5 mg/day	Follow-up at weeks 1, 3, and 6	Mean scores of Hamilton Depression Rating Scale, Beck Depression Rating Scale,	"Flupentixol, in low dosage, is a useful alternative antidepressant for	Small sample. Data suggest similar efficacy with a slight trend favoring flupenthixol.

				n (no diagnostic criteria mentioned)	Mean age: 37.35 years; 21 males, 30 females	(n=30). All treatments given for six weeks		and overall severity did not statistically differ between treatment groups (p > 0.05)	depressed outpatients."	
Standish-Barry 1983 (score=4.0)	Amitriptyline/Sulpiride	RCT	Sponsored by Chemitechna Ltd. No mention of COI.	N = 36 patients with major depressive disorder (DSM-III)	Mean age: 44 years; 22 males, 20 females	Sulpiride Group: received 200-400 mg daily sulpiride (n=18) vs Amitriptyline Group: received 50-150 mg daily of amitriptyline (n=18) All patients received medication for 24 weeks.	4, 6, 12, 24 weeks	Amitriptyline group showed a greater reduction on Hamilton and Wakefield scores compared to sulpiride group (p<0.05).	"Our results show that supiride appears to have antidepressant and anxiolytic properties comparable to amitriptyline up to 12 weeks of treatment."	Data suggest at 24 weeks, amitriptyline was better than sulpiride.
Rapp 1978 (score=4.0)	Amitriptyline	RCT	No mention of sponsorship or COI.	N = 43 patients with depressive syndromes (no specific	Mean age: 51.1 years; 12 males, 31 females	Group A: received 25 mg amitriptyline (n=21) vs Group D: received 25 mg	1, 3, 6 months	Depressive symptoms were improved from 0.7 to 1.7 in Group A compared to 0.9 to 1.5 in	"Amitriptyline-N-oxide appears to show a tendency to a some-what more rapid onset of	Data suggest comparable efficacy with a slightly earlier onset of action with fewer adverse effects in amitriptyline-N-oxide group.

				diagnostic criteria)		amitriptyline-N-oxide (n=22) All patients received 1 tablet daily until day 2 then increased by 1 tablet for 1 week, then increased to 3 tablets daily for 6 months		Group D (p>0.05)	effect and less side effects."	
Clomipramine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Chistyakov 2005 (score=6.0)	Clomipramine/rTMS	RCT	No COI. Sponsored by the Stanley Research Institute.	N = 59 participants meeting DSM-IV criteria for major depression	Mean age: 60.46 years; 15 males, 44 females	3 Hz left prefrontal repetitive transcranial magnetic stimulation (rTMS) with placebo medication (n=12) vs. 3 Hz right prefrontal rTMS with placebo medication (n=12) vs.	Follow-up at 1 and 2 weeks	Percentage of participants that had at least 50% reduction in the Hamilton Depression Rating Scale after treatment: 3 Hz left active rTMS = 54.5% ($p < 0.05$), 3 Hz right active rTMS = 16.7%, 10 Hz left active rTMS = 16.7%, 10 Hz	"Our results suggest that 3 Hz left rTMS has a higher therapeutic efficacy and tolerability in patients with MD. "	Small group sizes. Data suggest administration of 3 Hz left rTMS was associated with better therapeutic efficacy than either 3 Hz right rTMS or 2 weeks of clomipramine.

						10 Hz left prefrontal rTMS with placebo medication (n=10) vs. 10 Hz prefrontal rTMS with placebo medication (n=9) vs. sham rTMS with clomipramine 150 mg/day (n=16). rTMS given in 10 daily sessions over a 2 week period		right active rTMS = 33.3%, clomipramine and sham rTMS = 13.3% (all other groups had non-significant percentages)		
Burnand 2002 (score=4.5)	Insight-Oriented Psychotherapy/Clomipramine	RCT	Sponsored by grant from the Swiss National Fund for Scientific Research. No mention of COI.	N = 74 patients with a diagnosis of major depressive episode (DSM-IV)	Mean age: 36.4 years; 29 males, 45 females	Combination Group: received psychodynamic psychotherapy(n=35) vs Clomipramine Group: received 25 mg of clomipramin	2, 4, 6, 8, 10 weeks	Mean HDRS scores showed a negative effect of time (8.9±7 in the combination group compared to 9.7±7.3 in the clomipramine group (F=286.4,	"Provision of supplemental psychodynamic psychotherapy to patients with major depression who are	Data suggest adding psychodynamic psychotherapy to antidepressant medication in the treatment of depression is associated with lower hospitalizations, lost workdays, improved global functioning,

						e on the first day and increased gradually to 125 mg on fifth day (received 2 electrocardiograms prior to treatment) and were switched to 20-40mg of citalopram per day if patients refused or had severe adverse effects for 10 weeks (n=39)		p<.001). Nine percent of combination group showed treatment failure compared to 28% of clomipramine group (p=0.04).	receiving antidepressant medication is cost-effective."	and may be cost effective.
Desipramine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Fava 2002 (score=5.5)	Fluoxetine /Desipramine/Lithium	RCT	No mention of COI. Sponsored by the National Institute of Mental Health.	N = 101 participants who met DSM-III-R criteria for major depressiv	Mean age: 41.6 years; 52 males, 49 females	High dose Fluoxetine 40-60 mg/day (n=33) vs. Fluoxetine 20 mg/day and Desipramine	Follow-up at 1, 2, 3 and 4 weeks	Mean change in Hamilton Depression Rating Scale scores from baseline to posttreatment: high-dose fluoxetine =	"We found not significant differences in efficacy among these three treatment strategies	Data suggest similar efficacy in all 3 groups with a trend towards higher response rates in the high fluoxetine group for both non-responders and partial responders.

				e disorder		25-50 mg/day (n=34) vs. Fluoxetine 20 mg/day and lithium 300-600 mg/day (n=34). All treatments administered daily for four weeks		5.1, fluoxetine and desipramine = 3.5, fluoxetine and lithium = 3.6 (F = 0.9, p = 0.4)	among patients who had failed to respond adequately to 8 weeks of treatment of fluoxetine 20 mg/day, although the high-fluoxetine group was associated with nonsignificantly higher response rates in both partial responders and nonresponders."	Limited information on baseline group details.
Bloch 1997 (score=5.5)	Desipramine/Lithium	RCT	No mention of COI. Sponsored by the Professor Milton Rosenbaum Endowment Fund for Research in the	N = 31 participants meeting DSM-III-R criteria for major depressive disorder	Mean age: 47.45 years; 14 males, 17 females	Desipramine alone: 25 mg twice daily for 1 week, then increased to 150 mg/day, placebo given daily as well (n=15) vs.	Follow-up at weeks 1, 2, 3, 4, and 5	Significant treatment effect on Hamilton Depression Rating Scale scores (F5, 155 = 40.45, p < 0.001)	"Concurrent treatment with Lithium did not demonstrate an enhancement of either DMI's efficacy or	Small sample (n=31). Data suggest lack of efficacy of combining lithium with desipramine (i.e., no quicker onset of action nor better efficacy than desipramine, alone and the combination group experience

			Psychiatric Sciences.			Desipramine and lithium: same desipramine dosage as above, lithium 300 mg twice daily for 1 week, then increased to 900 mg/day (n=16). All treatments administered for 5 weeks			its onset of action in these patients, suggesting that this strategy may not confer any additional benefit compared with DMI alone in mild or moderately depression patients who are not preselected for nonresponse to an AD during their current depressive episode."	more adverse effects).
Kennedy 1991 (score=5.0)	Adinazolam/ Desipramine	RCT	Sponsored by Upjohn Canada. No mention of COI.	N = 31 participants meeting DSM-III-R criteria for major depressiv	Mean age: 42.52 years; 6 males, 25 females	Adinazolam 10 mg daily for three days, then increased to 120 mg daily (n=16) vs.	Follow-up at weeks 1, 2, 3, 4, 5, and 6	No significant between group differences or group x time interactions for Hamilton Depression Rating Scale	"In this study patients treated with adinazolam had a comparable response to	Small sample size (n=31). Data suggest comparable response to both adinazolam and desipramine in treatment of major depression.

				e disorder		Desipramine 25 mg daily for three days, then increased to 300 mg daily (n=15). Medications administered for six weeks		scores between the two treatments (p > 0.05)	desipramine in both measures of depression and anxiety."	
Remick 1985 (score=4.5)	Alprazolam/ Desipramine	RCT	No mention of COI or sponsorship.	N = 54 participants with major depressive disorder as defined by Research Diagnostic Criteria (RDC)	Mean age: 37.85 years; 19 males, 33 females (gender data only available for 52 participants)	Alprazolam 0.5 mg capsules, 3-9 capsules given daily to outpatients, 3-12 capsules given daily to inpatients (n=29), Desipramine 25 mg capsules, same capsule count given as the group above (n=25). Medications for both	Follow-up at weeks 1, 2, 4 and 6	Main effect for medication on Hamilton Depression Rating Scale scores (F=4.16, p=0.044), with alprazolam being higher.	"Alprazolam appeared as effective as desipramine in the pharmacotherapy of this group of depressed outpatient and inpatients. Alprazolam appeared well-tolerated by most subjects although drowsiness was a common – and at times	Data suggest a trend towards desipramine being better than alprazolam in moderately severely depression patients but not significant. Both drugs had only modest efficacy with alprazolam being associated with excessive drowsiness.

						groups administered for six weeks			serious – medication side effect."	
Thompson 2001 (score=4.0)	Cognitive Behavioral Therapy/ Desipramine	RCT	Sponsored by a grant from the National Institute of Mental Health. No mention of COI.	N = 102 subjects with MDD according to the Research Diagnostic Criteria.	Mean age: 66.8 years; 33 males, 67 women.	Desipramine 10mg and increased slowly (n=33) vs. CBT-Alone - group: each session was 50-60 minutes with a cognitive behavioral therapist (n=31) vs. Combined group – received same dosage of desipramine and amount of CBT as other groups (n=36). All participants seen for 16-20 sessions over 3-4 month period.	Follow up at 10 days	Reduction in depressive symptoms in the low severity group according to the BDI-SF was significantly greater in separate comparisons of Desipramine-Alone with CBT-Alone ($t[844]=2.45$; $p<0.05$) and with the Combined treatment ($t[844]=2.13$; $p<0.05$)	"The results indicate that psychotherapy can be an effective treatment for older adult outpatients with moderate levels of depression."	Data suggest all 3 treatment groups improved but combined treatment was best for severely depressed patients.

						Sessions twice a week for 1 week, then once per week for next 8-12 weeks				
Dothiepin										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Boening 1983 (score=4.5)	Dothiepin	RCT	No mention of COI or sponsorship.	N = 30 participants meeting ICD-9 criteria for endogenous type of depression	Mean age: 53 years; 6 males, 24 females	Dothiepin three times per day (n=15) vs. Dothiepin single nighttime dose per day (n=15). Dosages range from 75 – 225 mg per day.	Follow-up at 1 and 3 weeks	No significant difference between groups regarding mean post-treatment scores of psychomotor, psychic and Zung Depression Inventory scores (p>0.0056, based on Bonferoni correction)	"This trial demonstrates that the therapeutic effect of both dosage regimes of dothiepin should be regarded as equivalent."	Data suggest therapeutic equivalence between the two different dothiepin regimens.
Imipramine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Vorbach 1994 (score=6.5)	St. John's Wort/Imipramine	RCT	No mention of sponsorship or COI.	N = 135 depressed patients (DSM-	Mean age: 53.4 years; 71	LI 160 Group: received hypericum extract	1, 2, 4, 6 weeks	Hamilton depression scale decreased from 20.2 to 8.8 in LI 160 group	"The analysis of CGI revealed comparable	Data suggest comparable efficacy to imipramine.

				III-R criteria)	males, 64 females	(3x300 mg) (n=67) vs Imipramine Group: received imipramine (3x25 mg) (n=68)		compared to imipramine group from 19.4 to 10.7 ($p<0.001$).	results in both treatment groups. Clinically relevant changes of the safety parameters were not found. In the LI 160 group fewer and milder side effects were found as compared to imipramine .”	
Woelk 2000 (score=6.5)	St. John’s Wort/Imipramine	RCT	Sponsored by Bayer AG. No COI.	N = 324 patients with mild to moderate depression (ICD-10 criteria)	Mean age: 45.9 years; 93 males, 231 females	Hypericum Group: received 0.2% hypericin extracted in ethanol 50% (250 mg film coated tablet 2 times daily) (n=157) vs Imipramine	6 weeks	Hamilton depression scale decreased from 12 to 11.53 for hypericum group compared to 12.75 to 11.21 in the imipramine group and neither were statistically significant.	“This Hypericum perforatum extract is therapeutically equivalent to imipramine in treating mild to moderate depression,	Data suggest comparable efficacy but patients appeared to tolerate hypericum perforatum better.

						Group: received 75 mg tablet of imipramine 2 times daily (dose increased form 25 mg twice daily for 3 days to 50 mg twice daily for 4 days) (n=167)		Patients tolerated hypericum better than imipramine ($p<0.01$).	but patients tolerate hypericum better."	
Wijkstra 2010 (score=6.5)	Quetiapine/ Venlafaxine/ Imipramine	RCT	Sponsored by grants from AstraZeneca and Wyeth Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 122 patients with psychotic major depression (DSM-IV-TR)	Mean age: 50.6 years; 60 males, 62 females	Imipramine: received 75-450 mg/day of imipramine (n=42) vs Venlafaxine: received 75-375 mg/day of venlafaxine (n=39) vs Quetiapine: received 75-375 mg/day of venlafaxine and 100-600 mg/day of quetiapine (n=41) All	1, 2, 3, 4, 5, 6, 7 weeks	Quetiapine group showed a better outcome of reduced HAM-D score compared to venlafaxine (OR=3.86, 95% cI 1.53-9.75). Imipramine did not show a greater improvement compared to venlafaxine group (OR=2.20, 95% CI 0.89-5.41) nor did quetiapine compared to	"That unipolar psychotic depression should be treated with a combination of an antidepressant and an antipsychotic and not with an antidepressant alone, can be considered evidence based with regard to	Data suggest the addition of an antipsychotic to an antidepressant is superior to antidepressant therapy alone (venlafaxine-quetiapine).

						patients were treated for 7 weeks.		imipramine (OR=1.75, 95% CI 0.72-4.25).	venlafaxine –quetiapine vs. venlafaxine monotherapy. Whether this is also the case for imipramine monotherapy is likely, but cannot be concluded from the data. "	
Boyer 1996 (Study 1: score=6.0, Study 2: score=5.5)	Amisulpride/ Amineptine/ Imipramine	2 RCTs	No mention of sponsorship or COI.	Study 1: N = 323 patients with primary dysthymia with or without major depressive episode (DSM-III-R) Study 2: N = 219 patients with	Study 1: Mean age: 48.2 years; 81 males, 242 females Study 2: Mean age: 42.9 years; 99 males,	Study 1: Amisulpride: received 50 mg/day amisulpride for 3 months (n=104) vs Amineptine: received 200 mg/day amineptine for 3 months (n=111) vs Placebo: (n=108) Study 2: Amisulpride	Study 1: 8 days, 1, 2, 3 months Study 2: 6 months	Study 1: Reduction in MADRS score was -8.63 in amisulpride and -8.21 in amineptine compared to -3.81 in placebo (p=0.0001). Study 2: MADRS score was reduced by -12.3 in amisulpride, -10.6 in imipramine, and	"Results of the intention to treat analysis and of the end-point analysis were compelling and very similar: significant differences were demonstrated for all	Data suggest in both studies amisulpride, imipramine, and amineptine were better than placebo vis MADRS, CGI, and SANS scores. However, in study 2, the 6 month study amisulpride more efficacious than imipramine.

				dysthymia or major depression (DSM-III-R)	120 females	: received 50 mg/day amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine (n=73) vs Placebo: (n=73)		-7.2 in placebo (placebo vs imipramine p=0.036, placebo vs amisulpride p<0.002, global p=0.007).	primary criteria between amisulpride and placebo and between imipramine and placebo but not between amisulpride and imipramine. For both primary criteria and the responder rate (CGI). Statistically significant differences were evidenced between amisulpride and placebo and amineptine and placebo."	

Weitz 2014 (score=5.5)	Cognitive Behavioral Therapy/Interpersonal Psychotherapy	RCT	No sponsorship or COI.	N = 239 participants with current major depressive episode (RDC criteria)	Mean age: 35 years; 72 males, 167 females	CBT Group: received cognitive behavioral therapy (no specific duration or protocol mentioned) (n=33) vs IPT Group: receiving interpersonal psychotherapy treatments consisting of 50- min sessions (n=38) vs Imipramine +CM Group: received clinical management consisting of medication management and 150-300 mg of imipramine (n=37) vs Placebo+C	6, 12, 18 months	Changes in HRSD scores showed an effect size of 0.43 for CBT Group, 0.56 for IPT Group, 0.55 for Imipramine Group, and 0.34 for the placebo group. IPT group and imipramine group showed the greatest reduction in suicide symptoms compared to placebo (imipramine vs placebo: b=0.47, p<0.05; IPT vs placebo: b=0.41, p<0.05).	"This study demonstrates the specific effectiveness of IPT and medications in reducing suicidal ideation (relative to placebo), albeit largely as a consequence of their more general effects on depression."	Data suggest medications to treat depression such as imipramine and IPT may reduce suicidal ideation.

						M Group: received clinical management consisting of medication management and placebo medication (50-60min sessions) (n=40)				
Lecrubier 1997 (score=5.5)	Amisulpride/Imipramine	RCT	No mention of sponsorship or COI.	N = 219 patients with primary dysthymia, dysthymia with major depression, or isolated chronic major depression (DSM-III-R)	Mean age: 42.9 years; 99 males, 120 females	Amisulpride: received 50 mg/day of amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine for 6 months (n=73) vs Placebo: (n=73)	1, 3, 6 months	Response rate was 33.3% in the placebo group, 68.6% in the imipramine group, and 72.2% in the amisulpride group. A MADRS score reduction ≤7 was achieved in 21.9% of placebo, 32.9% in imipramine group, and 35.6% in amisulpride (placebo vs imipramine p=0.032, placebo vs amisulpride	"These results confirm the interest of a drug acting on dopaminergic transmission such as amisulpride in the treatment of depressed patients."	Data suggest comparable efficacy between amisulpride and imipramine with both drugs performing significantly better than placebo.

								p=0.004, imipramine vs amilsulpride p=0.01).		
Siwek 2009 (score=5.5)	Imipramine/ Zinc Supplement	RCT	No COI. Sponsored by the Funds for Statutory Activity of Collegium Medicum, Jagiellonian University Krakow and the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.	N = 60 patients with unipolar depression meeting DSM-IV criteria for major depression without psychotic symptoms	Mean age: 45.9 years; 20 males, 40 females	Imipramine (~140mg/day) plus daily placebo (n=30) vs. Imipramine (~140mg/day) plus daily zinc supplementation (25mg/day) (n=30). Both groups received treatment for 12 weeks	Follow-up at 2, 6 and 12 weeks	ANOVA analysis showed imipramine and zinc treatment had lower Hamilton Depression Rating Scale scores compared to placebo [F(1,48) = 6.4 (p<0.025)]	"These data suggest the participation of disturbed zinc/glutamatergic transmission in the pathophysiology of drug resistance."	Data suggest zinc supplementation speeds up the imipramine therapeutic response especially in non-responders to previous antidepressants.
Pickering 1965 (score=5.0)	Imipramine/ Phenelzine/ ECT	RCT	No mention of sponsorship or COI.	N = 269 patients with primary diagnosis of depression, diagnostic criteria not listed	Mean age: 55.3 years; 81 males, 169 females	ECT Group: received 4-8 treatments of electroconvulsive therapy for 3.5 weeks (n=65) vs Imipramine Group: received 50	5, 8, 12, 24 weeks, 6 months	Imipramine was superior to both phenelzine and placebo. ECT group and imipramine were similar with 83% of patients and 85% of patients discharged from the hospital.	"[I]t appears that that ECT and imipramine increased the frequency of recovery over and above the spontaneou	Data suggest imipramine and ECT were better than phenelzine and placebo for improving depressive symptoms.

						mg of imipramine for 3.5 weeks (n=63) vs Phenelzine Group: received 15 mg of phenelzine for 3.5 weeks (n=61) vs Placebo: received placebo pill (n=61)		Phenelzine showed 70% of patients discharged compared to 86% of placebo group.	s rate shown by patients on the placebo."	
Philipp 1999 (score=4.5)	St. John's Wort/Imipramine	RCT	Sponsored by Steiner Arzneimittel, Berlin, Germany. COI: KOH is an employee of Steiner Arzneimittel. RK is a head of a contract research organization involved with hypericum	N = 263 patients with moderate depression (ICD-10)	Mean age: 47±12 years; 66 males, 197 females	Hypericum Extract: received 350 mg per capsule (total daily dose of 1050 mg) of hypericum extract (n=106) vs Imipramine: received 50 mg imipramine on the 1st day, 75 mg on days 2-4,	1, 2, 4, 6, 8 weeks	Hamilton depression score improved in 74% of hypericum group, 71% in the imipramine group, and 50% in the placebo group.	"In summary, this trial adds to the growing evidence on the effectiveness of hypericum in mildly and moderately depressed patients."	Data suggest comparable efficacy between hypericum extract and imipramine in the treatment of mild to moderate depression.

			extract for different pharmaceutical companies.			and 100 mg (50mg, 25mg, 25 mg, thereafter) (n=110) vs Placebo: (n=47)				
Thase 2002 (score=4.5)	Imipramine/ Sertraline	RCT	Sponsored by Pfizer Inc. Multiple authors have served as paid consultants for Pfizer Inc.	N = 168 nonresponders to 12 weeks of medication treatment, all met DSM-III-R criteria for chronic major depressive disorder	Mean age: 40.5; 56 males, 112 females	Imipramine nonresponders received sertraline (mean dosage = 163 mg/day) (n=51) vs. Sertraline nonresponders received imipramine (mean dosage = 221 mg/day) (n=117). Medications given for 12 weeks	Follow-up weekly for 6 weekly, then biweekly for another 6 weeks	Hamilton Depression Rating Scale scores (HAMD) mean end point improvement: Imipramine = 9.3, Sertraline = 12.1 (p = 0.57)	"More than 50% of chronically depressed antidepressant nonresponders benefits from a switch from imipramine to sertraline, or vice versa, despite a high degree of chronicity."	Data suggest a benefit in switching to an antidepressant of a different class after first-line therapy has failed.
Paykel 1968 (score=4.0)	Imipramine/Chlorpromazine	RCT	Sponsored by Geigy (UK) Ltd. No mention of COI.	N = 114 patients with a depressive illness suitable	Mean age and gender distribution only describe	Imipramine – four 25mg capsules taken daily for 2 days, then four	No follow-up	No statistical difference between groups for Psychiatrists' Interview Scale scores, Nurses'	"None of the measures employed has revealed	Data suggest comparable efficacy between drugs.

				for drug treatment, no diagnostic criteria listed	d for those included in analysis (n=99). Mean age: 41.5 years; 24 males, 75 females	50mg capsules taken daily for 19 days (n=57) vs. Chlorpromazine – same dosage and timing as imipramine group (n=57)		Rating Scale scores, and Patients' Self-Rating Questionnaire scores (all p>0.05).	significant differences in symptom change between imipramine and chlorpromazine treatment in the overall groups of depressed patients in this study."	
Gangadhar 1982 (score=4.0)	Imipramine/ECT	RCT	No mention of COI or sponsorship.	N = 32 patients with depression (ICD-9) and had primary affective disorder and endogenous depression	Mean age: 44.13 years; 14 males, 18 females	Modified bilateral ECT – six ECTs on alternate days for two weeks, then one ECT weekly for two weeks, followed by 'maintenance' ECTs once on the 6th, 8th, and 12th week, received placebo pills	Follow-up at 3 and 6 months	ECT group had significantly lower Hamilton Scale for Depression (HRDS) score at end of week 2 (p<0.05). However there were not statistical differences between treatment groups at any other time period afterwards (all p>0.05)	"…it can be confidently claimed that from an overall point of view ECT is a superior form of treatment for endogenous depression than	Data suggest ECT worked faster and was not associated with organic brain dysfunction at the end of both three and six months.

						(n=16) vs. Imipramine – 25mg capsules, three daily during first week, six daily during 2nd-11th week. Received same ECT as above group (n=16)			imipramine.”	
Gelenberg 1990 (score=4.0)	Imipramine/ Tyrosine	RCT	Sponsored by USPHS grants. No mention of COI.	N = 65 with major depressive disorder via Research Diagnostic Criteria, also had modified Hamilton Depression Rating Scale score (HAM-D) ≥ 20	Mean age: 39.5 years; 46 males, 19 females	Tyrosine – 500mg daily (n=21) vs. Imipramine – 12.5mg daily (n=22) vs. Placebo – lactose (n=22). Treatments received for 4 weeks	No follow-up	No statistical difference between groups at end of week 4 in mean Hamilton Depression Scale Rating scores (HAM-D) ($p>0.05$)	“Our earlier positive impressions about the antidepressant efficacy of tyrosine at comparable doses (Gelenberg et al., 1980, 1983) were not borne out by the present study, which we believe is	Data suggest lack of efficacy of tyrosine for depression.

									the largest of its kind so far reported."	
Maprotiline										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Harrer 1994 (score=5.5)	St. John's Wort/ Maprotiline	RCT	No mention of COI or sponsorship.	N = 102 participants meeting ICD-10 depression criteria	Mean age: 45.7 years; 29 males, 73 females	300 mg of hypericum extract LI 160 three times a day (n=51) vs. 25 mg of maprotiline three times a day (n=51). All treatments given for a total of 4 weeks	Follow-up at 2 and 4 weeks	At four weeks the mean score of Hamilton Depression Rating Scale (HAMD) for hypericum group went from 20.5 to 12.2 and for maprotiline group went from 21.5 to 10.5 (different not significant, $p > 0.05$)	"Statistical evaluation of the results in the three psychometric scales used in this study (HAMD, D-S, and CGI) demonstrated a roughly equal efficacy for maprotiline and hypericum after 4 weeks of treatment."	Data suggest maprotiline and Hypericum Extract LI 160 have similar efficacy but maprotiline effects are observed earlier.
Radmayr 1986 (score=5.5)	Maprotiline/Minaprine	RCT	No mention of COI or sponsorship.	N = 40 participants meeting ICD-9 criteria for endogeno	Mean age: 47.5 years; 10 males, 30 females	Minaprine – 150 mg/day (n=20) vs. Maprotiline – 75 mg/day (n=20). Both treatments	Follow-up at 1, 2, 3, 4, 5, and 6 weeks	Both treatments resulted in significantly decreased mean scores in Hamilton Depression Scale and	"Both groups showed a comparable and significant improvement on the total scores of the	Data suggest comparable therapeutic efficacy between maprotiline and minaprine.

				us-type depression		given for six weeks		Montgomery and Asberg Depression Scale (both $p < 0.01$). There was no statistical difference in mean scores between treatment groups ($p > 0.01$)	psychiatric rating scales. The incidence of side-effects was comparable in both groups, their intensity tended to be greater in the maprotiline group."	
O'Hara 1978 (score=4.5)	Maprotiline, Fluphenazine, Nortriptyline	RCT	No mention of COI or sponsorship.	N = 75 participants with disorders on the spectrum of depressive conditions, no formal diagnostic criteria given	Mean age: 52 years; gender distribution not specified	1.5 mg fluphenazine and 30 mg nortriptyline per day (n=34) vs. 75 mg maprotiline daily (n=37). Both treatments given for four weeks	Follow-up at days 3, 10, and 28	Mean adjusted Clinical rating scale scores for depression at day 28 for combination medication = 0.96 ($p < 0.05$), for maprotiline = 1.33 ($p > 0.05$)	"The greater antidepressant effect of fluphenazine/nortriptyline after 4 weeks' treatment was the continuation of the trend already evident at day 10, and thus followed a similar time course to that expected of the antidepressa	Data suggest maprotiline better than combination fluphenazine/nortriptyline (Motipress).

									nt effect of tricyclic compounds."	
Coppen 1976 (score=4.5)	Maprotiline/Lithium	RCT	No mention of COI or sponsorship.	N = 39 attending a lithium clinical for at least 1 year and had at least three affective disorders attacks, no diagnostic criteria given	Mean age: 51.54 years; 10 males, 29 females	Maprotiline – 150 mg/day (n=18) vs. Lithium carbonate – single dose to maintain plasma lithium level between 0.8 – 1.2 mEq/l in blood the following morning (n=21).	Follow-up every six weeks for 11 months	Lithium group superior to maprotiline group for number of those who suffered no conspicuous affective morbidity during the trial ($p < 0.02$)	"The study showed lithium to be significantly superior to maprotiline in its prophylactic anti depressant effect in unipolar affective disorders, and from this point of view we believe that the investigation is valuable in providing additional evidence for the prophylactic action of lithium in unipolar depressives even when it is measured against an	Small sample sizes for both groups. High dropout rates attributed to adverse events. Data suggest lithium better than maprotiline in treatment of unipolar depression.

									active antidepressant and not an inert placebo."	
Donald 1977 (score=4.0)	Maprotiline	RCT	No mention of sponsorship or COI.	N = 191 depressed patients (no specific diagnostic criteria)	No mention of mean age, range 18-40 years; 51 males, 180 females	Group 1: received 10 mg/day of maprotiline 3 times daily (30 mg/day total) (n=59) vs Group 2: received 30 mg/day maprotiline once daily at night (n=57) vs Group 3: received 25 mg/day maprotiline three times daily (75 mg/day total) (n=57) vs Group 4: received 75 mg/day maprotiline once daily at night (n=58)	7, 14, 28 days	All treatment groups improved by 80% in symptoms of depressed mood, anxiety, and tension. Mean score reduction was -9 in group 1, -9.9 in group 2, -8.4 in group 3, and -7.9 in group 4 (p>0.05).	"In this study, the physicians assessment showed no difference between the four treatment groups. However, the results from the patients 10 cm line scores indicated that overall the 25 mg three times daily regime seemed to be the most satisfactory, but not significantly so, when compared with the 10 mg thrice	Significant baseline differences in family history of depression. Data suggest maprotiline 25 mg three times per day best but not significantly better than any of the other dosing regimens."

									daily and 75 mg nocte regimes."	
Mianserin										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Ferreri 2001 (score=6.5)	Mianserin /Fluoxetine	RCT	No mention of sponsorship or COI.	N = 104 patients with major depression (DSM-III-R)	Mean age: 46.6 years; 27 males, 77 females	Mianserin: received placebo identical to fluoxetine and 60 mg/day of mianserin (n=34) vs Fluoxetine: received placebo identical to mianserin and 20 mg of fluoxetine (n=38) vs Fluoxetine+ Mianserin: received 20 mg of fluoxetine and 60 mg of mianserin (n=32) All patients received	7, 14, 42 days	Mean HAM-D score was decreased by -16.1±7.0 points in fluoxetine+mianserin group compared to -11.3±7.4 points in fluoxetine group ($p \leq 0.03$).	"Mianserin augmentation of fluoxetine in patients non-responders to fluoxetine 20 mg/day increases response to treatment and is well tolerated."	Data suggest augmenting fluoxetine with mianserin in major depressive fluoxetine non-responders resulted in an increased therapeutic response.

						medication for 6 weeks.				
Malt 1999 (score=5.5)	Mianserin /Sertraline	RCT	Sponsored by Pfizer Norway. COI: One or more of the sponsors have received or will receive benefits for personal or professional use.	N = 372 patients with depression (DSM-III-R)	Mean age: 48.2 years; 101 males, 269 females	Sertraline: received 50-200 mg/day of sertraline over 6 weeks (n=122) vs Mianserin: received 30-120 mg/day of mianserin over 6 weeks (n=121) vs Placebo: receive no specific dose of placebo (n=129) All patients received psychological treatment.	1, 2, 3, 4, 6, 8, 12, 16, 20, 24 weeks	Mean change in depression score was -14.9 points in sertraline, -15.5 points in mianserin, and -12.5 in placebo (p=0.034). Efficacy of sertraline versus placebo was OR=0.63 (95% CI 0.36-1.11) compared to mianserin versus placebo OR=0.83 (95% CI 0.47-1.47).	"The combination of active drug and simple psychological treatment (counseling, emotional support, and close follow up over a 24 week period) was more effective than simple psychological treatment alone, in particular for those with recurrent depression."	Study suggests medication is only slightly better than placebo as data suggest remission occurred in 47% placebo randomized group 54% mianserin group, and 61% sertraline. Data suggest a combination of either sertraline or mianserin with psychological treatment is more effective than psychological treatment alone especially in those with recurrent depression.
Ahlfors 1988 (score=5.0)	Mianserin /Citalopram	RCT	No mention of sponsorship or COI.	N = 71 depressed patients (no specific diagnosti	Mean age: 46.2 years; 36 males, 20 females	Citalopram: received 40-60 mg of citalopram daily for 4 weeks (n=37) vs Mianserin:	1, 2, 4 weeks	Endogenous depression patients showed a reduced MADRS total score of more than 50% in 8	"In this study comparing citalopram double-blindly with mianserin in the treatment	Data suggest similar efficacy between citalopram and mianserin at 4 weeks in endogenous depression scores but there was a significantly greater

				c criteria)		received 60-90 mg mianserin daily for 4 weeks (n=34)		patients in citalopram group and 10 in the mianserin group. Non-endogenous depression patients showed a reduced MADRS score from 29.4 to 19.0 in citalopram group ($p<0.01$) and from 31.0 to 6.7 in mianserin group ($p<0.001$).	of depressed patients referred to a psychiatric hospital, a significant reduction in the severity of the depressive symptoms was observed in patients with endogenous depression after only 1 week of treatment in both groups."	reduction in MADRS scores in the mianserin group at 4 weeks in non-endogenous depression.
Montgomery 1978 (score=4.5)	Mianserin	RCT	No mention of sponsorship or COI.	N = 57 patients with primary depressive illness (no specific diagnostic criteria)	Mean age: 44.44±14.99 years; 13 males, 37 females	Group 1: received 2-10 mg tablets of mianserin three times daily plus 6 tablets of matching placebo nightly (n=25) vs Group 2: received 2	1, 2, 3, 4 weeks	No differences were observed between the two dosage regimens in HRS, BSRI, and MADS. Decrease in HRS score was 13.8 vs 11.1. Decrease in BSRI was 19.5 vs 16.5; considering	"We found no clinical advantage for the divided dose regimen or disadvantage for the single night-time dosage in terms of therapeutic outcome or side-effects."	Baseline characteristic of study population sparse. Data suggest no benefit from administration of a divided dose of mianserin versus a single night-time dose of mianserin.

						tablets of placebo three times daily plus six 10-mg tablets of mianserin nightly (n=25)		baseline there were no differences.		
Dam 1998 (score=4.5)	Mianserin / Fluoxetine	RCT	Sponsored by Organon and Eli Lilly. No mention of COI.	N = 34 patients with major depression (DSM-III-R)	No mention of mean age, range from 18-70 years; no mention of sex.	Fluoxetine Alone: received 20 mg of fluoxetine (n=18) vs Mianserin+ Fluoxetine: received 30 mg of mianserin and 20 mg of fluoxetine (n=16)	1, 2, 3, 4, 5, 6 weeks	Combination group showed an effect change of 0.69 in HAM-D scores ($p<0.05$) with the greater change in HAM-D scores compared to fluoxetine group.	"In conclusion, we found in the efficacy analysis, though not in the intention-to-treat analysis, that the combination of fluoxetine and mianserin was superior to fluoxetine alone."	Data suggest combo mianserin plus fluoxetine better than fluoxetine alone.
Mirtazapine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Blier 2009 (score=4.5)	Mirtazapine/ Paroxetine	RCT	Sponsored by Organon Pharmaceuticals. COI: One or more	N = 61 participants with a DSM-IV	Mean age: 43.10 years; 33	Mirtazapine 30 mg/day (n=21) vs. Paroxetine 20 mg/day	Follow-up at days 4, 7, 10, 14, 21,	Statistically greater decrease in Montgomery-Asberg	"These results indicate that the combined	Data suggest combination therapy leads to better results than monotherapy.

			of the authors have received or will receive benefits for personal or professional use.	diagnosis of unipolar depression	males, 28 females	(n=19) vs. Combination Group: received 30 mg/day mirtazapine and 20 mg/day paroxetine (n=21). All medications given for six weeks	28, 35, 42, 49, and 56	Depression Rating Scale (MADRS) scores in combination therapy compared to monotherapies at day 42 (F = 7.17, p = 0.002).	use of two antidepressants was well tolerated and produced a greater improvement than monotherapy."	
Blier 2010 (score=4.5)	Fluoxetine/ Mirtazapine	RCT	Sponsored by Organon Pharmaceuticals. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 105 patients meeting DSM-IV criteria for major depressive disorder	Mean age: 43.81 years; gender distribution not mentioned	Fluoxetine 20 mg daily (n=28) vs. Mirtazapine 30 mg and Fluoxetine 20 mg daily (n=25) vs. Mirtazapine 30 mg and Venlafaxine 225 mg daily titrated in 2 weeks (n=26) vs. Mirtazapine 30 mg and Bupropion 150 mg daily (n=26). All treatments	Follow-up at days 4, 7, 10, 14, 21, 28, 35, and 42	Statistically significant difference in mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS) between monotherapy and 3 combination treatments (p = 0.09).	"The combination treatments were as well tolerated as fluoxetine monotherapy and more clinically effective. The study results, which add to a growing body of evidence, suggest that use of antidepressant combinations from	Data suggest all 3 combination therapies were superior to fluoxetine monotherapy [mirtazapine + fluoxetine, mirtazapine + venlafaxine, mirtazapine + bupropion].

						given for 6 weeks.			treatment initiation may double the likelihood of remission compared with use of a single medication."	
Nortriptyline										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Sackheim 2001 (score=7.0)	Electroconvulsive Therapy/ Nortriptyline	RCT	Sponsored by National Institute of Mental Health grants, Solvay Pharmaceuticals Inc., and MECTA Corporation. No mention of COI.	N = 84 patients with major depressive disorder meeting Research Diagnostic Criteria (RDC)	Mean age: 57.4 years; 28 males, 56 females	Nortriptyline: received 75-125 ng/mL of nortriptyline (n=27) vs Nortriptyline and Lithium: received a combination of nortriptyline and lithium 0.5-0.9 mEq/L (n=28) vs Placebo: (n=29). All participants	4, 8, 12, 16, 20, 24 weeks	Relapse observed in 84% of placebo group, 60% of nortriptyline group, and 39% for nortriptyline-lithium group. Patients that relapsed showed higher HRSD scores compared to patients who did not relapse.	"Our study indicates that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT. Monotherapy wit nortriptyline has limited efficacy. The combination of	Data suggest relapse at 6 months is highly probable without continuation pharmacotherapy post ECT. In addition, monotherapy less effective than combination therapy but relapse rate is high in both groups during first month post ECT.

						had undergone an open ECT treatment phase			nortriptyline and lithium is more effective, but the relapse rate is still high, particularly during the first month of continuation therapy."	
Reynolds 1999 (score=5.0)	Interpersonal Psychotherapy (IPT)/Nortriptyline	RCT	Sponsored by National Institute of Mental Health. No mention of COI.	N = 180 patients with recurrent non-psychotic unipolar major depression (MINI, Hamilton)	Mean age: 67.6±5.8 years; 45 males, 135 females	Nortriptyline+IPT Group: received 80-120 ng/mL nortriptyline hydrochloride and biweekly interpersonal psychotherapy (n=25) vs Nortriptyline+MC Group: received medication clinic consisting of 30 minute visits by a	1, 2, 3 years	The Nortriptyline+IPT group, Nortriptyline+MC group, and the IPT+Placebo group were better at preventing recurrence of depression compared to placebo (p<.001, p<.001, p=.03; respectively.)	"In geriatric patients with recurrent major depression, maintenance treatment with nortriptyline or IPT is superior to placebo in preventing or delaying recurrence. Combined treatment using both appears to be the optimal clinical strategy in	Data suggest the 3 active treatment arms showed decreased time to recurrence versus placebo. Combined treatment of nortriptyline and IPT showed the lowest recurrence rates at 3 years.

						nonphysician clinician and a psychiatrist as well as 80-120 ng/mL of nortriptyline hydrochloride (n=28) vs Placebo+IPT: received placebo medication and biweekly interpersonal psychotherapy (n=25) vs Placebo+MC: received medication clinic consisting of 30 minute visits by a nonphysician clinician and a psychiatrist as well as placebo medication (n=29)			preserving recovery."	

O'Hara 1978 (score=4.5)	Maprotiline, Fluphenazine, Nortriptyline	RCT	No mention of COI or sponsorship.	N = 75 participants with disorders on the spectrum of depressive conditions, no formal diagnostic criteria given	Mean age: 52 years; gender distribution not specified	1.5 mg fluphenazine and 30 mg nortriptyline per day (n=34) vs. 75 mg maprotiline daily (n=37). Both treatments given for four weeks	Follow-up at days 3, 10, and 28	Mean adjusted Clinical rating scale scores for depression at day 28 for combination medication = 0.96 ($p < 0.05$), for maprotiline = 1.33 ($p > 0.05$)	"The greater antidepressant effect of fluphenazine/nortriptyline after 4 weeks' treatment was the continuation of the trend already evident at day 10, and thus followed a similar time course to that expected of the antidepressant effect of tricyclic compounds."	Data suggest maprotiline better than combination fluphenazine/nortriptyline (Motipress).
Shelton 2005 (score=4.5)	Nortriptyline/Fluoxetine/Olanzapine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or	N = 500 subjects with unipolar, nonpsychotic MDD (DSM-IV)	Mean age: 42.4 years; 160 males, 340 females	OFC: received either 6 mg/day olanzapine and 25 mg/day fluoxetine or 12 mg/day olanzapine and 50	0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks	OFC group showed a greater decrease in MADRS scores than OLZ group ($p=0.005$). Remission rates were 16.9% for OFC group,	"The olanzapine/fluoxetine combination did not differ significantly from the other therapies at endpoint, although it	Data suggest comparability of all 4 treatment groups but combo olanzapine/fluoxetine resulted in a quicker response.

			professional use.			mg/day fluoxetine (n=146) vs OLZ: received 6 mg/day of olanzapine (ranged from 6-12 mg/day (n=144) vs FLX: received 25 mg/day fluoxetine (ranged from 25-50 mg/day) (n=142) vs NRT: received 25 mg/day nortriptyline (increased to 50 mg/day on day 2, and 75 mg/day by day 4) (n=68)		12.9% for OLZ group, 13.3% for FLX, and 18.2% for NRT group (p=0.62).	demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization."	
Protriptyline										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:

Rickels 1967 (score=4.5)	Protriptyline/Meprobamate	RCT	No mention of COI. Sponsored by the National Institute of Mental Health	N = 157 participants with mild to moderate depression, no diagnostic criteria given	No mean age given; 24 males, 133 females	Stage 1 – protriptyline hydrochloride 30-45 md/day given in three divided doses (n=46) vs. placebo (same dosage as protriptyline) (n=26). Stage 2 – meprobamate 1,600 mg/day (n=39) vs. meprobamate 1,600 mg/day and protriptyline hydrochloride 40 mg/day (n=46). All medications for both stages given for four weeks	Follow-up at 2 and 4 weeks	Total Score of the Depression Scale at end of four weeks: Combination = 9.07, Protriptyline = 10.47, Meprobamate = 10.26, Placebo = 16.06 ($F = 4.98$, $p < 0.01$) – showing all drugs more effective than placebo	"The results showed that over the four-week study period patients improved significantly more while receiving the three drugs than while receiving placebo."	Placebo controlled trial with all drugs better than placebo. Relatively short treatment duration (4 weeks). Data suggest individuals with high anxiety responded best to combination meprobamate and protriptyline which was better than meprobamate alone. Low anxiety individuals responded best to stand alone protriptyline.
Monoamine Oxidase Inhibitors										

Moclobemide										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Gagiano 1994 (score=6.5)	Moclobemide	RCT	No mention of COI or sponsorship.	N = 170 participants meeting DSM-III-R criteria for major depressive episode	Mean age: 35.02 years; 42 males, 128 females	Moclobemide – 100 mg three times daily (n=56) vs. Moclobemide – 150 mg three times daily (n=56) vs. Moclobemide – 150 mg twice daily (n=58)	Follow-up at days 3, 7, 14, 21, 28 and 42	No statistical difference between treatment groups in mean change in total score on Hamilton Depressing Rating Scale (HAM-D) or Zung Depression Inventory (no p-value or test statistic given)	"In conclusion, the three dosage schedules of moclobemide studied are effective and very well tolerated in the treatment of patients with major depressive episode. Moclobemide 150 mg b.i.d. is the optimal dosage with which to initiate treatment of depression patients."	Data suggest all 3 treatment regimens led to a significant improvement in depression scores via the Hamilton Depression and Anxiety Rating Scales but moclobemide 150 mg bid appears to be the best dose for improving HAM-D scores.
Newbum 1995 (score=5.0)	Moclobemide	RCT	Sponsored by F. Hoffmann-La Roche	N = 189 participants meeting DSM-	Mean age: 43.15 years; 91	Single daily dosage of Moclobemide 450 mg (n=94) vs.	Follow-up at days 2, 7, 14,	Mean reduction in Hamilton Depression Rating Scale (HAMD)	"In this study, the antidepressant effect of moclobemid	Data suggest comparable efficacy for treatment of MDD of either dose

			Ltd., Base, Switzerland.	III-R criteria for major depressive episode	males, 98 females	Three times daily dosage of 150 mg (n=95). Placebo capsules were used in single daily dosage group. All treatments given for six weeks	21, 28, and 42	scores was statistically significant for both groups but there was no statistical difference between groups (mean percentage reduction: single dose = 73.8%, three doses = 72.9%)	e is at least as effective given as an OD dose compared with TDS."	regimen of moclobemide.
Phenelzine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Jarrett 1999 (score=5.0)	CBT/Phenelzine	RCT	Sponsored by grants from National Institute of Mental Health. No mention of COI.	N = 108 patients with major depressive disorder (DSM-IV)	Mean age: 39.6 years; 35 males, 73 females	CBT Group: received cognitive behavioral therapy consisting of 20 individual sessions 2 times weekly for 10 weeks (n=36) vs Phenelzine Group: received	4, 7, 10 weeks	Response rate was 58% in CBT group, 58% in phenelzine group, and 28% in placebo group. Phenelzine reduced the mean HRSD-21 scores more than the placebo group at 4 weeks (p=0.01). For	"Cognitive therapy may offer an effective alternative to standard acute-phase treatment with a monoamine oxidase inhibitor for outpatients with major depressive disorder and	Baseline data differs in terms of duration and type of depression. Data suggest both CBT and phenelzine had comparable efficacy and were both superior to placebo but high dropout rate in placebo group.

						phenelzine sulfate (0.85 mg/kg to 1 mg/kg consisting of 11 sessions over 10 weeks (n=36) vs Placebo: received identical dosing as phenelzine of a placebo pill (n=36)		weeks 7 and 10, both CBT group and phenelzine group reduced the HRSD-21 group compared to placebo (CBT vs Placebo 7 weeks: F1,103=7.29, p<0.01; 10 weeks: F1,103=8.94, p<0.01; Phenelzine vs Placebo 7 weeks: F1,103=12.60, p<0.001; 10 weeks F1,103=9.30, p<0.01).	atypical features."	
Pickering 1965 (score=5.0)	Imipramine/ Phenelzine/ ECT	RCT	No mention of sponsorship or COI.	N = 269 patients with primary diagnosis of depression, diagnostic criteria not listed	Mean age: 55.3 years; 81 males, 169 females	ECT Group: received 4-8 treatments of electroconvulsive therapy for 3.5 weeks (n=65) vs Imipramine Group:	5, 8, 12, 24 weeks, 6 months	Imipramine was superior to both phenelzine and placebo. ECT group and imipramine were similar with 83% of patients and 85% of patients discharged	"[I]t appears that that ECT and imipramine increased the frequency of recovery over and above the spontaneous rate shown	Data suggest imipramine and ECT were better than phenelzine and placebo for improving depressive symptoms.

						received 50 mg of imipramine for 3.5 weeks (n=63) vs Phenelzine Group: received 15 mg of phenelzine for 3.5 weeks (n=61) vs Placebo: received placebo pill (n=61)		from the hospital. Phenelzine showed 70% of patients discharged compared to 86% of placebo group.	by patients on the placebo."	
Liebowitz 1984 (score=5.0)	Phenelzine/Imipramine	RCT	Sponsored by grants from the Public Health Service. No mention of COI.	N = 60 patients with atypical depression (DSM-III)	Mean age: 36.2±9.7 years; 26 males, 34 females	Imipramine Group: received imipramine hydrochloride 50 mg at bedtime for 3 days and 100 mg at bedtime for the next 4 days, then increased to 150 mg/day at bedtime for the second	6 weeks	Response rate was 67% in phenelzine group, 43% in imipramine group, and 29% in placebo group. Imipramine group was superior to placebo in depression on SCL-90 ($p \leq .04$), CGI scale ($p \leq .09$), and anxiety on	"Atypical depressive patients with a history of spontaneous panic attacks and hysteroid dysphoric patients both showed extremely low rates of response to placebo and high rates of response to	Data suggest multiple subtypes of atypical depression. Small group sizes. Data suggest in atypical depression at week 6, phenelzine was superior to placebo for several measures while imipramine was better than placebo but not as good as phenelzine. It appears as though patients with significant histories

						week, then to 200 mg/day at bedtime for the third and fourth week, then 250 mg/day for fifth week, then 300 mg/day at bedtime for the sixth week (n=21) vs Phenelzine Group: received phenelzine 15mg/day in the morning for 3 days, 30 mg/day for next 4 days, 45 mg/day for second week, 60 mg/day for week 3 and 4, 75 mg/day for fifth week, 90 mg/day for sixth		SCL-90 ((p≤.06). Phenelzine was superior to placebo on both severity and change scales of CGI (p≤.003, p≤.01; respectively). Phenelzine was superior to imipramine on all scales.	phenelzine. Conversely, those without panic or hysteroid dysphoric features responded equally to all three treatments. Responders to phenelzine also had greater platelet monoamine oxidase inhibition while receiving drug therapy than did non-responders."	of panic attacks respond better to phenelzine but those without panic attacks respond equally to both meds as well as placebo.

						week(n=15) vs Placebo Group: received placebo in same manner of increasing dose (n=24)				

Raskin 1974 (score=4.5)	Phenelzine/Diazepam	RCT	No mention of sponsorship or COI.	N = 325 depressed patients (no specific diagnostic criteria)	No mention of mean age (median 40 years for men, and 37 years for women); 107 males, 218 females	Diazepam: received 30 mg of diazepam for 5 weeks (n=104) vs Phenelzine: received 45 mg of phenelzine for 5 weeks (n=110) vs Placebo: received placebo (n=111)	5 weeks	Diazepam patients showed greater improvement in sleep disturbances compared to phenelzine or placebo (p=.05).At weeks 1 and 3, hostile depressive patients reported more improvement on phenelzine than placebo (p=.01). Negative effects of diazepam for hostile-depression patients were apparent in depression symptoms.	"There was a significant number of anxious-depressive patients who were diazepam responders, ie, their symptoms subsided on this treatment and became worse when this drug was discontinued. In contrast, diazepam was a poor treatment for the hostile depressions. These symptoms persisted on diazepam and improved on either phenelzine or a placebo."	High Dropout rate. Data suggest diazepam best for anxious depressives where phenelzine better for treating hostility associated depression. Also, placebo better than diazepam for hostile depression.

Atypical Antidepressants										
Agomelatine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lôo 2002 (score=5.5)	Agomelatine/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 711 participants meeting DSM-IV major depressive disorder criteria	Mean age: 42.3 years; 238 males, 473 females	Group 1: received 1 mg/day agomelatine (n=141) vs Group 2: received 5 mg/day agomelatine (n=147) vs Group 3: received 25 mg/day agomelatine (n=137) vs Group 4: received 20 mg paroxetine (n=147) vs Group 5: received 20 mg placebo capsule (n=139)	1, 2, 4, 6, 8 weeks	Groups 1-3 showed reduced mean HAM-D scores compared to placebo (p=0.037). Mean HAM-D score was lower in paroxetine group compared to placebo (p=0.03) and a similar observation was made for group 3 (agomelatine 25 mg) compared to placebo (p<0.05).	"In conclusion, this placebo-controlled study clearly shows that, of the three doses tested, agomelatine 25 mg is effective in the treatment of major depression and is identified as the target dose."	Data suggest 25 mg of agomelatine was comparable to paroxetine and both medications were superior to placebo.
Kennedy 2014 (score=5.5)	Agomelatine	RCT	Sponsored by Servier. COI: One or more of the	N = 549 patients with a primary	Mean age: 45.0 years;	Group 1: received 10 mg agomelatine	6 weeks	Mean HAM-D17 scores were decreased in group 1 by	"This study provides evidence of a dose effect	Data suggest all doses of agomelatine were better than placebo but a dose

			authors have received or will receive benefits for personal or professional use.	diagnosis of mild depressive disorder (DSM-IV-TR)	148 males, 401 females	(n=133) vs Group 2: received 25 mg/day agomelatine (n=138) vs Group 3: received 25-50 mg/day agomelatine (n=137) vs Group 4: received placebo (n=141)		2.46±0.76 points (p=0.001), 4.71±0.75 points in group 2 (p<0.0001), and 4.92±0.76 points in group 3 (p<0.0001) compared to group 4 (placebo).	for agomelatine between 10 mg and the therapeutic dose regimen of agomelatine 25-50 mg; the efficacy of the higher dose regimens being more efficacious than the lowest (10 mg) daily dose."	response was observed where the higher doses were associated with more symptom improvement.
Kennedy 2016 (score=5.5)	Agomelatine	RCT	Sponsored by Servier. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 549 patients with a primary diagnosis of mild depressive disorder (DSM-IV-TR)	Mean age: 45.0 years; 148 males, 401 females	Group 1: received 10 mg agomelatine (n=100) vs Group 2: received 25 mg/day agomelatine (n=111) vs Group 3: received 25-50 mg/day agomelatine (n=115) vs Group 4:	6 months	Mean HAM-D17 scores were decreased in group 1 by 4.51±1.06 points (p<0.0001), 7.74±1.05 points in group 2 (p<0.0001), 7.72±1.05 points in group 3 (p<0.0001) compared to placebo.	"Long term agomelatine treatment improves both mood symptoms and social and occupational functioning of moderately to severely depressed patients."	Data suggest that at 24 weeks agomelatine improves mood and social functioning in moderate to severe depression.

						received placebo (n=85)				
Stahl 2010 (score=4.5)	Agomelatine	RCT	Sponsored by Novartis Pharma AG. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 503 patients with a diagnosis of MDD, single or recurrent episode (DSM-IV)	Mean age: 43.33 ± 12.29 years; 174 males, 329 females.	Group 1: patients received 25 mg/d Agomelatine for 8 weeks (n = 168) vs Group 2: patients received 50 mg/d Agomelatine for 8 weeks (n = 169) vs Group 3: patients receive a placebo (n = 166)	2, 4, 6, 8, 10 weeks	In the intent-to-treat (ITT) population (n = 482) group 1 reduced HDRS17 scores compared to the placebo (p= 0.01). In group 2, reduction in HDRS17 was not maintained at week 8 (p=0.144).	"Agomelatine 25 mg/d was effective in the treatment of patients with moderate-to-severe MDD and was safe and well tolerated. Agomelatine 50 mg/d provided evidence for its antidepressant efficacy until week 6 and was also safe and well tolerated."	Data suggest Agomelatine 25 mg was effective in decreasing depressive symptoms versus placebo.

Zajecka 2010 (score=4.5)	Agomelatine	RCT	Sponsored by Novartis Pharma AG. COI: One or more author have received or will receive benefits for personal or professional use.	N = 511 patients with a diagnosed MDD, single or recurrent (DSM-IV)	Mean age: 43.8 ± 12.22 years: 170 males, 341 females.	Group 1: patients received 25 mg Agomelatine for 8 weeks (n=170) vs Group 2: patients received 50 mg Agomelatine for 8 weeks (n=168) vs Group 3: patients received placebo (n= 173)	2, 4, 6, 8, 10 weeks	Group 2 (50 mg) showed a reduction of 2.5 in the HAM-D17 scores when compared to the placebo group (p=0.004). Group 1 did not show a statistically significant improvement in HAM-D scores (p=0.505).	”In the present study, agomelatine 50 mg showed greater and rapid reduction in all core symptoms of depression compared with placebo.”	Data suggest significant antidepressant efficacy of agomelatine compared to placebo and also improved sleep.
Amineptine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Boyer 1999 (score=6.0)	Amineptine/Amisulpride	RCT	No mention of COI or sponsorship.	N = 323 participants meeting DSM-III-R for primary dysthymia	Mean age: 48 years; 81 males, 242 females	Amisulpride – 50 mg/day (n=104) vs. Amineptine – 200 mg/day (n=111) vs. Placebo (n=108). All medications	Follow-up at 1 week and 1, 2, and 3 months	Montgomery-Asberg Depression Rating Scale (MADRS) mean score changes: placebo = -3.8, amisulpride = -8.6, amineptide	“Results show that amisulpride can improve symptoms of chronic depression in dysthymia.”	Data suggest amisulpride comparable to amineptine and both medications are superior to placebo.

						given for 3 months		= -8.2 (p < 0.0001). Scale for the Assessment of Negative Symptoms (SANS) mean score changes: placebo = -11.2, amisulpride = -17.6, amineptide = -19.9 (p < 0.0001)		
Boyer 1996 (Study 1: score=6.0, Study 2: score=5.5)	Amisulpride/ Amineptine/ Imipramine	2 RCTs	No mention of sponsorship or COI.	Study 1: N = 323 patients with primary dysthymia with or without major depressive episode (DSM-III-R) Study 2: N = 219 patients with dysthymia or major depression	Study 1: Mean age: 48.2 years; 81 males, 242 females Study 2: Mean age: 42.9 years; 99 males, 120	Study 1: Amisulpride: received 50 mg/day amisulpride for 3 months (n=104) vs Amineptine: received 200 mg/day amineptine for 3 months (n=111) vs Placebo: (n=108) Study 2: Amisulpride: received 50 mg/day amisulpride	Study 1: 8 days, 1, 2, 3 months Study 2: 6 months	Study 1: Reduction in MADRS score was -8.63 in amisulpride and -8.21 in amineptine compared to -3.81 in placebo (p=0.0001). Study 2: MADRS score was reduced by -12.3 in amisulpride, -10.6 in imipramine, and -7.2 in placebo (placebo vs	"Results of the intention to treat analysis and of the end-point analysis were compelling and very similar: significant differences were demonstrated for all primary criteria between amisulpride	Data suggest in both studies amisulpride, imipramine, and amineptine were better than placebo vis MADRS, CGI, and SANS scores. However, in study 2, the 6 month study amisulpride more efficacious than imipramine.

				(DSM-III-R)	female s	for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine (n=73) vs Placebo: (n=73)		imipramine p=0.036, placebo vs amisulpride p<0.002, global p=0.007).	and placebo and between imipramine and placebo but not between amisulpride and imipramine. For both primary criteria and the responder rate (CGI). Statistically significant differences were evidenced between amisulpride and placebo and amineptine and placebo."	
Bupropion										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Fornaro 2014 (score=5.5)	Duloxetine/Bupropion	RCT	Sponsored by University	N = 46 patients with major	Mean age: 39.0 years;	Duloxetine +Placebo: received 60-120 mg/day	2, 4, 6 weeks	Withdrawal rate of 68% in placebo group compared to	"Additional studies, including an adequate	Lack of efficacy as data suggest only 21.7% of patients receiving

			of Genova. No COI.	depression (DSM-IV)	16 males, 30 females	of duloxetine plus one 150-300 mg/day dummy pill of placebo for 6 weeks (n=23) vs Duloxetine+ Bupropion: received 60-120 mg/day of duloxetine plus 1 capsule of bupropion (150-300 mg/day) sustained release for 6 weeks(n=23)		61% in bupropion group. Placebo group showed 18.2% response at week 4 compared to 28.6% in bupropion group. Placebo group showed an additional response in 13.6% at week 6 compared to 1% in bupropion group.	course of duloxetine trial, are nonetheless aimed to allow a firm conclusion about the usefulness of the combination of duloxetine and bupropion for treatment-resistant cases of major depression with atypical features."	duloxetine-placebo achieved response vs 26.1% receiving duloxetine-bupropion.
Stewart 2014 (score=5.0)	Escitalopram/Bupropion	RCT	Sponsored by grants from NIMH. COI: One or more of the authors have received or will receive benefits for	N = 245 outpatients with non-bipolar major depression (DSM-IV-TR)	Mean age: 40.3 years; 82 males, 163 females	Bupropion+ Placebo: received 150 mg/day bupropion for first week, increased to 300 mg/day for next 2 weeks, then	1, 2, 3, 4, 6, 8, 10, 12 weeks	Remission was not achieved earlier for dual group compared to bupropion or escitalopram alone groups (p=0.258, p=0.960, respectively).	"These results do not support initial use of bupropion plus escitalopram to speed or enhance antidepressa	Data suggest comparable efficacy between bupropion, escitalopram, and combination bupropion-escitalopram suggesting no benefit is achieved with combination therapy for

			personal or professional use.			to 450 mg/day for remaining 12 weeks and a placebo matching escitalopram dosing (n=83) vs Bupropion+ Escitalopram: received 150 mg/day bupropion for first week, increased to 300 mg/day for next 2 weeks, then to 450 mg/day for remaining 12 weeks and received 10 mg escitalopram for first week, and 10 mg increase weekly to 40 mg/day at week 4		Dual group showed highest rate of remission compared to both monotherapy groups, until final follow up where escitalopram group showed same remission rate in HAM-D scores.	nt response."	prevention of remission.

						and beyond (n=78) vs Escitalopram+Placebo: received 10 mg escitalopram for first week, and 10 mg increase weekly to 40 mg/day at week 4 and beyond (n=84)				
Mohamed 2017 (score=4.5)	Aripiprazole, Bupropion	RCT	Sponsored by Veterans Affairs Cooperative Studies Program and Bristol-Myers Squibb. One or more of the authors have received or will receive benefits for personal or	N = 1522 US Veterans Health Administration patients with anti-depressant resistant Major Depressive Disorder diagnosis according to DSM-IV-TR criteria	Mean age: 54.4 years; 1296 male, 226 female	Switched antidepressant medication to bupropion (starting dose 150 mg/d to 300-400 mg/d) (n=511) vs. Augmented current antidepressant treatment with bupropion (starting dose 150	Follow up at baseline, 1, 2, 4, 6, 8, 10, and 12 weeks. Optional continuation phase had follow-ups at 16, 20, 24, 28, 32, and	Remission was higher for augmented aripiprazole group at 28.9% compared with switched group at 22.3% (p=0.02) but not significantly different than augmented bupropion group at 26.9% (p=0.47). Remission defined as a score of 5 or	"Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly	Predominantly male pop. Data suggest benefit from aripiprazole augmentation in MDD patients who are unresponsive to ADT but this only resulted in a modest likelihood of remission.

			professional use.			mg/d to 300-400 mg/d) (n=506) vs. Augmented current antidepressant treatment with aripiprazole at 2mg, 5mg, 20mg, or 15mg/d (n=505)	36 weeks.	less on the QIDS-C16.	increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy."	
Trivedi 2006 (score=4.0)	Bupropion/ Citalopram/Buspirone	RCT	Sponsored by the National Institute of Mental Health, National Institutes of Health. COI, one or more authors have received or will received benefits for personal or professional use.	N = 565 patients with nonpsychotic major depressive disorder without remission who had received 12 weeks of citalopram therapy, no mention of diagnostic criteria	Mean age: 41.1 years; 233 males, 332 females	Augmentation of citalopram with sustained-release bupropion. Initial dose of sustained-release bupropion = 200 mg daily for 2 weeks, 300 mg daily at week 4, 400 mg daily at week 6 (n=279) vs. Augmentation of	Follow-up at 2, 4, 6, 9, and 12 weeks	Both treatments had similar rates for Hamilton Rating Scale for Depression remission (HRSD-17) (29.7% vs. 30.1%) and for 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR-16) remission (39.0% vs. 32.9%). Sustained-release	"Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings."	Data suggest similar efficacy between bupropion SR and buspirone for prevention of depression relapse.

						citalopram with buspirone. Initial dose of buspirone = 15 mg daily for 1 week, 30 mg daily for 1 week, 45 mg daily for weeks 3 to 5, 60 mg daily during week 6 (n=286). All medications taken twice daily		bupropion had greater reduction QIDS-SR-16 scores (25.3% vs. 17.1%, p<0.04)		
Nefazodone										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Schatzberg 2005 (score=5.0)	Nefazodone/ Psychotherapy	Crossover trial	Sponsored by Bristol-Myers Squibb Co, New York, NY. Author Borian was associate with Bristol-	N = 140 patients meeting DSM-IV criteria for chronic major depressive disorder, "double depression" (current	Mean age: 43.1 years; 48 males, 92 females	Received nefazodone first: 100-600 mg daily, for 12 weeks (n=61) vs. Received CBASP first: cognitive behavioral	No long term follow-up	Switching from nefazodone to CBASP and from switch from CBASP to nefazodone resulted in statistically significant improvements in symptoms (p = 0.03).	"Among chronically depressed individuals, CBASP appears to be efficacious for nonresponders to nefazodone,	Data suggest in chronically depression non-responders, switching from CBASP to nefazodone or nefazodone to CBASP results in similar therapeutic efficacy in treatment

			Myers Squibb Co.	major depressive episode superimposed on antecedent dysthymic disorder), or recurrent major depressive disorder with incomplete interepisode recovery		analysis system of psychotherapy, twice weekly for 4 weeks, then once weekly for 8 weeks (n=79)		Response and remission rates were not significantly different between completers	and nefazodone appears to be effective for CBASP nonresponders. A switch from an antidepressant medication to psychotherapy or vice versa appears to be useful for nonresponders to the initial treatment."	of depressive symptoms.
Maddux 2009 (score=4.0)	Nefazodone/CBT	RCT	Sponsored by Bristol-Myers Squibb. Author Thase serves on the Speakers Bureau and acts as a Consultant for the Bristol-	N = 681 participants meeting DSM-IV criteria for chronic major depressive disorder, major depressive disorder superimposed on	Mean age: 42.3 years; 236 males, 445 females	Nefazodone: 300-600 mg daily (n=227) vs. Cognitive behavioral analysis system of psychotherapy (CBASP): 16-20 sessions, 2 sessions	No follow-up	Patients with comorbid personality disorders (PDs) statistically lower Hamilton Depression Rating Scale scores (mean=12.2) compared to those without comorbid PDs (mean=13.5,	"Comorbid Axis II disorders did not negatively affect treatment outcome and did not differentially affect response to psychotherapy versus	Data suggest that chronic depression with comorbid personality disorders do not respond to treatment with nefazodone or psychotherapy differently than those who are chronically depressed without personality disorders.

			Myers Squibb Company.	antecedent dysthymic disorder, or recurrent major depressive disorder with incomplete remission between episodes		weekly for 4 weeks, 1 session weekly for 8 weeks (n=227) vs. Combination of both treatments (n=227)		partial n2 = 0.008).	medication. Treatment formulations for chronically depressed patients with certain PDs may not need to differ from treatment formulations of chronically depressed patients without co-occurring PDs."	
Trazadone										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Klieser 1989 (score=5.5)	Trazodone/Amitriptyline/Haloperidol	RCT	No mention of COI or sponsorship.	N = 45 patients with major depressive disorder and 75 with acute schizoph	Mean age: 42.6 years; 49 males, 71 females	400 mg trazodone daily (n=30) vs. 20 mg haloperidol daily (n=30) vs. 150 mg amitriptyline daily (n=30) vs. Placebo	No follow-up	Hamilton Depression Rating Scale (HAM-D) scores decreased in all drug treatments. Mean change in HAM-D scores at 3	"After only 7 days of trazodone treatment, a relatively reliable decision can be established as to whether a	Mixed population of depression and schizophrenic patients. Data suggest trazodone appears to not have antipsychotic action on schizophrenia but depression patients did respond to trazodone.

				renia, no diagnostic criteria listed		daily (n=30). All treatments given for three weeks		weeks: trazodone = -3.1, amitriptyline = -12.1, haloperidol = -4.0, placebo = -4.1	therapeutically success can be expected if treatment is continued."	
Davey 1988 (score=5.5)	Trazodone	RCT	No mention of COI or sponsorship.	N = 182 participants meeting DSM-III criteria for major depressive episode	Mean age not given, age range from 18 – 65; 54 males, 128 females	50 mg trazodone three times daily (n=87) vs. 150 mg trazodone once daily (n=95). Medications were given for six weeks	Follow-up at 1, 2, 4, and 6 weeks	No significant differences between treatment groups at any individual time or overall efficacy (no p-value given)	"In this study single dose administration of 150 mg trazodone nocte was a convenient, effective and tolerable alternative to the more conventional divided dose regimen."	Data suggest single dose trazodone is effective, convenient and provides better quality sleep.
Bayer 1989 (score=5.0)	Trazodone	RCT	Sponsored by Roussel Laboratories Limited. No mention of COI.	N = 166 participants meeting DSM-III criteria for primary depressive illness	Mean age: 78 years; 23 males, 60 females	Conventional 100 mg trazodone once daily for 1 week, then 200 mg or less for 3 weeks (n=83) vs. Controlled-release 100 mg	Follow-up at day 8, 15, 22, 29, and 36	Mean change in Hamilton Depression Rating Scale (HRS-D) between groups was not significant at any time point or overall (no p-value given)	"There was a tendency for fewer side effects to be recorded during the first week of treatment in patients receiving the controlled-release	Data suggest a trend in CR-trazodone to elicit fewer adverse events but comparable efficacy.

						trazodone once daily for 1 week, then 200 mg or less for 3 weeks (n=83)			formulation but no difference reached statistical significance. "	
Moon 1990 (score=5.0)	Trazodone	RCT	No mention of COI or sponsorship.	N = 347 participants satisfying at least four of eight symptoms for major depressive episode in DSM-III criteria	No mean age given, median age: 42 years; 127 males, 220 females	Controlled-release trazodone 150 mg daily (n=172) vs. Standard trazodone 150 mg daily (n=175). Medication given for six weeks	Follow-up at 1, 2, 4, and 6 weeks	Hamilton Depression Rating Scale scores decreased significantly in both groups ($p<0.0001$). There was no statistical difference between groups efficacy	"Treatment differences, revealed in a five symptom adverse event checklist used throughout the study, were small, although in favour of the controlled-release tablet in the majority of cases, but not statistically significant."	Data suggest a trend in better efficacy of controlled-release trazodone compared to the standard formulation.

Vortioxetine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Mahableshwarkar 2015 (score=5.5)	Vortioxetine/ Duloxetine	RCT	Sponsored by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 614 participants with primary diagnosis of recurrent MDD meeting DSM-IV criteria	Mean age: 42.9 years; 160 males, 454 females	Vortioxetine 15 mg daily (n=147) vs. Vortioxetine 20 mg daily (n=154) vs. Duloxetine 60 mg daily (n=152) vs. Placebo daily (n=161). All medications received for 8 weeks	No long term follow-up	Mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS): placebo = −12.83, vortioxetine 15 mg = −14.30 ($p = 0.224$, compared to placebo), vortioxetine 20 mg = −15.57 ($p = 0.023$), and duloxetine 60 mg = −16.90 ($p < 0.001$)	"Vortioxetine 20 mg significantly reduced MADRS total scores after 8 weeks of treatment. Both vortioxetine doses were well tolerated."	Data suggest 20 mg dose of vortioxetine comparable to duloxetine and both superior to placebo.
Jacobsen 2015 (score=4.5)	Vortioxetine	RCT	Sponsored by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S. COI, one or more	N = 462 with primary diagnosis of recurrent major depressive disorder	Mean age: 42.83 years; 127 males, 335 females	Vortioxetine 10 mg daily (n=155) vs. Vortioxetine 20 mg daily (n=150) vs. Placebo daily (n=157). Treatments	No long term follow-up	Mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS) at 8 weeks: placebo = -10.8, vortioxetine 10	"Vortioxetine 20 mg significantly reduced MADRS total score at 8 weeks in this study population. Overall,	Data suggest 20 mg vortioxetine superior to placebo at 8 weeks for treating adults with major depressive disorder.

			of the authors have received benefits for personal or professional use.	meeting DSM-IV criteria		administered for 8 weeks.		mg = -13.0 (difference from placebo = -2.2, p = 0.058), vortioxetine 20 = -14.4 (difference from placebo = -3.6, p = 0.002)	vortioxetine was well tolerated in this study."	

Antidepressant versus Antimanic Medications										
Lithium										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Fava 2002 (score=5.5)	Fluoxetine/Desipramine/Lithium	RCT	No mention of COI. Sponsored by the National Institute of Mental Health.	N = 101 participants who met DSM-III-R criteria for major depressive disorder	Mean age: 41.6 years; 52 males, 49 females	High dose Fluoxetine 40-60 mg/day (n=33) vs. Fluoxetine 20 mg/day and Desipramine 25-50 mg/day (n=34) vs. Fluoxetine 20 mg/day and lithium 300-600 mg/day (n=34). All treatments administered daily for four weeks	Follow-up at 1, 2, 3 and 4 weeks	Mean change in Hamilton Depression Rating Scale scores from baseline to posttreatment: high-dose fluoxetine = 5.1, fluoxetine and desipramine = 3.5, fluoxetine and lithium = 3.6 (F = 0.9, p = 0.4)	"We found not significant differences in efficacy among these three treatment strategies among patients who had failed to respond adequately to 8 weeks of treatment of fluoxetine 20 mg/day, although the high-fluoxetine group was associated with nonsignificantly higher response rates in both partial	Data suggest similar efficacy in all 3 groups with a trend towards higher response rates in the high fluoxetine group for both non-responders and partial responders. Limited information on baseline group details.

									responders and nonresponders."	
Bloch 1997 (score=5.5)	Desipramine/Lithium	RCT	No mention of COI. Sponsored by the Professor Milton Rosenbaum Endowment Fund for Research in the Psychiatric Sciences.	N = 31 participants meeting DSM-III-R criteria for major depressive disorder	Mean age: 47.45 years; 14 males, 17 females	Desipramine alone: 25 mg twice daily for 1 week, then increased to 150 mg/day, placebo given daily as well (n=15) vs. Desipramine and lithium: same desipramine dosage as above, lithium 300 mg twice daily for 1 week, then increased to 900 mg/day (n=16). All treatments administered for 5 weeks	Follow-up at weeks 1, 2, 3, 4, and 5	Significant treatment effect on Hamilton Depression Rating Scale scores (F5, 155 = 40.45, p < 0.001)	"Concurrent treatment with Lithium did not demonstrate an enhancement of either DMI's efficacy or its onset of action in these patients, suggesting that this strategy may not confer any additional benefit compared with DMI alone in mild or moderately depression patients who are not preselected	Small sample (n=31). Data suggest lack of efficacy of combining lithium with desipramine (i.e., no quicker onset of action nor better efficacy than desipramine, alone and the combination group experience more adverse effects).

									for nonresponse to an AD during their current depressive episode."	
Franchini 1994 (score=5.5)	Fluvoxamine/Lithium	RCT	No mention of sponsorship or COI.	N = 64 inpatients with unipolar recurrent major depressive episode (DSM-III-R)	Mean age: 49.6 years; 10 males, 54 females	Lithium Group: received 600-900 mg of lithium salts (n=32) vs Fluvoxamine Group: received 200 mg of fluvoxamine (n=32)	5, 10, 15, 20, 25 months	Patients in fluvoxamine group had a probability of not having recurrence of 87.5% at 22 months compared to 75% in lithium patients at 14 months. HDRS mean relapse score was 30.7±4.2 in lithium group compared to 34.2±54.6 in fluvoxamine group.	"Unipolar patients on lithium treatment had a worse outcome with a higher frequency on new recurrences compared with of new recurrences compared with patients on fluvoxamine during the course of preventive treatment."	Data suggest at 2 years, fluvoxamine treated patient had better treatment outcomes and fewer relapses than lithium treated patients.
Coppen 1976 (score=4.5)	Maprotiline/Lithium	RCT	No mention of COI or sponsorship.	N = 39 attending a lithium clinical for at least 1	Mean age: 51.54 years; 10 males,	Maprotiline – 150 mg/day (n=18) vs. Lithium carbonate –	Follow-up every six weeks for 11 months	Lithium group superior to maprotiline group for number of those who	"The study showed lithium to be significantly superior to maprotiline	Small sample sizes for both groups. High dropout rates attributed to adverse events. Data suggest lithium better than

				year and had at least three affective disorders attacks, no diagnostic criteria given	29 females	single dose to maintain plasma lithium level between 0.8 – 1.2 mEq/l in blood the following morning (n=21)		suffered no conspicuous affective morbidity during the trial ($p < 0.02$)	in its prophylactic antidepressant effect in unipolar affective disorders, and from this point of view we believe that the investigation is valuable in providing additional evidence for the prophylactic action of lithium in unipolar depressives even when it is measured against an active antidepressant and not an inert placebo."	maprotiline in treatment of unipolar depression.
Bauer 1999 (score=4.5)	Paroxetine/ Amitript	RCT	Sponsored by SmithKline Beecham	N = 42 participants on a stable	Mean age: 48.59 years;	Paroxetine 20 mg daily, then increased	Follow-up at weeks 1,	At 4 weeks patients taking paroxetine had higher	"The main finding of this study is that, in a	Small sample size. Data suggest after 4 weeks there were more patients

	yline/ Lithium		Pharma GmbH. No mention of COI.	lithium regimen with major depressive episode meeting DSM-III-R criteria	18 males, 24 females	to 40 mg daily after 2 weeks (n=19) vs. Amitriptyline 50 mg daily, then increased to 150 mg daily after 2 weeks (n=23). Medications given for six weeks	2, 3, 4, 5, and 6	proportion of 50% reduction in Hamilton Depression Rating Scale scores compared to amitriptyline group (79% vs. 39%, p = 0.04). At 6 weeks the difference was not significant.	population of patients on long-term lithium prophylaxis, the addition of paroxetine or amitriptyline to treat an episode of major depression seems to be effective and safe."	achieving a 50% reduction in HAM-D scores than in the amitriptyline group.

Antidepressant versus Antipsychotic Medications										
Amisulpride										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Ravizza 1999 (score=6.5)	Antipsychotic/Amisulpride/Amitriptyline	RCT	No mention of COI or sponsorship.	N = 253 participants with a dysthymia or single episode of major depressio	Mean age: 47.05 years; 90 males, 163 females	Amisulpride 50 mg/day (n=166) vs. Amitriptyline 25-75 mg/day (n=87). Medication	Follow-up at days 14 and 28 and months 2, 4, and 6	Montgomery and Asberg Rating Scale mean total score at baseline and 6-months: amisulpride = 21.0, 10.2,	"Results of the present study in a large patient population further confirm the safe use of amisulpride	Data suggest comparable drug efficacy in the treatment of dysthymia.

				n in partial remission (DSM-III-R criteria)		s were given for six months		amitriptyline = 21.7, 10.1 (p = 0.495)	in dysthymia and support its administration upon a medium-term treatment period."	
Amore 2001 (score=6.5)	Amisulpride/Sertraline	RCT	No mention of sponsorship or COI.	N = 313 patients with dysthymia with or without a superimposed episode of major depressive disorder (DSM-IV)	Mean age: 47.1 years; 100 males, 213 females	Amisulpride: received 50 mg/day of amisulpride for 12 weeks (n=157) vs Sertraline: received 50-100 mg/day of sertraline for 12 weeks (n=156)	5, 10, 15 days, 4, 8, 12 weeks	Reduction in HAM-D total score was achieved better in the amisulpride group compared to the sertraline group ($p<0.0121$). Response rate at 8 weeks for MADRS scale was 54% in amisulpride compared to 69% in sertraline.	"The tolerability of both drugs was satisfactory. Amisulpride is significantly more effective than sertraline during the first weeks of treatment in dysthymia."	Data suggest faster onset of action of amisulpride than sertraline at 4 weeks and faster time to initial improvement, but at week 12 both drugs showed comparable efficacy.
Boyer 1999 (score=6.0)	Amineptine/Amisulpride	RCT	No mention of COI or sponsorship.	N = 323 participants meeting DSM-III-R for	Mean age: 48 years; 81 males,	Amisulpride – 50 mg/day (n=104) vs. Amineptine – 200	Follow-up at 1 week and 1, 2, and 3 months	Montgomery-Asberg Depression Rating Scale (MADRS) mean score	"Results show that amisulpride can improve symptoms of chronic	Data suggest amisulpride comparable to amineptine and both medications are superior to placebo.

				primary dysthymia	242 females	mg/day (n=111) vs. Placebo (n=108). All medications given for 3 months		changes: placebo = -3.8, amisulpride = -8.6, amineptide = -8.2 ($p < 0.0001$). Scale for the Assessment of Negative Symptoms (SANS) mean score changes: placebo = -11.2, amisulpride = -17.6, amineptide = -19.9 ($p < 0.0001$)	depression in dysthymia."	
Boyer 1996 (Study 1: score=6.0, Study 2: score=5.5)	Amisulpride/ Amineptine/ Imipramine	2 RCTs	No mention of sponsorship or COI.	Study 1: N = 323 patients with primary dysthymia with or without major depressive episode (DSM-III-R) Study 2: N = 219 patients	Study 1: Mean age: 48.2 years; 81 males, 242 females Study 2: Mean age: 42.9 years; 99 males,	Study 1: Amisulpride: received 50 mg/day amisulpride for 3 months (n=104) vs Amineptine: received 200 mg/day amineptine for 3 months (n=111) vs	Study 1: 8 days, 1, 2, 3 months Study 2: 6 months	Study 1: Reduction in MADRS score was -8.63 in amisulpride and -8.21 in amineptine compared to -3.81 in placebo ($p=0.0001$). Study 2: MADRS score was reduced by -12.3 in amisulpride, -10.6 in	"Results of the intention to treat analysis and of the end-point analysis were compelling and very similar: significant differences were demonstrated for all	Data suggest in both studies amisulpride, imipramine, and amineptine were better than placebo vis MADRS, CGI, and SANS scores. However, in study 2, the 6 month study amisulpride more efficacious than imipramine.

				with dysthymia or major depression (DSM-III-R)	120 females	Placebo: (n=108) Study 2: Amisulpride: received 50 mg/day amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine (n=73) vs Placebo: (n=73)		imipramine, and -7.2 in placebo (placebo vs imipramine p=0.036, placebo vs amisulpride p<0.002, global p=0.007).	primary criteria between amisulpride and placebo and between imipramine and placebo but not between amisulpride and imipramine. For both primary criteria and the responder rate (CGI). Statistically significant differences were evidenced between amisulpride and placebo and amineptine and placebo."	
Lecrubier 1997 (score=5.5)	Amisulpride/ Imipramine	RCT	No mention of sponsorship or COI.	N = 219 patients with primary	Mean age: 42.9 years;	Amisulpride: received 50 mg/day of	1, 3, 6 months	Response rate was 33.3% in the placebo group, 68.6%	"These results confirm the interest of a	Data suggest comparable efficacy between amisulpride and imipramine with

				dysthymia, dysthymia with major depression, or isolated chronic major depression (DSM-III-R)	99 males, 120 females	amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine for 6 months (n=73) vs Placebo: (n=73)		in the imipramine group, and 72.2% in the amisulpride group. A MADRS score reduction ≤7 was achieved in 21.9% of placebo, 32.9% in imipramine group, and 35.6% in amisulpride (placebo vs imipramine p=0.032, placebo vs amisulpride p=0.004, imipramine vs amisulpride p=0.01).	drug acting on dopaminergic transmission such as amisulpride in the treatment of depressed patients."	both drugs performing significantly better than placebo.
Smeraldi 1998 (score=5.5)	Amisulpride/ Fluoxetine	RCT	No mention of sponsorship or COI.	N = 268 patients with dysthymia or a single episode of major depression (DSM-III-R)	Mean age: 49.4 years; 86 males, 182 females	Amisulpride: received 50 mg/day of amisulpride for 3 months (n=139) vs Fluoxetine: received 20 mg/day of	3 months	MADRES score reduction of ≥50% was achieved in 74% in amisulpride and in 67% in fluoxetine group (p=0.23). Response rate was 73% in	"No statistically significant differences were found between the two drugs for MADRS, ERD, Sheehan	Data suggest a similar response rate as measured by a decrease in MADRS score of at least 50% but the fluoxetine group was slightly (non-statistically significantly) better than amisulpride group in partial

						fluoxetine for 3 months (n=129)		amisulpride compared to 67% in fluoxetine (p=0.316).	Disability Scale, and CGI."	depressive remission.
Cassano 2002 (score=5.5)	Amisulpride/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 275 patients with major depressive disorder (DSM-IV)	Mean age: 51.25 years; 63 males, 200 females	Amisulpride: received 50 mg/day amisulpride for 8 weeks (n=136) vs Paroxetine: received 20 mg/day of paroxetine for 8 weeks (n=136)	7, 14, 28, 42, and 56 days	Response rate was 76% in amisulpride compared to 84% in paroxetine. Remission in HAM-D total score was reduced in both groups, but was similar (p=0.37).	"In conclusion, in the present study, paroxetine and amisulpride were highly effective and well tolerated. We believe that statistical results of a non-inferiority trial should be carefully evaluated in the light of the overall study findings."	Data suggest therapeutic equivalence between amisulpride and paroxetine at 8 weeks with tolerability favoring amisulpride.
Standish-Barry 1983 (score=4.0)	Amitriptyline/Amisulpride	RCT	Sponsored by Chemitechna Ltd. No	N = 36 patients with major	Mean age: 44 years; 22	Sulpiride Group: received 200-400	4, 6, 12, 24 weeks	Amitriptyline group showed a greater reduction on	"Our results show that sulpiride appears to	Data suggest at 24 weeks, amitriptyline was better than sulpiride.

			mention of COI.	depressive disorder (DSM-III)	males, 20 females	mg daily sulpiride (n=18) vs Amitriptyline Group: received 50-150 mg daily of amitriptyline (n=18) All patients received medication for 24 weeks.		Hamilton and Wakefield scores compared to sulpiride group ($p<0.05$).	have antidepressant and anxiolytic properties comparable to amitriptyline up to 12 weeks of treatment."	
Aripiprazole										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Mohamed 2017 (score=4.5)	Aripiprazole, Bupropion	RCT	Sponsored by Veterans Affairs Cooperative Studies Program and Bristol-Myers Squibb. One or more of the authors have received or will receive benefits for personal or	N = 1522 US Veterans Health Administration patients with anti-depressant resistant Major Depressive Disorder diagnosis	Mean age: 54.4 years; 1296 male, 226 female	Switched antidepressant medication to bupropion (starting dose 150 mg/d to 300-400 mg/d) (n=511) vs. Augmented current antidepressant	Follow up at baseline, 1, 2, 4, 6, 8, 10, and 12 weeks. Optional continuation phase had follow-ups at 16, 20, 24, 28,	Remission was higher for augmented aripiprazole group at 28.9% compared with switched group at 22.3% ($p=0.02$) but not significantly different than augmented bupropion group at 26.9% ($p=0.47$).	"Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically	Predominantly male pop. Data suggest benefit from aripiprazole augmentation in MDD patients who are unresponsive to ADT but this only resulted in a modest likelihood of remission.

			professional use.	according to DSM-IV-TR criteria		treatment with bupropion (starting dose 150 mg/d to 300-400 mg/d) (n=506) vs. Augmented current antidepressant treatment with aripiprazole at 2mg, 5mg, 20mg, or 15mg/d (n=505)	32, and 36 weeks.	Remission defined as a score of 5 or less on the QIDS-C16.	significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy."	
Han 2013 (score=4.5)	Aripiprazole, Escitalopram	RCT	Sponsored by Korea Otsuka Pharmaceuticals. No COI.	N = 35 patients with comorbid major depression and alcohol dependence according to DSM-IV criteria	Mean age: 39.6 years; 23 male, 12 female	Group 1: Given flexible dose of aripiprazole (5-15 mg) and escitalopram (10-20 mg) daily for 6 weeks (n=17) vs Group 2: Given 10-	Follow up at baseline, and 6 weeks	Mean Beck Depression Index (BDI) scores for Group 1 was 32.1 at baseline and 16.0 at week 6 (p=0.01). Mean BDI score for Group 2 was 29.6 at baseline and 16.9 (p<0.01). There	"The change of brain activity within the left anterior cingulate gyrus in all patients with co-morbid alcohol dependence and major depressive disorder was	Small sample. Data suggest escitalopram plus aripiprazole decreased alcohol craving and depression scores.

						20 mg of escitalopram daily (n=18).		were 4 non-responders in Group 1 and 6 non-responders in Group 2 (p=0.15).	negatively correlated with the change in craving for alcohol. These findings suggest that the effects of aripiprazole on anterior cingulate cortex might mediate the successful treatment of alcohol dependence in patients with major depressive disorder."	
Buspirone										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Trivedi 2006 (score=4.0)	Bupropion/ Citalopram/Buspirone	RCT	Sponsored by the National Institute of Mental Health, National	N = 565 patients with nonpsychotic major depressiv	Mean age: 41.1 years; 233 males,	Augmentation of citalopram with sustained-release bupropion.	Follow-up at 2, 4, 6, 9, and 12 weeks	Both treatments had similar rates for Hamilton Rating Scale for Depression remission	"Augmentation of citalopram with either sustained-release bupropion	Data suggest similar efficacy between bupropion SR and buspirone for prevention of depression relapse.

			Institutes of Health. COI, one or more authors have received or will received benefits for personal or professional use.	e disorder without remission who had received 12 weeks of citalopram therapy, no mention of diagnostic criteria	332 females	Initial dose of sustained-release bupropion = 200 mg daily for 2 weeks, 300 mg daily at week 4, 400 mg daily at week 6 (n=279) vs. Augmentation of citalopram with buspirone. Initial dose of buspirone = 15 mg daily for 1 week, 30 mg daily for 1 week, 45 mg daily for weeks 3 to 5, 60 mg daily during week 6 (n=286).		(HRSD-17) (29.7% vs. 30.1%) and for 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR-16) remission (39.0% vs. 32.9%). Sustained-release bupropion had greater reduction QIDS-SR-16 scores (25.3% vs. 17.1%, p<0.04)	or buspirone appears to be useful in actual clinical settings."	

						All medications taken twice daily				
Chlorpromazine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Paykel 1968 (score=4.0)	Imipramine/Chlorpromazine	RCT	Sponsored by Geigy (UK) Ltd. No mention of COI.	N = 114 patients with a depressive illness suitable for drug treatment, no diagnostic criteria listed	Mean age and gender distribution only described for those included in analysis (n=99). Mean age: 41.5 years; 24 males, 75 females	Imipramine – four 25mg capsules taken daily for 2 days, then four 50mg capsules taken daily for 19 days (n=57) vs. Chlorpromazine – same dosage and timing as imipramine group (n=57)	No follow-up	No statistical difference between groups for Psychiatrists' Interview Scale scores, Nurses' Rating Scale scores, and Patients' Self-Rating Questionnaire scores (all p>0.05).	"None of the measures employed has revealed significant differences in symptom change between imipramine and chlorpromazine treatment in the overall groups of depressed patients in this study."	Data suggest comparable efficacy between drugs.
Deanxit										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:

Wang 2015 (score=6.0)	Sertraline /Deanxit	RCT	Sponsored by Guangdong Natural Science Foundation, Science and Technology Planning Project of Guangzhou City, and the fund of West China Psychiatric Association. No COI.	N = 75 patients diagnosed with depression by the HAM-D and anxiety with the HAM-A scales.	Mean age: 62.2 years; 28 males, 47 females.	Deanxit: Sertraline (75 mg/day) and deanxit (a combination medication of 10 mg melitracen and 0.5 mg of flupentixol- a tricyclic antidepressant and an antipsychotic) (one piece/day) (n=38) vs. Placebo: Sertraline (75 mg/day) and placebo (on piece/day) (n=37)	Follow-up at 2 weeks.	Overall, there was no distinct differences between the groups at the end point, with the exception of difference in scores between the deanxit and placebo group on day 8 (p=0.006) and day 15 (p=0.001). HAM-A scores were favoring the deanxit group on day 4, 8, and 15 (p=0.006, p=0.001, p=0.002).	"The rapid onset of sertraline plus short-term deanxit indicated that it might be an inspiring strategy to manage depression and anxiety within the first two weeks in chronic somatic diseases."	Data suggest sertraline plus short term deanxit may benefit patients with depression and anxiety.
Flupethixol										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:

Young 1976 (score=4.0)	Flupethixol, Amitriptyline	RCT	No mention of COI or sponsorship.	N = 60 participants with mild to moderately severe depression (no diagnostic criteria mentioned)	Age and sex data only available for 51 participants. Mean age: 37.35 years; 21 males, 30 females	Amitriptyline 75-225 mg/day (n=30) vs. Flupenthixol 1.5-4.5 mg/day (n=30). All treatments given for six weeks	Follow-up at weeks 1, 3, and 6	Mean scores of Hamilton Depression Rating Scale, Beck Depression Rating Scale, and overall severity did not statistically differ between treatment groups ($p > 0.05$)	"Flupenthixol, in low dosage, is a useful alternative antidepressant for depressed outpatients."	Small sample. Data suggest similar efficacy with a slight trend favoring flupenthixol.
Fluphenazine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
O'Hara 1978 (score=4.5)	Maprotiline, Fluphenazine, Nortriptyline	RCT	No mention of COI or sponsorship.	N = 75 participants with disorders on the spectrum of depressive conditions, no formal diagnostic criteria given	Mean age: 52 years; gender distribution not specified	1.5 mg fluphenazine and 30 mg nortriptyline per day (n=34) vs. 75 mg maprotiline daily (n=37). Both treatments given for four weeks	Follow-up at days 3, 10, and 28	Mean adjusted Clinical rating scale scores for depression at day 28 for combination medication = 0.96 ($p < 0.05$), for maprotiline = 1.33 ($p > 0.05$)	"The greater antidepressant effect of fluphenazine/nortriptyline after 4 weeks' treatment was the continuation of the trend already evident at day 10, and thus	Data suggest maprotiline better than combination fluphenazine/nortriptyline (Motipress).

									followed a similar time course to that expected of the antidepressant effect of tricyclic compounds.”	
Haloperidol										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Klieser 1989 (score=5.5)	Trazodone/Amitriptyline/Haloperidol	RCT	No mention of COI or sponsorship.	N = 45 patients with major depressive disorder and 75 with acute schizophrenia, no diagnostic criteria listed	Mean age: 42.6 years; 49 males, 71 females	400 mg trazodone daily (n=30) vs. 20 mg haloperidol daily (n=30) vs. 150 mg amitriptyline daily (n=30) vs. Placebo daily (n=30). All treatments given for three weeks	No follow-up	Hamilton Depression Rating Scale (HAM-D) scores decreased in all drug treatments. Mean change in HAM-D scores at 3 weeks: trazodone = -3.1, amitriptyline = -12.1, haloperidol = -4.0, placebo = -4.1	“After only 7 days of trazodone treatment, a relatively reliable decision can be established as to whether a therapeutically success can be expected if treatment is continued.”	Mixed population of depression and schizophrenic patients. Data suggest trazodone appears to not have antipsychotic action on schizophrenia but depression patients did respond to trazodone.

Olanzapine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Meyers 2009 (score=6.0)	Sertraline /Olanzapine	RCT	Sponsored by United States Public Health Services and the National Institute of Mental Health. No COI.	N = 259 patients with unipolar MDpsy with a score of 2 or less on the Delusional Assessment Scale (DAS) and a score 3 or less on the Schedule of Affective Disorder and Schizophrenia (SADS).	Mean age: 58.0 years; 103 males, 156 females	Sertraline + Olanzapine: 150-200 mg/day of sertraline and 15-20 mg/day of olanzapine (n=129) vs. Olanzapine + Placebo: 15-20 mg/day of olanzapine and 150-200 mg/day of placebo (n=130)	Follow-up every week until 6 weeks, then every other week until 12 weeks.	Combination therapy was found to be superior in in young adults than older adults (p=.02, p=0.01). Olanzapine/Sertraline was seen to have higher remission rate when compared to Olanzapine/placebo (p<.001).	"Combination pharmacotherapy is efficacious for the treatment of MDpsy. Future research must determine the benefits of continuing atypical antipsychotic medications beyond twelve weeks against the associated metabolic effects."	High attrition rate. Data suggest combination therapy in beneficial for psychotic depression.
Shelton 2005 (score=4.5)	Nortriptyline/Fluoxetine/Olanzapine	RCT	Sponsored by Eli Lilly and Company.	N = 500 subjects with unipolar,	Mean age: 42.4 years;	OFC: received either 6 mg/day	0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks	OFC group showed a greater decrease in	"The olanzapine/fluoxetine combination	Data suggest comparability of all 4 treatment groups but combo

			COI: One or more of the authors have received or will receive benefits for personal or professional use.	nonpsychotic MDD (DSM-IV)	160 males, 340 females	olanzapine and 25 mg/day fluoxetine or 12 mg/day olanzapine and 50 mg/day fluoxetine (n=146) vs OLZ: received 6 mg/day of olanzapine (ranged from 6-12 mg/day (n=144) vs FLX: received 25 mg/day fluoxetine (ranged from 25-50 mg/day) (n=142) vs NRT: received 25 mg/day nortriptyline (increased to 50 mg/day on		MADRS scores than OLZ group (p=0.005). Remission rates were 16.9% for OFC group, 12.9% for OLZ group, 13.3% for FLX, and 18.2% for NRT group (p=0.62).	did not differ significantly from the other therapies at endpoint, although it demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization."	olanzapine/fluoxetine resulted in a quicker response.

						day 2, and 75 mg/day by day 4) (n=68)				
Corya 2006 (score=4.0)	Olanzapine/Fluoxetine/Venlafaxine	RCT	Sponsored by Lilly Research Laboratories. No mention of COI.	N = 483 subjects with major depressive disorder (DSM-IV)	Mean age: 45.7±10.8 years; 133 males, 350 females	All groups received medications for 12 weeks. Group 1: received 1 mg/day of olanzapine and 5 mg/day of fluoxetine (n=59) vs Group 2: received 6 mg/day of olanzapine and 25 mg/day fluoxetine (n=63) vs Group 3: received 6 mg/day of olanzapine and 50 mg/day of fluoxetine (n=63) vs Group 4: received 12	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks	For analysis, group 1-5 were combined. Group 1-5 showed a greater improvement in MADRS mean score (-7.2) compared to group 6 (-4.8, p=0.03), group 7 (-4.7, p=0.03), and group 8 (-3.7, p=0.002). Groups 1-5 showed greater advantage to group 6 overall (-14.1 vs -7.7, p<0.001).	"In conclusion, the OFC showed a rapid and robust antidepressant effect in this sample of TRD patients, along with a safety profile comparable to its component monotherapies."	No baseline data stratified by group. Data suggest similar efficacy between olanzapine, fluoxetine, venlafaxine, and combination olanzapine/fluoxetine for the treatment of treatment resistant depression.

						mg/day olanzapine and 25 mg/day of fluoxetine (n=60) vs Group 5: received 12 mg/day olanzapine and 50 mg/day fluoxetine (n=57) vs Group 6: received 6 or 12 mg/day olanzapine (n=62) vs Group 7: received 25 mg/day or 50 mg/day of fluoxetine (n=60) vs Group 8: received 75-375 mg/day of venlafaxine (n=59)				

Brunner 2014 (score=4.0)	Olanzapine/Fluoxetine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 444 patients with single or recurrent unipolar mild depressive disorder (DSM-IV-TR)	Mean age: 44.4 years; 513 males, 1034 females	OFC Group: received an initial dose of 3 mg/day olanzapine and increased up to 18 mg/day and an initial dose of 25 mg/day fluoxetine and increased up to 50 mg/day (n=221) vs Fluoxetine Group: received 25-50 mg/day of fluoxetine (n=223) for 27 weeks	12 weeks, then weekly thereafter until week 47	Relapse time was longer in OFC group compared with fluoxetine group ($p<0.001$). Mean MADRS score change was 30.4 to 9.3.	"We believe this is the first controlled relapse-prevention study in subjects with TRD that supports continued use of a second-generation antipsychotic beyond stabilization."	High dropout rates. Data suggest time to relapse was significantly longer in the combo olanzapine/fluoxetine group.
Perphenazine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Anton 1993 (score=4.5)	Amitriptyline/ Amoxapi	RCT	Sponsored by Lederle Laboratories	N = 37 inpatients, 21	Mean age: 45.97	Amoxapine 100 mg four times	No follow-up	Through ANCOVA analysis on	"The data suggest that classifying	Small sample size. Data suggest comparable efficacy

	ne/ Perphenazine		, a division of American Cyanamid. No mention of COI.	having mood congruent (MC) psychotic depression and 16 having mood incongruent (MI) psychotic depression, all meeting DSM-III criteria for major depression with psychotic features	years; 32 males, 5 females	a day (n=17) vs. Amitriptyline 50 mg + Perphenazine 8 mg daily four times a day (n=20). All treatments were given for 4 weeks		Hamilton Rating Scale for Depression score a main effect for treatment was present (F = 12.13, p < 0.002)	psychotic depression into MC versus MI subtypes may have limited acute prognostic value in pharmacotherapy response rates."	in the treatment of psychotic depression subtypes between amoxapine and combination amitriptyline-perphenazine.
Spiker 1985 (score=4.5)	Perphenazine, Amitriptyline	RCT	Sponsored by NIMH grants. No mention of COI.	N = 58 patients with major depressive disorder, primary type, and psychotic subtype, according to the	Mean age: 44.1 years; 22 males, 36 females	Amitriptyline at 50 mg 4 times per day (n=19) vs. Perphenazine 16 mg 4 times per day (n=17) vs. amitriptyline at 50 mg +	Follow-up at days 7, 14, 21, 28 and 35	Mean HAMD score decreased from 26.0 to 13.1 in perphenazine group, from 30.6 to 11.6 in amitriptyline group, and from 28.7 to 5.6 in amitriptyline plus	"[T]his study demonstrated that although there are clearly some patients who respond to amitriptyline alone, and to perphenazin	Data suggest combination amitriptyline and perphenazine resulted in a better response than either amitriptyline or perphenazine alone.

				Research Diagnostic Criteria (RDC)		perphenazine at 16 mg 4 times per day (n=22)		perphenazine group (p=0.01).	e alone, amitriptyline plus perphenazine is the treatment of choice."	
Quetiapine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Wijkstra 2010 (score=6.5)	Quetiapine/ Venlafaxine/ Imipramine	RCT	Sponsored by grants from AstraZeneca and Wyeth Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 122 patients with psychotic major depression (DSM-IV-TR)	Mean age: 50.6 years; 60 males, 62 females	Imipramine: received 75-450 mg/day of imipramine (n=42) vs Venlafaxine: received 75-375 mg/day of venlafaxine (n=39) vs Quetiapine: received 75-375 mg/day of venlafaxine and 100-600 mg/day of quetiapine (n=41) All patients were	1, 2, 3, 4, 5, 6, 7 weeks	Quetiapine group showed a better outcome of reduced HAM-D score compared to venlafaxine (OR=3.86, 95% cI 1.53-9.75). Imipramine did not show a greater improvement compared to venlafaxine group (OR=2.20, 95% CI 0.89-5.41) nor did quetiapine compared to imipramine (OR=1.75, 95% CI 0.72-4.25).	"That unipolar psychotic depression should be treated with a combination of an antidepressant and an antipsychotic and not with an antidepressant alone, can be considered evidence based with regard to venlafaxine –quetiapine vs.	Data suggest the addition of an antipsychotic to an antidepressant is superior to antidepressant therapy alone (venlafaxine-quetiapine).

						treated for 7 weeks.			venlafaxine monotherapy. Whether this is also the case for imipramine monotherapy is likely, but cannot be concluded from the data. "	
Cutler 2009 (score=6.0)	Quetiapine/ Duloxetine	RCT	Sponsored by AstaZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 612 patients with mild depressive disorder (DSM-IV)	Mean age: 41.3 years; 233 males, 354 females	Duloxetine: received 60 mg/day of duloxetine (n=141) vs Placebo: (n=152) vs Quetiapine XR 150: received 150 mg/day of quetiapine XR (n=147) vs Quetiapine XR 300: received 300 mg/day of quetiapine	1, 2, 4, 6 weeks	Mean MADRS score was reduced by 14.81 in quetiapine XR 150 group (p<.001), 15.29 in quetiapine XR 300 group (p<.001), and 14.64 in duloxetine (p<.01), and 11.18 in placebo. Response rates were 54.4% in quetiapine XR 150, 55.1% in quetiapine XR 300, 49.6% in	"Quetiapine XR monotherapy (150 mg/day and 300 mg/day) is effective, with safety and tolerability consistent with the known profile of quetiapine XR, in the treatment of patients with MDD, with onset of symptom	Data suggest at week 6 there were significantly improved MADRS scores with both doses of quetiapine and duloxetine compared to placebo. Remission rates were also improved in quetiapine 300 mg and duloxetine but not 150 mg quetiapine improvement with quetiapine occurs as early as week one.

						XR (n=147)		duloxetine, and 36.2% in placebo.	improvement demonstrated at week 1."	
McIntyre 2007 (score=5.5)	Quetiapine/ Venlafaxine	RCT	No mention of sponsorship or COI.	N = 58 patients with a diagnosis of major depression (DSM-IV)	Mean age: 44.5 years; 22 males, 36 females	Quetiapine: received 50-200 mg/day (n=29) vs Venlafaxine: no specific dose of venlafaxine (n=29)	1, 2, 4, 6, 8 weeks	Response rates for HAM-D (≥50% reduction) were 48% in quetiapine and 28% in placebo (p=0.008). HAM-A response rate (≥50% reduction) was 62% in quetiapine and 28% in placebo (p=0.002).	"In summary, quetiapine as an adjunct to an SSRI/SNRI was effective in reducing symptoms of major depressive disorder and comorbid anxiety in patients who had residual depressive symptoms despite having received treatment with an SSRI/SNRI."	Data suggest quetiapine added to SSRI/venlafaxine patients with major depression was significantly better than placebo in improving depressive symptoms.
Wang 2014 (score=5.5)	Quetiapine/	RCT	Sponsored by AstaZeneca	N = 471 patients with mild	Mean age: 40.0	Quetiapine XR: received	1, 3, 5, 7, 14	Reduction in MADRS total score was -	"In this study, neither	Data suggest lack of efficacy as neither quetiapine XR at

	Escitalopram		Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	depressive disorder (DSM-IV)	years; 131 males, 328 females	150 mg/day of quetiapine XR (50 mg for 2 days, then increased to 150 mg on days 3-14) if no response, increased to 300 mg/day for remainder of study (n=154) vs Escitalopram: received 10 mg/day of escitalopram (n=152) vs Placebo: (n=153)	days, 8 weeks	17.21 (p=0.174) in quetiapine XR, -16.73 (p=0.346) in escitalopram, compared to -15.61 in placebo. Response rate was 44.8% (p=0.376) in quetiapine XR, 48.0% (p=0.157) in escitalopram, compared to 40.5% in placebo.	quetiapine XR (150/300 mg/day) nor escitalopram (10/20 mg/day) showed significant separation from placebo. Both compounds have been shown previously to be effective in the treatment of MDD; possible reasons for this failed study are discussed. Quetiapine XR was generally well tolerated, with a profile similar to	150 mg/d or 300 mg/d nor escitalopram 10 mg/d were significantly better than placebo in treating patients with MDD.

									that reported previously."	

Sulpiride										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Uchida 2005 (score=4.5)	Sulpiride, Paroxetine	RCT	No mention of COI or sponsorship.	N = 41 participants meeting DSM-IV criteria for major depressive disorder without psychotic features	Mean age: 38.94 years; 25 males, 16 females	Paroxetine 10-40 mg/day plus Sulpiride 100 mg/day (n=20) vs. Paroxetine 10-40 mg/day alone (n=21)	Follow-up at weeks 1, 2, 4, 6, 8, and 12	Mean change in Montgomery-Asberg Depression Rating Scale: Paroxetine + sulpiride group = 34.4 to 5.6, Paroxetine alone group = 32.2 to 10.4 ($p < 0.001$). Combined group had greater reduction in Hamilton Rating Scale for Depression and Zung Depression Scale scores between week 1 and 12 ($p < 0.05$)	"The combination treatment may be a safe and effective strategy for accelerating antidepressant response."	Small study sample. Open label trial. Data suggest addition of sulpiride to paroxetine resulted in significant improved depression scores.
Thioridazine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:

Stabl 1995 (score=6.0)	Moclobemide/Thioridazine	RCT	No mention of sponsorship or COI.	N = 78 patients with severe depression (DSM-III-R)	Mean age: 52.0 years; 34 males, 44 females	Group 1: received 150 mg moclobemide 3 times daily and 100 mg placebo for 4 weeks (n=40) vs Group 2: received 150 mg moclobemide and 100 mg thioridazine 3 times daily for 4 weeks (n=38)	3, 7, 14, 21, 28 days, 4 weeks, 6 months	Improvement in depression of at least 50% was observed in 77% of group 1 compared to 74% in group 2 (p>0.2).	"[T]he study shows a remarkable antidepressant effect of moclobemide in severe refractory depression, even in patients with an existing depressive episode of long duration. The addition of thioridazine did not further increase efficacy or speed of onset. Moclobemide was well tolerated, and the addition of thioridazine did not significantly impair its tolerability."	Small sample size per group. Data suggest addition of thioridazine did not increase efficacy of moclobemide.

Thioridazine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Papakostas 2015 (score=7.5)	Ziprasidone, Escitalopram	RCT	Sponsored by the NIMH, Pfizer and Forest Laboratories. COI, one or more of the authors have received or will receive benefits for personal or professional use	N = 139 participants who had 8 weeks of open-label escitalopram and still met DSM-IV criteria for major depressive disorder	Mean age: 44.46 years; 41 males, 98 females	Escitalopram 10-30 mg/day plus Ziprasidone dosage range of 20–80 mg twice daily (n=71) vs. Escitalopram 10-30 mg/day plus placebo of 20–80 mg twice daily (n=68). All treatments were given for 8 weeks	Follow-up at weeks 1, 2, 3, 4, 5, 6, 7 and 8	Mean improvement in Hamilton Depression Rating Scale scores at 8 weeks: ziprasidone group = -6.4, placebo group = -3.3 (p=0.04)	"Ziprasidone as an adjunct to escitalopram demonstrated antidepressant efficacy in adult patients with major depressive disorder experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram."	Data suggest ziprasidone as adjunctive therapy to escitalopram shows efficacy in patients with MDD who have persistent symptoms after 8 weeks of escitalopram monotherapy.

Antidepressant versus Anxiolytic Medications										
Adinazolam										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Kennedy 1991 (score=5.0)	Adinazolam/ Desipramine	RCT	Sponsored by Upjohn Canada. No mention of COI.	N = 31 participants meeting DSM-III-R criteria for major depressive disorder	Mean age: 42.52 years; 6 males, 25 females	Adinizolam 10 mg daily for three days, then increased to 120 mg daily (n=16) vs. Desipramine 25 mg daily for three days, then increased to 300 mg daily (n=15). Medications administered for six weeks	Follow-up at weeks 1, 2, 3, 4, 5, and 6	No significant between group differences or group x time interactions for Hamilton Depression Rating Scale scores between the two treatments (p > 0.05)	"In this study patients treated with adinazolam had a comparable response to desipramine in both measures of depression and anxiety."	Small sample size (n=31). Data suggest comparable response to both adinazolam and desipramine in treatment of major depression.
Alprazolam										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Singh 1988 (score=4.5)	Amitriptyline Hydrochl	RCT	No mention of sponsorship or COI.	N = 130 outpatients with a clinical	Mean age: 38.9 years;	Alprazolam Group: received 0.5 mg	1, 2, 3, 6 weeks	Mean HAM-D score decreased 77% in the alprazolam	"In this study, both alprazolam and	Data suggest comparable efficacy in non-clinically

	oride/Alprazolam			diagnosis of moderate depression (ICD-9)	73 males, 57 females	alprazolam (n=67) vs Amitriptyline Group: received 25 mg amitriptyline hydrochloride (n=63) All patients received a daily maximum of nine capsules (4.5 mg alprazolam, 225 mg amitriptyline hydrochloride)		group compared to 72% in the amitriptyline group (p>0.01).	amitriptyline hydrochloride produced significant improvement in the symptoms of nonpsychotic depression."	depressed outpatients.
Remick 1985 (score=4.5)	Alprazolam, Desipramine	RCT	No mention of COI or sponsorship.	N = 54 participants with major depressive disorder as defined by Research Diagnosti	Mean age: 37.85 years; 19 males, 33 females (gender data only availabl	Alprazolam 0.5 mg capsules, 3-9 capsules given daily to outpatients, 3-12 capsules given daily to inpatients	Follow-up at weeks 1, 2, 4 and 6	Main effect for medication on Hamilton Depression Rating Scale scores (F=4.16, p=0.044), with alprazolam being higher.	"Alprazolam appeared as effective as desipramine in the pharmacotherapy of this group of depressed outpatient and	Data suggest a trend towards desipramine being better than alprazolam in moderately severely depression patients but not significant. Both drugs had only modest efficacy with alprazolam being associated with

				c Criteria (RDC)	e for 52 participants)	(n=29), Desipramine 25 mg capsules, same capsule count given as the group above (n=25). Medications for both groups administered for six weeks			inpatients. Alprazolam appeared well-tolerated by most subjects although drowsiness was a common – and at times serious – medication side effect."	excessive drowsiness.

Antidepressant versus Allied Health Interventions										
Acupuncture										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Qu, 2013 (score=6.0)	Acupuncture/Paroxetine	RCT	Sponsored by Key Project of the National Eleventh-Five Year Research Program of China, Key Project of Phase III	N = 160 patients with a diagnosis of MDD via the International Classification of Diseases (10th	Mean age: 33.3 years; 75 males, 85 females.	Group 1: Paroxetine (PRX) alone – those not medicated had initial dose of 10 mg/day, escalated to 20 mg/day in one	Follow-up at 1 month.	Group comparisons through HAMD-17 revealed significant differences between the 3 (PRX— r2= 0.725; MA + PRX -- r2= 0.655; EA +	"[A]s most antidepressant agents have broad side effects, acupuncture in manual and electrical stimulation modes provides a	Contact bias with acupuncture group. Data suggest electrical acupuncture better than manual acupuncture for sustained benefits and may be synergistic with antidepressant

			of Guangdong and General Research Fund of Research Grant Council of HKSAR. No COI.	version) (ICD-10)		week, PRX taken for 6 weeks (n = 48) vs. Group 2: Manual manipulation acupuncture treatment (MA), 3 30-minute sessions per week for 6 weeks, along with PRX (n = 54) vs. Group 3: Manual manipulations with electrical stimulation (EA), 3 30-minutes sessions per week for 6 weeks, along with PRX (n = 58)		PRX -- r2 = 0.784). MA and EA treatments produced significantly higher reductions in scores compared to PRX alone (p=0.000), although no noteworthy differences were demonstrated through the two acupuncture groups. Higher response rates were seen through the MA and EA groups compared to PRX (69.8% and 69.6% vs 41.7%, p= 0.004).	safe and effective treatment in augmenting the antidepressant efficacy and reducing the incidence of exacerbation of depression in the early phase of SSRI treatment."	effects like those from Paroxetine.
Acupuncture										

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lam 2006 (score=9.0)	Light Therapy	RCT	One or more of the authors is a consultant or on the Speaker/Advisory Boards or has received research funds from: AstraZeneca, Canadian Institutes of Health Research, Eli Lilly, GlaxoSmith Kline, Janssen, Lundbock, Merck, Roche, Servier, Vancouver Hospital Foundation, and Wyeth.	N = 96 patients with a DSM-IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.	Mean age: 43.5 years; 32 males, 64 females.	Light group: Exposure to white fluorescent light box (Model Daylight 10000, ultraviolet filter, rated at 10,000 lux at distance of 14 in from screen to cornea),with 20mg placebo pill 30 minutes after waking up (n=48) vs Fluoxetine group: Identical light box fitted with a neutral density gel filter to reduce light	Follow up at weeks 1, 2, 4, and 8 or at unexpected termination.	No significant differences between light and fluoxetine group for clinical response rate ($\chi 2=0$, df=1, p=1.00) and CGI improvement since last visit (mean=1.90 [SD=1.15] versus 1.92 [SD=1.09], respectively) (t=0.09, df=94, p=0.93). Light group had greater improvement at only week 1. Fluoxetine group had greater treatment emergent adverse events.	"Light treatment showed earlier response onset and lower rate of some adverse events relative to fluoxetine, but there were no other significant differences in outcome between light therapy and antidepressant medication."	Data suggest light treatment resulted in an earlier response rate compared to fluoxetine but otherwise comparable efficacy.

						exposure to 100 lux, with 20mg of fluoxetine 30 minutes after waking up (n=48)				
Michalak 2007 (score=NA)	Light Therapy	CAN-SAD study/ secondary analyses	Sponsored by the Canadian Institutes of Health Research. No COI.	N = 96 patients with a DSM-IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.	Mean age: 66.7 years; 32 males, 64 females	Light group: 10,000 lux light treatment (Uplift Technologies Inc., Model Daylight) and a placebo (n=48) vs Fluoxetine group: 100 lux light and 20mg of fluoxetine. (n=48) Light treatment was done asap after waking up between	Follow up at 1, 2, 3, 4, 5, 6, 7, and 8 weeks	Q-LES-Q measures in the light group had average improvements (20.56; SD=13.11) compared with fluoxetine group (21.77; SD=17.04) [F(1,79=0.13, N.S.]. SF-20 scores in the light group was 7.82 (SD=15.49) vs 9.38 (SD=14.39) in the fluoxetine group [F(1,79=0.22, N.S.]	"Patients with SAD report markedly impaired QoL during the winter months. Treatment with light therapy or antidepressant medication is associated with equivalent marked improvement in perceived QoL. Studies of treatment interventions for SAD	Data suggest quality of life markedly improved with light therapy suggesting it has similar benefits as antidepressant therapy.

						07:00 and 08:00 hours. Medication treatment was taken daily after light treatment. Treatments lasted for 8 weeks.			should routinely include broader indices of patient outcome, such as the assessment of psychosocial functioning or life quality."	
Enns 2006 (score=NA)	Light Therapy	CAN-SAD post hoc analyses	Sponsored by the Canadian Institutes of Health Research. No mention of COI.	N = 95 patients with a DSM-IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depressi	Mean age: 43.8 years; 32 males, 63 females	Light group: Received light therapy (10,000 lux) for 30 min in the morning and a placebo pill daily for 8 weeks. (n=48) vs Fluoxetine group: Received fluoxetine (20mg) and morning dim light	Follow up at 8 weeks and during summer (July or August)	Mean BDI-II score of SAD was 23.8 while non-SAD was 23.7. Sad group had lower neuroticism scores but higher openness scores than non-SAD group.	"The personality profile of SAD patients differs from both non-seasonal depressed patients and norms. Elevated openness scores appear to be a unique feature of patients with SAD. Since mood state has a	Data suggest personality profile of SAD patients different from non-seasonal depressed patients as SAD patients tend to be more open

				on Rating Scale.		exposure (200 lux) daily for 8 weeks. (n=48)			significant impact on personality scores, assessment of personality in SAD patients should ideally be conducted when they are in remission."	
Lam 2016 (score=8.0)	Light Therapy	RCT	Sponsored by grant MCT-94832 from the Canadian Institutes of Health Research. One or more of the authors have received research funds, grants, honoraria, or have served on the advisory boards.	N = 122 adults with MDD (DSM-IV-TR) of at least moderate severity in outpatient psychiatry clinics in academic medical centers, MDD diagnosis	Mean age: 36.8 years; 46 males, 76 females.	10,000-lux fluorescent white light box for 30 min/d in morning plus 20mg placebo (n=32) vs Inactive negative ion generator for 30 min/d plus fluoxetine hydrochloride, 20mg/d) (n=31) vs	Follow up at weeks 0, 1, 2, 4, 6, and 8 or at unexpected termination	Mean (SD) changes in MADRS score for the light was 13.4 (7.5), fluoxetine was 8.8 (9.9), combination was 16.9 (9.2), and placebo was 6.5 (9.6). Combination therapy was better than placebo in MADRS response (β = 1.70; df = 1; P = .005)	"Bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with non-seasonal MDD. The combination treatment	Data suggest all treatment groups improved but that combination bright light and fluoxetine therapy was most efficacious

				confirmed with Mini International Neuropsychiatric Interview (MINI), also had Hamilton Depression on Rating Scale score of 20 or above		Receiving light therapy and fluoxetine (n=29) vs Sham light therapy and placebo. (n=30). All patients took the pill every morning			had the most consistent effects."	
Ruhrmann 1998 (score=7.5)	Light Therapy	RCT	Sponsored by a grant from Eli Lilly, Germany. No mention of COI.	N = 42 patients with a total score of at least 16 on the 21-items Hamilton Depression on Rating Scale (HDRS) at entry and after the placebo phase	Mean age: 41.1 years; 9 males, 33 females.	Fluoxetine group: Placebo during the 1st week then 5 weeks placebo light condition and 20mg of fluoxetine per day (n=20) vs Bright light group: placebo	Follow up weekly	Remission rate in bright light (50%) was better than fluoxetine (25%) (p=0.10). HDRS scores improved faster in Light therapy than fluoxetine. However, atypical symptoms in fluoxetine had a quicker effect.	"Both treatments produced a good antidepressant effect and were well tolerated. An apparently better response to bright light requires confirmation in a larger sample."	Data suggest comparable efficacy between fluoxetine and bright light for the treatment of SAD

				(1st week)		during the 1st week then 5 weeks of bright light (2 hr a day, 3,000 lux and a placebo pill)				
Ozdemir 2015 (score=4.0)	Light Therapy	RCT	Sponsored by Yuzuncu Yil University Scientific Research Projects Office. No COI.	N = 50 patients diagnosed with Major Depressive Disorder for the first time diagnosed using the DSM-IV	Mean age: 35.5 years; 23 males, 27 females	Group 1: Venlafaxine starting at 75mg/day and increased to 150mg/day for 8 weeks (n=25) vs Group 2: Treated with Venlafaxine (same dosages as Group 1) and Bright Light Therapy (7000 lux) for 1 hour in the morning, daily for 8	Outcomes measured at week 1, 2, 4, and 8 of treatment duration. No mention of follow-up past duration of 8-week treatment	The mean HDRS depression score in decreased in both groups, the decrease in mean scores for Group 1 was 29.28 to 7.40, and the decrease in mean scores for Group 2 was 29.88 to 5.72 after 8 weeks of treatment ($p<0.01$).	"Both venlafaxine and venlafaxine + bright light therapy treatment strategies significantly reversed the depressive mood of patients with severe MDD; however, the latter induced significantly stronger and more rapid beneficial effects."	Data suggest either monotherapy of venlafaxine or combination therapy (venlafaxine and bright light therapy) significantly improved MDD symptoms but combo therapy resulted in stronger and more rapid results.

						weeks. (n=25)				

Antidepressant versus Cognitive Behavioral Therapy (CBT)										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Schramm 2015 (score=5.0)	CBT/Escitalopram	RCT	Sponsored by Lundbeck GmbH, Hamburg, Germany. No mention of COI.	N = 60 patients with chronic major depression (DSM-IV)	Mean age: 43.63±10.56 years; 28 males, 32 females	CBASP Group: received 22 sessions of cognitive behavioral analysis system of psychotherapy (n=29) vs ESC/CM Group: received 18 session over 28 weeks of escitalopram 10 mg/day for first week then increased to 20 mg/day for rest of study and clinical management consisting of psychoeducation, support and empathy	8, 28 weeks	Improvement in MADRS scores was observed for both groups at 8 weeks ($p<0.001$) and at 28 weeks ($p<0.001$). Response rate was 68.4% in CBASP and 60.0% in ESC/CM group with neither group being superior.	"CABSP and ESC/CM appear to be equally effective treatment options for chronically depressed outpatients. For nonimprovers to the initial treatment, it is efficacious to augment with medication in the case of nonresponse to CBASP and vice versa."	Small sample size. Data suggest both CBT and escitalopram were effective in the treatment of chronic major depression.

						intervention (n=30)				
Jarrett 1999 (score=5.0)	Phenelzine/CBT	RCT	Sponsored by grants from National Institute of Mental Health. No mention of COI.	N = 108 patients with major depressive disorder (DSM-IV)	Mean age: 39.6 years; 35 males, 73 females	CBT Group: received cognitive behavioral therapy consisting of 20 individual sessions 2 times weekly for 10 weeks (n=36) vs Phenelzine Group: received phenelzine sulfate (0.85 mg/kg to 1 mg/kg consisting of 11 sessions over 10 weeks (n=36) vs Placebo: received identical dosing as phenelzine of a placebo pill (n=36)	4, 7, 10 weeks	Response rate was 58% in CBT group, 58% in phenelzine group, and 28% in placebo group. Phenelzine reduced the mean HRSD-21 scores more than the placebo group at 4 weeks ($p=0.01$). For weeks 7 and 10, both CBT group and phenelzine group reduced the HRSD-21 group compared to placebo (CBT vs Placebo 7 weeks: $F1,103=7.29$, $p<0.01$; 10 weeks: $F1,103=8.94$, $p<0.01$; Phenelzine vs	"Cognitive therapy may offer an effective alternative to standard acute-phase treatment with a monoamine oxidase inhibitor for outpatients with major depressive disorder and atypical features."	Baseline data differs in terms of duration and type of depression. Data suggest both CBT and phenelzine had comparable efficacy and were both superior to placebo but high dropout rate in placebo group.

								Placebo 7 weeks: F1,103=12.60, p<0.001; 10 weeks F1,103=9.30, p<0.01).		
Lam 2013 (score=5.0)	CBT/Escitalopram	RCT	Sponsored by grant from Lundbeck Canada. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 99 patients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 43.3 years; 45 males, 54 females	CBT Group: received 10 mg/day escitalopram (increased to 20 mg/day at week 2) and telephone-based cognitive behavioral therapy consisting of 8 sessions (each 30-40 min) over 8-10 weeks including motivation-exercises, identify, challenge and distance negative thoughts training, and personal	2, 4, 8, 12 weeks	Decrease in MADRS score was 63% in CBT group compared to 61% in control group (p=0.86). Remission rates were 56% in CBT group compared to 53% in control group (p=0.74). Work functioning LEAP total score and LEAPS productivity scale showed greater improvement in CBT group compared to control group	"Combined treatment with escitalopram and telephone-administered CBT significantly improved some self-reported work functioning outcomes, but not symptom-based outcomes, compared with escitalopram alone."	Data suggest depression scores were most improved via escitalopram compared to telephone-delivered CBT although self-reported work functions showed improvement with telephone delivered CBT.

						care and self-management skills (n=48) vs Control Group: received 10-minute structured phone call weekly for 8 weeks and received 10 mg/day escitalopram (increased to 20 mg/day at week 2) (n=51)		(p=0.046, p=0.036, respectively).		
Dimidjian 2006 (score=4.5)	Cognitive Behavioral Therapy/Paroxetine	RCT	Sponsored by National Institute of Mental Health Grant. COI: Dunner is a consultant or on the advisory board for, and serves on the speaker's bureau of a	N = 241 subjects with major depression on the scale of DSM-IV.	Mean age: 39.9 years; 82 males, 159 females	Behavioral Activation (BA) group: received max twenty-four 50-minute sessions over 16 weeks, sessions twice weekly for first 8 weeks, and then only	Follow up at 8 and 16 weeks	Subjects in BA improved significantly greater than participants in CT on both the BDI, t(81)=2.23 (p=.029), and the HRSD, t(188)= 2.09 (p=.038). Participants in ADM improved significantly	"Among more severely depressed patients, behavioral activation was comparable to antidepressant medication, and both significantly outperformed cognitive therapy."	Data suggest BA comparable to ADM and better than CBT.

			number of pharmaceutical companies, including GlaxoSmithKline.			weekly after (n=43) vs. Cognitive Therapy (CT) group: same session schedule and frequency as BA group (n=45) vs. Antidepressants (ADM): received 16 weeks of paroxetine, started at 10mg/day, then 20mg/day at week 2, then 30mg/day at week 4, then 40mg/day at week 6, and 50mg/day dosage at week 12 (n=100) vs. Placebo (PLA) group: received 8		greater than participants in CT on both the BDI, $t(81)= 2.76$, ($p=.007$), and the HRSD, $t(188)=2.31$, ($p=.022$). When comparing participants in BA and ADM, were no significant differences in the rates of improvement on the BDI, $t(81)= 0.25$, ($p= .80$), or on the HRSD, $t(188)=0.05$, ($p=.96$).		

						for weeks (n=53)				
Dunlop 2017 (score=4.5)	CBT/Duloxetine/Escitalopram	RCT	Sponsored by NIH grants. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 344 patients with current major depressive disorder (DSM-IV)	Mean age: 40.0±11.7 years; 148 males, 196 females	CBT Group: received 16 individual sessions of cognitive behavioral therapy consisting of 50 min sessions (n=115) vs Escitalopram Group: received 10-20 mg/day escitalopram (n=114) vs Duloxetine Group: received 30-60 mg/day duloxetine (n=115)	2, 4, 6, 8, 10, 12 weeks	Mean HAM-D score reduction was 10.9 points, but did not differ across the groups (F=0.53, p=0.589). Remission rates were 41.9% for CBT group, 46.7% in escitalopram group, and 54.7% in duloxetine group (p=0.170).	"Treatment guidelines that recommend either an evidence-based psychotherapy or antidepressant medication for nonpsychotic major depression can be extended to treatment-naïve patients. Treatment preferences among patients without prior treatment exposure do not significantly moderate symptomatic outcomes."	Data suggest patient preference towards CBT or pharmacotherapy did not significantly impact treatment outcomes in patients not receiving prior treatment.
DeRubeis 2005 (score=4.5)	Paroxetine /CBT	RCT	Sponsored by the National Institute of Mental Health.	N = 240 participants with moderate to severe major depressive	Mean age: 40 years; 98 males, 142 females	Paroxetine 10-50 mg/day for 16 weeks (n=120) vs. Placebo 10-50 mg/day	Follow-up at weeks 2, 4, 6, 8, 10, 12, 14, and 16	At 8 weeks there was a significant difference in response rates between groups	"Cognitive therapy can be as effective as medications for the initial treatment of moderate to	Data suggest at 8 weeks the response rates to both paroxetine and CBT were comparable.

				disorder meeting DSM-IV major depressive disorder criteria		for 8 weeks (n=60) vs. Cognitive Therapy (CT) for 16 weeks, 50-minute sessions twice weekly for 4 weeks then 1-2 times weekly for 8 weeks, then weekly for 4 weeks (n=60)		(paroxetine = 50%, placebo = 25%, CT = 43%, p = 0.006). At 16 weeks there was no difference in response rates between groups (paroxetine = 58%, CT = 58%, p = 0.92)	severe major depression, but this degree of effectiveness may depend on a high level of therapist experience or expertise."	
Hollon 2005 (score=N/A)	Paroxetine /CBT	Secondary Analysis of DeRubeis 2005	Sponsored by the National Institute of Mental Health. No mention of COI.	N = 104 participants with moderate to severe major depressive disorder meeting DSM-IV major depressive disorder criteria, met criteria for continuation phase	Mean age and gender distribution not reported	Continuation of paroxetine (cAMD) (n=34) vs. Withdrawal onto placebo (n=35) vs. Cognitive Therapy responders – given up to 3 booster sessions during 12-month continuation	Follow-up at weeks 1, 2, 4, 6, and 8 and months 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12	Patients who withdrew from CT were less likely to relapse during the continuation phase than those who withdrew from medications (30.8%, 76.2%, p = 0.004). Patients who withdrew from CT were	"Cognitive therapy has an enduring effect that extends beyond the end of treatment. It seems to be as effective as keeping patients on medication."	Data suggest CT effects persist after treatment and is as effective as prolonged ADT.

				portion of study		phase (n=35)		no more likely to relapse than those who kept taking medications (30.8%, 47.2%, p = 0.20)		
Thompson 2001 (score=4.0)	Cognitive Behavioral Therapy/Desirpamine	RCT	Sponsored by a grant from the National Institute of Mental Health. No mention of COI.	N = 102 subjects with MDD according to the Research Diagnostic Criteria.	Mean age: 66.8 years; 33 males, 67 women.	Desipramine 10mg and increased slowly (n=33) vs. CBT-Alone - group: each session was 50-60 minutes with a cognitive behavioral therapist (n=31) vs. Combined group – received same dosage of desipramine and amount of CBT as other groups (n=36). All participants seen for 16-	Follow up at 10 days	Reduction in depressive symptoms in the low severity group according to the BDI-SF was significantly greater in separate comparisons of Desipramine-Alone with CBT-Alone ($t[844]=2.45$; $p<0.05$) and with the Combined treatment ($t[844]=2.13$; $p<0.05$)	"The results indicate that psychotherapy can be an effective treatment for older adult outpatients with moderate levels of depression."	Data suggest all 3 treatment groups improved but combined treatment was best for severely depressed patients.

						20 sessions over 3-4 month period. Sessions twice a week for 1 week, then once per week for next 8-12 weeks				

Antidepressant versus Electrical Stimulation Therapy										
Repetitive Transcranial Magnetic Stimulation (rTMS)										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Rossini 2005 (score=7.5)	rTMS/Escitalopram	RCT	No sponsorship or COI.	N = 99 patients with major depressive episode (DSM-IV)	Mean age: 47.4±12.9 years; 20 males, 79 females	Active Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225 mg venlafaxine (n=17) and 10 consecutive days of active repetitive transcranial magnetic stimulation (15 hz, 30 trains of 30 pulses 2 seconds each with 28 second inter-train interval (n=50) vs	5 weeks	Active group showed greater favor in HAM-D score reduction compared to sham group (F=7.6, p=0.0073). Response rates were greater in active group (p=0.002). HAM-D score reduction was not significant among medications in either the active or sham group.	"These findings support the efficacy of rTMS in hastening the response to antidepressant drugs in patients with major depressive disorder. The effect of rTMS seems to be unaffected by the specific concomitantly administered drug."	Data suggest rTMS accelerates patient response to escitalopram, sertraline or venlafaxine in patients with MDD.

						Sham Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225 mg venlafaxine (n=16) and sham rTMS (n=49)				
Bares 2009 (score=7.5)	TMS/Venlafaxine	RCT	Supported by a grant from Ministry of Education of Czech Republic MSMT 1M0517. No COI.	N = 60 inpatients with DSM-IV criteria depressive disorder who did not respond to at least one antidepressant treatment before	Mean age: 44.7 years; 12 males, 48 females	1Hz rTMS (Magstim Super Rapid stimulator), every weekday at 100% of MT with 600 pulses/session, sessions being 600 s. Coil placed 45° from midline of scalp. Given placebo capsule (n=29) vs Receiving	Follow up at baseline and weekly up to week 4	Regarding MADRS score, there was no significant difference between the two groups (time x group interaction, F=1.01, df=4,224, p=0.38). Regarding the rating scale BDI-SF, there was no significant differences (F=0.73,	"The findings of this study suggest that, at least in the acute treatment, the right sided rTMS produces clinically relevant reduction of depressive symptomatology in patients with resistant depression comparable to venlafaxine ER. Larger sample sizes are required to	Both groups showed significant reduction of depressive symptoms. Data suggest right side rTMS reduces symptoms of depression equivalent efficacy to venlafaxine ER (comparable efficacy).

						venlafaxine ER (75mg) on days 1-5 with dose increasing to 150mg/day. Sham treatment of rTMS, but with coil rotated 90° away from scalp. Voltage reduced to 70% (n=31)		df=4,224, p=0.56). Regarding rating scale CGI, there was also no significant difference (F=1.73, df=4,224, p=0.17). Response rates also were not statistically significant, as rTMS was 33% and venlafaxine was 39%	confirm these results."	
Chistyakov 2005 (score=6.0)	Clomipramine/ rTMS	RCT	No COI. Sponsored by the Stanley Research Institute.	N = 59 participants meeting DSM-IV criteria for major depression	Mean age: 60.46 years; 15 males, 44 females	3 Hz left prefrontal repetitive transcranial magnetic stimulation (rTMS) with placebo medication (n=12) vs. 3 Hz right prefrontal rTMS with placebo medication (n=12) vs.	Follow-up at 1 and 2 weeks	Percentage of participants that had at least 50% reduction in the Hamilton Depression Rating Scale after treatment: 3 Hz left active rTMS = 54.5% ($p < 0.05$), 3 Hz right active rTMS =	"Our results suggest that 3 Hz left rTMS has a higher therapeutic efficacy and tolerability in patients with MD. "	Small group sizes. Data suggest administration of 3 Hz left rTMS was associated with better therapeutic efficacy than either 3 Hz right rTMS or 2 weeks of clomipramine.

						10 Hz left prefrontal rTMS with placebo medication (n=10) vs. 10 Hz prefrontal rTMS with placebo medication (n=9) vs. sham rTMS with clomipramine 150 mg/day (n=16). rTMS given in 10 daily sessions over a 2 week period		16.7%, 10 Hz left active rTMS = 16.7%, 10 Hz right active rTMS = 33.3%, clomipramine and sham rTMS = 13.3% (all other groups had non-significant percentages)		
Electroconvulsive Therapy (ECT)										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Sackheim 2001 (score=7.0)	Electroconvulsive Therapy/Nortriptyline	RCT	Sponsored by National Institute of Mental Health grants, Solvay Pharmaceut	N = 84 patients with major depressive disorder meeting Research Diagnostic	Mean age: 57.4 years; 28 males, 56 females	Nortriptyline: received 75-125 ng/mL of nortriptyline (n=27) vs Nortriptyline and	4, 8, 12, 16, 20, 24 weeks	Relapse observed in 84% of placebo group, 60% of nortriptyline group, and 39% for	"Our study indicates that without active treatment, virtually all remitted patients relapse within 6 months of	Data suggest relapse at 6 months is highly probable without continuation pharmacothera

			icals Inc., and MECTA Corporation. No mention of COI.	Criteria (RDC)		Lithium: received a combination of nortriptyline and lithium 0.5-0.9 mEq/L (n=28) vs Placebo: (n=29). All participants had undergone an open ECT treatment phase		nortriptyline-lithium group. Patients that relapsed showed higher HRSD scores compared to patients who did not relapse.	stopping ECT. Monotherapy wit nortriptyline has limited efficacy. The combination of nortriptyline and lithium is more effective, but the relapse rate is still high, particularly during the first month of continuation therapy."	py post ECT. In addition, monotherapy less effective than combination therapy but relapse rate is high in both groups during first month post ECT.
Brunoni 2017 (score=6.0)	Escitalopram/tDCS	RCT	Sponsored by a grant from Fundacão de Ampara à Pesquisa do Estado de São Paulo, NARSAD Young Investigator from the Brain and Behavior Research Foundation	N = 245 patients with unipolar depression (DSM-5)	Mean age: 42.7 years; 79 males, 166 females	Escitalopram: received 10 mg escitalopram for 3 weeks and 20 mg thereafter (n=94) vs tDCS: received transcranial direct-current stimulation (tDCS) with 22 sessions each 30-min	10 weeks	Mean HRDS-17 scores decreased by 11.3±6.5 points in escitalopram group compared to 9.0±7.1 points in tDCS group, and 5.8±7.9 points in the placebo group. Escitalopram was superior to placebo	"In conclusion, tDCS did not show noninferiority to escitalopram in this placebo-controlled trial involving patients with unipolar major depressive disorder."	Data suggest escitalopram superior to tDCS which was better than placebo but tDCS was associated with increased new onset mania (escitalopram> tDCS> placebo).

			, FAPESP Young Researcher from the São Paulo State Foundation, and the National Council for Scientific and Technological Development Associacão Beneficente Alzira Denise Hertzog da Silva, and scholarships from Brazilian Coordination, and FAPESP. No mention of COI.			per day (2 mA of 15 sessions each day during the week then 7 sessions once a week until week 10) (n=94) vs Placebo: received same dosing as escitalopram group of a placebo pill (n=60)		(p<0.001) and tDCS was superior to placebo (p=0.01).		
Pickering 1965 (score=5.0)	Imipramine/ Phenelzine/ ECT	RCT	No mention of sponsorship or COI.	N = 269 patients with primary	Mean age: 55.3 years; 81	ECT Group: received 4-8 treatments of	5, 8, 12, 24 weeks, 6 months	Imipramine was superior to both phenelzine	"[I]t appears that that ECT and imipramine increased the	Data suggest imipramine and ECT were better than

				diagnosis of depression, diagnostic criteria not listed	males, 169 females	electroconvulsive therapy for 3.5 weeks (n=65) vs Imipramine Group: received 50 mg of imipramine for 3.5 weeks (n=63) vs Phenelzine Group: received 15 mg of phenelzine for 3.5 weeks (n=61) vs Placebo: received placebo pill (n=61)		and placebo. ECT group and imipramine were similar with 83% of patients and 85% of patients discharged from the hospital. Phenelzine showed 70% of patients discharged compared to 86% of placebo group.	frequency of recovery over and above the spontaneous rate shown by patients on the placebo."	phenelzine and placebo for improving depressive symptoms.
Folkerts, 1997 (score=4.5)	Electroconvulsive Therapy/Paroxetine	RCT	No mention of sponsorship or COI.	N = 39 patients who had a major depressive episode using ICD-10 guidelines	Mean age: 49.8 years; 18 males, 21 females.	Group 1 was given 0.5 atropine sulphate, 0.75-1.38 mg/kg methohexital, and 0.7-1.0 mg/kg succinylchol	4 weeks	There was a 59% decrease in HAMD score for group 1 vs 29% in group 2 ($p<0.001$). Prior treatment had a significant	"The present study found ECT to be superior to paroxetine in medication-resistant major depression, in terms of both degree and	Data suggest ECT better than paroxetine for treatment-resistant depression in terms of magnitude or response.

						ine via IV with right unilateral ECT 3 times a week (n=21) vs group 2 was given 20 mg paroxetine daily and 40 mg within 7 days. Mean dose was 44 mg daily for 4 weeks (n=18)		effect on the outcome ($p<0.05$). Group 2 had better results after the open study phase ($p<0.03$).	speed of response"	
Brunoni 2013 (score=4.5)	Sertraline/ tDCS	RCT	No COI. Sponsored by the São Paulo Research Foundation.	N = 120 participants who were antidepressant-free meeting DSM-IV criteria for unipolar, nonpsychotic major depressive disorder	No mention of age or sex distribution	Placebo medication and sham transcranial direct current stimulation (tDCS) (n=30) vs. Placebo medication and active tDCS (n=30) vs. Sertraline medication and sham tDCS (n=30) vs.	Follow-up at 2, 4, and 6 weeks	Significant difference in Montgomery-Asberg Depression Rating Scale scores between active tDCS and sertraline versus sertraline group (mean difference = 8.5; p = 0.02), versus tDCS group (5.9, p = 0.03), and	"In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety to tDCS and sertraline did not differ."	Data suggest combination sertraline plus ECT is synergistic.

						Sertraline medication and active tDCS (n=30). All treatments given for six weeks. tDCS included 2-mA anodal left/cathodal right prefrontal tDCS (twelve 30-minute sessions). Sertraline hydrochloride dosage was 50 mg/day.		versus placebo/sham tDCS (11.5, $p < 0.001$).		
Gangadhar 1982 (score=4.0)	Imipramine/ECT	RCT	No mention of COI or sponsorship.	N = 32 patients with depression (ICD-9) and had primary affective disorder and endogenou	Mean age: 44.13 years; 14 males, 18 females	Modified bilateral ECT – six ECTs on alternate days for two weeks, then one ECT weekly for two weeks, followed by 'maintenanc	Follow-up at 3 and 6 months	ECT group had significantly lower Hamilton Scale for Depression (HRDS) score at end of week 2 ($p<0.05$). However there were not	"…it can be confidently claimed that from an overall point of view ECT is a superior form of treatment for endogenous depression than imipramine."	Data suggest ECT worked faster and was not associated with organic brain dysfunction at the end of both three and six months.

				s depression		e' ECTs once on the 6th, 8th, and 12th week, received placebo pills (n=16) vs. Imipramine – 25mg capsules, three daily during first week, six daily during 2nd-11th week. Received same ECT as above group (n=16)		statistical differences between treatment groups at any other time period afterwards (all p>0.05)		

Antidepressant versus Exercise										
Exercise (Aerobic, Strengthening, Flexibility)										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Brenes 2007 (score=6.5)	Exercise (Aerobic, Strengthening, Flexibility)/Sertraline	RCT	Sponsored by grant form Wake Forest University School of Medicine	N = 37 adults with minor depression (DSM-IV criteria)	Mean age: 74.5 years; 14 males, 23 females	Medication Group: received open-label sertraline 25 mg/day for	2, 6, 10, 14 weeks, and 4 months	Depression HRSD scale was reduced in exercise and sertraline group compared to an	"Individuals in the exercise condition showed greater improvements	Pilot study with usual care bias. Data suggest both exercise and sertraline benefit late life

			Women's Health Center of Excellence for Research, Leadership, and Education, The Claude D. Pepper Older Adults Independence Center and the Wake Forest University General Clinical Research Center, and National Institute of Mental Health Grant. No mention of COI.			week 1 and 50 mg/day for week 2 (increasing 25 mg dose increments for a max of 150 mg) (n=11) vs Exercise Group: completed a 3 days a week for 16 weeks exercise program of aerobic and resistance exercise training (60-min sessions) (n=14) vs Usual Care Group: received a phone call by research staff at weeks 2, 6, 10, 14 weeks by research staff about		increase in usual care condition (p=0.005). All groups showed an improvement in SF-36 scale while the improvement in exercise and sertraline group showed greater improvement compared to the usual care group (p=0.11).	in physical functioning than individuals in the usual care condition. Both sertraline and exercise show promise as treatments for late-life minor depression. However, exercise has the added benefit of improving physical functioning as well."	depression but exercise also improves the individual's physical function.

						patient's general health status (n=12)				
Murri 2015 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU) grant. No COI.	N = 121 patients with major depression on Hamilton Rating Scale for Depression (HRSD) score ≥ 18	Mean age: 75.2 years; 35 males, 86 females	Sertraline Only: received 50 mg sertraline (n=42) vs Sertraline+Non-progressive Exercise (S+PAE): received 50 mg sertraline and 3 session per week for 24 weeks of exercise sessions(n=37) vs Sertraline+Progressive Aerobic Exercise (S+NPE): received 50 mg sertraline and exercise involving	4, 8, 12, 24 weeks	Remission rates at 4 weeks were 36% for S+PAE group, 40% for S+NPE group, and 7% for sertraline only group (p=0.001). Remission rates at 8 weeks were 60% in S+PAE group, 49% in S+NPE group, and 40% for sertraline only group (p=0.22). Remission rates at 12 weeks were 83% for S+PAE group, 54% for S+NPE group, and 45% for sertraline only group (p=0.001).	"Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression."	Data suggest exercise as adjunct therapy for depression in late life individuals.

						improved cardiopulmonary condition (n=42)		HRSD scores decreases more in the exercise groups compared to the sertraline only group.		
Blumenthal 1999 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)/Sertraline	RCT	Sponsored by the National Institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 156 people with major depressive disorder via DMS-IV criteria, assessed by the Diagnostic Interview Schedule and the Hamilton Rating Scale for Depression (HAM-D)	Mean age: 57 years; 43 males, 113 females	Sertraline initiated with 50 mg and titrated until well tolerated group (n = 48) vs three supervised exercise sessions per week group (n = 53) vs both sertraline and exercise as above group (n = 55)	Follow up at 1, 2, 3, 4, 6, 8, and 12 weeks.	Growth curve analysis of HAM-D showed the rate of treatment response differed across the treatment groups (P=0.02). 60.4% of the exercise group, 68.8% of the medication group and 65.5% of the combination group no longer met DSM-IV criteria for MDD post treatment (No statistical difference found)	"An exercise training program may be considered an alternative to antidepressants for treatment of depression in older persons. Although antidepressants may facilitate a more rapid initial therapeutic response than exercise, after 16 weeks of treatment exercise was equally effective in reducing depression among	Data suggest comparable response between all 3 groups and antidepressant appeared to result in a faster response but at the end of the 16-week intervention, exercise and antidepressant were equally effective for treating MDD symptoms.

									patients with MDD.	
Babyak 2000 (score=5.5)	Exercise (Aerobic, Strengthening, Flexibility)	Secondary Analysis of Blumenthal 1999	Sponsored by the National institutes of Health and Pfizer Pharmaceuticals. No mention of COI.	N = 133 volunteers who met DSM-IV criteria for MDD and scored at least 13 on the HRSD at study entry.	Mean age and gender information not reported	Group that did three supervised exercise sessions per week for 16 weeks at 70%-85% heart rate reserves with a 10 min warm up, 30 minutes at proper intensity and 5 min cool down (n = 44) vs group that received sertraline initiated at 50 mg and titrated until well-tolerated up to 200 mg (n = 42) vs group that did both the exercise and medication	Follow up at 2, 6, 10, 14, and 16 weeks in original study. Follow up at 4 and 10 months for secondary study.	At 10 months 30% of the exercise group were still considered depressed based on DSM-IV diagnosis or an HRSD score greater than 7 vs 52% in the medication group and 55% in the combination group (p=0.028). Looking at the 83 patients assessed as being in remission at 4 months, at 10 months participants in the exercise group had an odds ratio of 6.10 (p=0.01) of being partially or fully recovered compared to	"Among individuals with MDD, exercise therapy is feasible and is associated with significant therapeutic benefit, especially if exercise is continued over time."	Data suggest exercise was associated with lower relapse rates than those associated with the medication group.

						interventions (n = 47)		the other two groups.		
Belvederi 2015 (score=4.5)	Exercise (Aerobic, Strengthening, Flexibility)/Sertraline	RCT	Sponsored by Emilia Romagna Region University Programme (PrRU) 2010-12 grant, area 2 for clinical Governance. No mention COI	N = 121 primary care patients with major depression (score of 18 or higher on the 17-item HRSD) selected by physicians and conditions were compatible with regular exercise	Mean age: 75.2 ± 6.0 years; 35 males, 86 females	Sertraline only (S): Prescribed drug 50 mg (2 week titration period, zolpidem 10mg/day and lorazepam 2mg/day was allowed for insomnia) (n=42) vs Sertraline plus non-progressive exercise (S+NPE): Prescribed 3 supervised group exercise sessions per week (60 min, 24 wks in groups of 3 to 6 participants) in addition to sertraline	None	45% of participants In Sertraline group, 73% of participants in (S+NPE) group, and 81% (S+PAE) group achieved remission ($p < 0.001$; 95% CI 1.27 – 3.54)	"Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression."	Data suggest significant efficacy in the physical exercise group.

						as in the sertraline group (n=37) vs Sertraline plus progressive aerobic exercise (S+PAE): Prescribed the same group exercise sessions, but training scheme was programmed to increase over the weeks (n=42)				
Hoffman, 2008 (score = 4.0)	Exercise (Aerobic, Strengthening, Flexibility)/Sertraline	RCT	Sponsored by Grant MH 49679 from National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center Program. COI	N = 202 sedentary participants who met DSM-IV and Hamilton Depression Rating Scale (HAM-D) criteria for MDD	Mean age: 51.7 ± 7.6 years; 49 males, 153 females	Supervised Aerobic Exercise: Exercise 3 a week for 16 weeks. Assigned training ranges between 70-85% of HR (n=51) vs Home-	None	Participants in al treatment groups experienced decreased symptoms of depression measured by HAM-D, BDI.	"These findings suggest that exercise does not confer clinically meaningful improvements in neurocognitive function among clinically	Data suggest exercise was no better than sertraline for memory or verbal fluency but better than sertraline for executive function. However individuals in the exercise

			Dr. Doraiswamy received grants and honoraria from serval pharmaceutical companies. Dr. Blumenthal previously received an investigator-initiated research grant from Pfizer/Eisai for an unrelated study.			Based Aerobic Exercise: participants received an initial exercise training session with an exercise physiologist, target HR between 70-85% HR (n=53) vs. Sertraline Group: received Zoloft (50 mg and titrated until 200mg), met with a staff (n=49) vs Placebo Pill group: met with a staff psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=49)			depressed adults. Exercise offered no clear benefit relative to placebo pill on any of the neuropsychological tests we used in this study."	groups demonstrated higher aerobic capacities then the non-exercise groups
Hoffman, 2011	Exercise (Aerobic,	Secondary	Sponsored by Grant MH	N = 172 sedentary	Mean age: 51.79 ±	Supervised Aerobic	1 year	46% of MDD remission	"The effects of aerobic	One-year follow-up of

(score = 4.0)	Strengthening, Flexibility)/Sertraline	analysis	49679 (J.A.B>) from the National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center Program, National Institutes of Health, own stock NovaDel Pharma, and receives royalties from John Wiley and Sons. No Mention of COI.	adults with MDD (scored 12 or more on Beck Depression Inventory-2) and were not receiving antidepressant medication of psychotherapy and physically inactive	7.64 years; 46 male, 126 females	Exercise group: participated 3 45 min exercise groups weekly. Each person was assigned individual target rate between 70-85% (n=43) vs Home-Based Aerobic Exercise: participated in initial training session with an exercise physiologist, as well as two follow up sessions after the first and second month (n=48) Sertraline Group: received Zoloft (50		increase at post treatment for 66% of participants available at follow up	exercise on MDD remission seem to be similar to sertraline after 4 months of treatment; exercise during the follow-up period seems to extend the short-term benefits of exercise and may augment the benefits of antidepressant use."	Hoffman 2008. Data suggest at one year there was a 50% chance of relapse to depressive symptoms in the exercise group but there were extended benefits of exercise, which perhaps may augment antidepressant use for 0-180 minutes of exercise per week.

						mg and titrated until 200mg), met with a staff vs. psychiatrist at 2,4,8,12 and 16 weeks (n=41) vs Placebo Pill group: met with a staff psychiatrist for 6 weeks treatment was titrated up to 200 mg (n=40)				
Tai Chi										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lavretsky 2011 (score=7.5)	Tai Chi/Escitalopram	RCT	Supported by the grants MH077650, MH86481, and AT003480 to Dr. Lavretsky and NIH grants T32-MH19925,	N = 112 older adults (60+ years old) with a current MDD episode, a 16 or higher on the	Mean age: 40.6±7.3; 28 males, 45 females.	TCC (n = 36) 4 weeks of escitalopram drug dosing then participated 2 hours of Tai Chi a week for 10 weeks vs.	Follow-up at baseline, 4, 6, and 14 weeks.	Final HAMD scores, TCC vs HE groups, percentage: 94% achieved HAMD score less than 10, 65% achieved remission (HAMD <6) vs. 77%	"Complementary use of a mind–body exercise, such as TCC, may provide additional improvements of clinical outcomes in the	Both groups experienced improvement in symptoms. Data suggest TCC and escitalopram group trended to show reduction in depressive

			HL079955, AG026364, CA10014152, CA116778, RR00827, and P30-AG028748. No mention of COI.	Hamilton Depression Rating Scale (HAMD), and a 26 or higher on the Mini-Mental State Exam		HE (n = 37) 4 weeks of escitalopram drug dosing and weekly health education sessions for 10 weeks		HAMD of 10 or less and 51% achieving remission (HAMD <6) (x2=3.68, p<0.06). Both groups demonstrated improvement in depression, but TCC group showed greater reductions (group*time interaction: F[5, 285]=2.26; p<0.05).	pharmacologic treatment of geriatric depression."	symptoms with remission than the HE and escitalopram group.

Antidepressant versus Supplements and Herbal Remedies										
Nepeta Menthoides										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Kolouri 2016 (score=5.5)	Sertraline/ Nepeta Menthoides	RCT	No COI. Sponsored by Shiraz University of Medical Sciences.	N = 72 participants meeting DSM-5 criteria for major depression	Mean age: 35.27 years; 49 males, 17 females. Mean age and gender informatio	Nepeta menthoides extract – 500 mg capsule, contained 400 mg of freeze-dried aqueous	Follow-up at 2, 4, and 6 weeks	Repeated measures ANOVA showed difference in Beck Depression Inventory II score in each	"Nepeta menthoides may have potential benefits in the control of mood in patients suffering from	Data suggest Nepeta menthoides may have some positive impact on mood.

					n only available for 66 participants	extract power and 100 mg starch (n=36) vs. Sertraline – 50 mg/day (n=36). Both groups given one capsule for five days and then increased to two capsules. Treatments given for four weeks		group (F=74.02, p < 0.001). There was a significant difference between the two groups (F = 17.6, p < 0.001)	major depression. Sustention of antidepressant effect and delay in the recurrence of depression could be considered worthwhile using this herb."	
Omega 3 Fatty Acids										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Jazayeri, 2008 (score=4.5)	Omega 3 fatty-acids	RCT	Sponsored by Vice-Chancellor for Research, Tehran University of Medical Sciences, Tehran, Iran. No mention of COI.	N = 60 outpatients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 34.8 years; 15 males, 45 females	Depressed patients given 1000 mg Eicosapentaenoic acid (EPA) daily for 8 weeks (n=16) vs 20 mg Fluoxetine daily for 8	Follow up at 4, 6, and 8 weeks	The fluoxetine and EPA combination is significantly better than fluoxetine or EPA alone. Fluoxetine and EPA appear to be equally effective in controlling	"In the present 8 week trial EPA and fluoxetine had equal therapeutic effects in major depressive disorder. EPA and fluoxetine combination	Data suggest EPA + fluoxetine better than either fluoxetine or EPA alone.

						weeks (n=16) vs 20 mg Fluoxetine + 1000 mg EPA daily for 8 weeks (n=16)		depressive symptoms. Response rates were 50%, 56% and 81% in the fluoxetine, EPA and combination groups, respectively.	was superior to either of them alone."	
Rhodiola Rosea										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Mao 2015 (score=6.5)	Sertraline/ R. Rosea	RCT	Sponsored by the National Institute of Health Center for Complementary and Alternative Medicine (NCCAM) and the Jack Warsaw Fund for Research in Biological Psychiatry. COI, Dr. Mao is supported by NCCAM.	N = 57 subject with a DSM-IV Axis I diagnosis of MDD.	Mean age: 44.9 years; 31 males, 26 females	R. Rosea: 340 mg capsule(n=20) vs. Sertraline: 50 mg capsule (n=19) vs. Placebo: capsule (n=18) 1 capsule during week 1; <50% reduction in HAMD-D after 2 weeks= 2 capsules	Follow-up at 8 and 12 weeks.	There was no significant difference in all treatment groups, R. Rosea, Sertraline, and Placebo (p=0.79, p=0.28, p=0.17). Sertraline had the greatest decline in HAM-D scores when compared to R. Rosea (95% CI). Sertraline	"These findings suggest that R. Rosea, although less effective than sertraline, may possess a more favorable risk to benefit ratio for individuals with mild to moderate depression."	Data suggest comparable results for all groups including placebo.

						week 3 and 4; <50% reduction after 4 weeks= 3 capsules weeks 5 and 6; <50% reduction in HAMD-D after 6 weeks= 4 capsules weeks 6-12.		also had the greatest decline in HAM-D scores when compared to placebo (95% CI).		
St. John's Wort										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Vorbach 1994 (score=6.5)	St. John's Wort/Imipramine	RCT	No mention of sponsorship or COI.	N = 135 depressed patients (DSM-III-R criteria)	Mean age: 53.4 years; 71 males, 64 females	LI 160 Group: received hypericum extract (3x300 mg) (n=67) vs Imipramine Group: received imipramine (3x25 mg) (n=68)	1, 2, 4, 6 weeks	Hamilton depression scale decreased from 20.2 to 8.8 in LI 160 group compared to imipramine group from 19.4 to 10.7 ($p<0.001$).	"The analysis of CGI revealed comparable results in both treatment groups. Clinically relevant changes of the safety parameters were not found. In the LI 160 group fewer and	Data suggest comparable efficacy to imipramine.

									milder side effects were found as compared to imipramine."	
Szegedi 2005 (score=6.5)	St. John's Wort/Paroxetine	RCT	Sponsored by Dr Willmar Schwabe Pharmaceuticals. COI: AS has received consultancy fees from Dr Willmar Schwabe Pharmaceuticals. RK is head of a contract research organization. AD and MK are employees of Dr. Willmar Schwabe Pharmaceuticals.	N = 251 patients with acute major depression (DSM-IV criteria)	Mean age: 47.3 years; 76 males, 168 females	Hypericum Group: received hydroalcoholic extract from herba hyperici with 3-6% hyperiforin and 0.12-0.28% hypericin (300-600 mg) (n=122) vs Paroxetine Group: received 20 mg tablets of paroxetine (40 mg per day) (n=122)	7, 14, 28, 42 days	Hamilton depression scores decreased by an average of 14.4±8.8 points for hypericum group compared to 11.4±8.6 points in the paroxetine group. Hypericum group showed better improvement in remission compared to paroxetine group (p=0.02).	"In the treatment of moderate to severe major depression, hypericum extract WS 5570 is at least as effective as paroxetine and is better tolerated."	Data suggest comparable efficacy to paroxetine and may be slightly better.
Woelk 2000 (score=6.5)	St. John's Wort/Imipramine	RCT	Sponsored by Bayer AG. No COI.	N = 324 patients with mild to moderate depression	Mean age: 45.9 years; 93 males, 231 females	Hypericum Group: received 0.2% hypericin extracted in	6 weeks	Hamilton depression scale decreased from 12 to 11.53 for hypericum	"This Hypericum perforatum extract is therapeutically equivalent to	Data suggest comparable efficacy but patients appeared to tolerate

				(ICD-10 criteria)		ethanol 50% (250 mg film coated tablet 2 times daily) (n=157) vs Imipramine Group: received 75 mg tablet of imipramine 2 times daily (dose increased form 25 mg twice daily for 3 days to 50 mg twice daily for 4 days) (n=167)		group compared to 12.75 to 11.21 in the imipramine group and neither were statistically significant. Patients tolerated hypericum better than imipramine ($p<0.01$).	imipramine in treating mild to moderate depression, but patients tolerate hypericum better."	hypericum perforatum better.
Hypericum Depression Trial Study Group 2002 (score=6.0)	St. John's Wort/Sertraline	RCT	Sponsored by National Center for Complementary and Alternative Medicine and the National Institute of Mental Health to Duke University Medical Center. No	N = 340 patients with major depressive disorder (DSM-IV)	Mean age: 42.3 years; 116 males, 224 females	Hypericum Group: received 900 mg/day hypericum (n=113) vs Placebo: received equivalent placebo (n=116) vs Sertraline: received 50mg/day	1, 8, 18 weeks	HAM-D scores were reduced by -9.20 (95% CI-10.51 to -7.89) for placebo compared to -8.68 (95% CI -10.01 to -7.35) for H perforatum ($p=0.59$) and -10.53 (95% CI –11.94 to -	"This study fails to support the efficacy of H perforatum in moderately severe major depression. The result may be due to low assay sensitivity of the trial, but the complete	Data suggest lack of efficacy as Hypericum perforatum not superior to placebo for treatment of major depression.

			mention of COI.			sertraline (n=111)		9.12) for sertraline (p=0.18).	absence of trends suggestive of efficacy for H perforatum is noteworthy."	
Gastpar 2005 (score=5.5)	St. John's Wort/Citalopram	RCT	No mention of sponsorship or COI.	N = 388 patients with major depressive episode and recurrent major depression (DSM-IV and ICD-10)	Mean age: 49.8 years; 125 males, 263 females	Hypericum Group: received 900 mg of hypericum perforatum extract/tablet (n=131) vs Citalopram Group: received 20 mg of citalopram (n=127) vs Placebo group: (n=130)	7, 21, 42 days	HAM-D scores decreased by 11.6 points in hypericum group compared to 11.5 points in citalopram group and 9.0 points in the placebo group. Superiority of citalopram to placebo ($p<0.0001$) as well as the comparison of hypericum group compared to placebo.	"The non-inferiority of hypericum extract as compared to citalopram and the superiority of both active compounds to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in comparison to citalopram. These results revealed that hypericum extract STW2-VI is a good alternative to chemically defined antidepressants in the	Data suggest comparable efficacy of hypericum extract STW3-C1 and citalopram and both are only slightly better than placebo group.

									treatment of outpatients with moderate depression."	
Brenner 2000 (score=5.5)	St. John's Wort/Sertraline	RCT	Sponsored by Lichtwer Pharma AG, Berlin, Germany. No mention of COI.	N = 30 patients diagnosed with major depression (recurrent, or single episode) (DSM-IV)	Mean age: 45 years; 11 males, 19 females	Hypericum Group: received LI 160 H. perforatum 600 mg/day during week 1, and 900 mg/day for remainder of trial (n=15) vs Sertraline: received 50 mg/day for week 1, and 75 mg/day for the rest of the trial (n=15)	2, 4, 7 weeks	HAM-D scores reduced by 40±30% in hypericum group compared to 42±24% in the placebo group.	"In a controlled, randomized comparison of hypericum extract (LI 160) and sertraline in the treatment of mild to moderate depression, hypericum was found to be at least as efficacious as the SSRI antidepressant. Both drugs were well tolerated."	Small sample. Data suggest comparable efficacy and may be slightly better.
Harrer 1994 (score=5.5)	St. John's Wort/ Maprotiline	RCT	No mention of COI or sponsorship.	N = 102 participants meeting ICD-10 depression criteria	Mean age: 45.7 years; 29 males, 73 females	300 mg of hypericum extract LI 160 three times a day (n=51) vs. 25 mg of maprotiline three times a day (n=51).	Follow-up at 2 and 4 weeks	At four weeks the mean score of Hamilton Depression Rating Scale (HAMD) for hypericum group went from 20.5 to 12.2 and for	"Statistical evaluation of the results in the three psychometric scales used in this study (HAMD, D-S, and CGI) demonstrated	Data suggest maprotiline and Hypericum Extract LI 160 have similar efficacy but maprotiline effects are observed earlier.

						All treatments given for a total of 4 weeks		maprotiline group went from 21.5 to 10.5 (different not significant, p > 0.05)	a roughly equal efficacy for maprotiline and hypericum after 4 weeks of treatment."	
Van Gurp 2002 (Score=5.0)	St. John's Wort/Sertraline/Fluoxetine	RCT	Sponsored by grant from St. Mary's Hospital Centre, grant from Pfizer Canada. No COI.	N = 87 patients diagnosed with major depression (DSM-IV)	Mean age: 40.1 years; 33 males, 52 females	St John's Wort: received 900 mg of st john's wort (3-300 mg tablets daily) (n=44) vs Sertraline: received 50 mg sertraline (16.67 mg tablets 3 times daily) (n=34)	2, 4, 8, 12 weeks, 6 months	Mean HAM-D and BDI scores were decreased for both groups (p=0.582, p=0.808, respectively).	"The more benign side effects of SJW make it a good first choice for this patient population."	Data suggest comparable efficacy with less adverse events than SJW.
Harrer 1999 (score=5.0)	St. John's Wort/Fluoxetine	RCT	No mention of sponsorship or COI.	N = 149 patients with mild to moderate depressive episodes (ICD-10)	Mean age: 68.8 years; 20 males, 129 females	SJW Group: received 2 coated tablets twice daily of 200 mg St John's Wort extract LoHyp-57 (Ze 117) (n=69) vs Fluoxetine	1, 2, 4, 6 weeks	HAM-D score reduced for both groups; however, neither were statistically significant. Response rate was 71.4% in SJW group and 72.2% in	"There was a trend towards somewhat better results with Hypericum in mild depressive episodes, and with fluoxetine in moderate	Data suggest comparable efficacy but there was a trend for St. John's Wort to be better in mild depression and fluoxetine better for moderate depression.

						Group: received 2 coated tablets twice daily of 5.6 mg fluoxetine-HCl (n=68)		fluoxetine group.	depressive episodes, but these differences were not statistically significant."	
Schrader 2000 (score=5.0)	St. John's Wort/Fluoxetine	RCT	No mention of sponsorship or COI.	N = 252 patients with depressive episode or recurrent depressive disorder (ICD-10)	Mean age: 46.5 years; 83 males, 157 females	Fluoxetine: received 20 mg once daily of fluoxetine (n=114) vs Hypericum: received 250 mg 2 times daily of hypericum (n=126)	6 weeks	Overall HAM-D scores were decreased for both groups ($p<0.09$). Mean CGI score was superior in hypericum compared to fluoxetine ($p<0.03$).	"We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is safety. Hypericum was superior to fluoxetine	Data suggest comparable efficacy but fewer adverse events with Ze 117.

									in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported."	
Sarris 2012 (score=5.0)	St. John's Wort/Sertraline	RCT	No sponsorship or COI.	N = 124 participants with major depressive disorder (DSM-IV)	Mean age: 44.4 years; 43 males, 77 females	SJW Group: received 900 mg/day hypericum (n=35) vs Placebo: received equivalent placebo (n=40) vs Sertraline: received 50mg/day sertraline (n=49)	8, 10, 14, 18, 22, 26 weeks	HAM-D scores were 6.6±4.5 in SJW group, 7.1±5.4 in the sertraline group, and 5.7±5.4 in the placebo group (p=0.036). Remission rates were 58% for sertraline, 63% for SJW group, and 74% for placebo (p=0.20).	"In conclusion, while the results of the continuation phase of this large RCT revealed similar findings to the acute phase, the surprising outcome that a placebo response was maintained, and the questions of why this occurred, are of considerable interest."	Placebo controlled. Data suggest comparable efficacy between all treatments at 26 weeks.
Philipp 1999	St. John's Wort/Imipramine	RCT	Sponsored by Steiner Arzneimittel,	N = 263 patients with	Mean age: 47±12 years; 66	Hypericum Extract: received 350	1, 2, 4, 6, 8 weeks	Hamilton depression score improved	"In summary, this trial adds to the growing	Data suggest comparable efficacy

(score=4.5)			Berlin, Germany. COI: KOH is an employee of Steiner Arzneimittel. RK is a head of a contract research organization involved with hypericum extract for different pharmaceutical companies.	moderate depression (ICD-10)	males, 197 females	mg per capsule (total daily dose of 1050 mg) of hypericum extract (n=106) vs Imipramine: received 50 mg imipramine on the 1st day, 75 mg on days 2-4, and 100 mg (50mg, 25mg, 25 mg, thereafter) (n=110) vs Placebo: (n=47)		in 74% of hypericum group, 71% in the imipramine group, and 50% in the placebo group.	evidence on the effectiveness of hypericum in mildly and moderately depressed patients."	between hypericum extract and imipramine in the treatment of mild to moderate depression.
Gastpar 2005 (score=4.5)	Sertraline/ St. John's Wort	RCT	No mention of COI or sponsorship.	N = 241 participants meeting ICD-10 criteria for moderate depressive disorder	Mean age: 48.89 years; 61 males, 180 females	Hypericum – ethanolic hypericum extract STW3 (Laif 600), 612 mg/day (n=123) vs. Sertraline – 50 mg/day (n=118). Treatments	Follow-up at weeks 1, 12 and 24	Hamilton Depression Rating Scale scores at 12 weeks: hypericum = 22.0, sertraline = 22.1) and at 24 weeks: hypericum = 5.7, sertraline = 7.1. Covariance	"The results indicate that hypericum extract STW 3 is not inferior to sertraline and that it is a well-tolerated drug for the treatment of moderate depression.	Data suggest hypericum extract STW3 is not inferior to sertraline and is well tolerated.

						were given for 24 weeks		analysis with respect to non-inferiority was significant (p < 0.0001) – hypericum was not inferior	These favorable effects were achieved with a once-daily dose of 612 mg of hypericum extract given for up to 24 weeks."	
B Vitamins										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Almeida 2014 (score=7.0)	B Vitamins	RCT	No COI. Sponsored by the National Health and Medical Council of Australia.	N = 153 participants with a major depressive episode in the context of a major depressive disorder (single episode or recurrent) per DSM-IV-TR.	No mention of mean age, all participants were aged ≥50 with a majority of participants being between 50 and 69 years; 67	Citalopram plus 0.5mg of vitamin B12, 2mg of folic acid and 25mg of vitamin B6 (n=77) vs. Citalopram plus placebo (n=76). Citalopram daily dosages were 10 mg, and then 2	Follow-up at 12, 26, and 52 weeks	At 12 weeks remission of depressive episode symptoms reached by 78.1% of those treated by placebo and 79.4% of those treated with vitamins (p = 0.84). At 26 weeks remission reached by	"B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Replication of these findings would mandate that	Data suggest 12 weeks of added B-vitamins did not enhance antidepressant response but maintained antidepressant response over one-year.

					males, 86 females	weeks later increased to 20 mg and could be maximized to 40 mg between 4 and 8 weeks. Vitamins and placebos were in capsules and were taken daily.		76.5% and 85.3%. At 52 weeks remission reached by 75.8% and 85.5% (effect of intervention over 52 weeks, odds ratio OR = 2.49).	treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to manage major depression in middle-aged and older adults."	
Vitamin D										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Khoraminya 2012 (score=6.5)	Vitamin D	RCT	No COI or sponsorship.	N = 42 patients (minus 2 dropouts) with diagnosis of major depressive disorder via DSM-IV.	Mean age: 38.88 years; 6 males, 34 females	1500 IU vitamin D3 plus 20 mg fluoxetine daily for 8 weeks (n=20) vs. 20 mg fluoxetine daily for 8 weeks (n=20)	Follow-up at 2, 4, 6 and 8 weeks during treatment	Hamilton Depression Rating Scale (HDRS) scores at base, week 2, week 4, week 6, and week 8, respectively: Fluoxetine only – 30.2, 25.23, 21.35, 19.00, 17.2, Vitamin D and Fluoxetine – 29.4, 23.94,	"In the present 8-week trial, the vitamin D + fluoxetine combination was superior to fluoxetine alone in controlling depressive symptoms."	Data suggest vitamin D plus fluoxetine was better than fluoxetine alone for decreasing symptoms of depression.

								18.5, 14.6, 11.7 (Repeated measure analysis of variance on time: F = 9.29, p = 0.004, Analysis of covariance adjusted for baseline values: F = 8.54, p = 0.006)		

Zinc Supplement										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Siwek 2009 (score=5.5)	Imipramine/ Zinc Supplement	RCT	No COI. Sponsored by the Funds for Statutory Activity of Collegium Medicum, Jagiellonian University Krakow and the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.	N = 60 patients with unipolar depression meeting DSM-IV criteria for major depression without psychotic symptoms	Mean age: 45.9 years; 20 males, 40 females	Imipramine (~140mg/day) plus daily placebo (n=30) vs. Imipramine (~140mg/day) plus daily zinc supplementation (25mg/day) (n=30). Both groups received treatment for 12 weeks	Follow-up at 2, 6 and 12 weeks	ANOVA analysis showed imipramine and zinc treatment had lower Hamilton Depression Rating Scale scores compared to placebo [$F(1,48) = 6.4$ ($p<0.025$)]	"These data suggest the participation of disturbed zinc/glutamatergic transmission in the pathophysiology of drug resistance."	Data suggest zinc supplementation speeds up the imipramine therapeutic response especially in non-responders to previous antidepressants.
Tyrosine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Gelenberg 1990 (score=4.0)	Imipramine/ Tyrosine	RCT	Sponsored by USPHS grants. No mention of COI.	N = 65 with major depressive disorder via Research Diagnostic Criteria,	Mean age: 39.5 years; 46 males, 19 females	Tyrosine – 500mg daily (n=21) vs. Imipramine – 12.5mg daily (n=22) vs. Placebo – lactose	No follow-up	No statistical difference between groups at end of week 4 in mean Hamilton Depression Scale Rating	"Our earlier positive impressions about the antidepressant efficacy of tyrosine at comparable	Data suggest lack of efficacy of tyrosine for depression.

				also had modified Hamilton Depression Rating Scale score (HAM-D) ≥ 20		(n=22). Treatments received for 4 weeks		scores (HAM-D) (p>0.05)	doses (Gelenberg et al., 1980, 1983) were not borne out by the present study, which we believe is the largest of its kind so far reported."	

Antidepressant versus Hormones										
Liothyronine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Cooper-Kazaz 2007 (score=7.0)	Sertraline/Liothyronine	RCT	Sponsored by the Stanley Medical Research Institute. No COI.	N = 124 adults meeting the DSM-IV criteria for major depressive disorder.	Mean age: 43.1 years; 66 males, 58 females	Sertraline hydrochloride and liothyronine sodium: 50mg/d for one week and 100mg/d thereafter; 20-25ug/d for one week and 40-50ug/d thereafter (n=64) vs. Sertraline	Follow-up at 8 weeks.	There was no indication of significant effects with the liothyronine supplements. Remission rates were higher in sertraline/liothyronine when compared to sertraline/placebo (58% vs 38%, p=.02). At baseline, values of patients with sertraline/liothyr	"These results demonstrate enhancement of the antidepressant effect of sertraline by concurrent treatment with liothyronine without a significant increase in adverse effects."	Data suggest sertraline enhanced with liothyronine increased antidepressant effect.

						and placebo: 50mg/d for one week and placebo; 50mg/d for one week and 100mg/d thereafter (n=60)		onine remission were lower than those without remission (p<.002).		
Triiodothyronine										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Appelhof 2004 (score=5.5)	Paroxetine/ Triiodothyronine	RCT	Sponsored by the Academic Medical Center Anton Meelmeijer Fund. No mention of COI.	N = 113 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 46.5 years; 43 males, 70 females	All participants received paroxetine for eight weeks. Doses titrated at 10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day for four weeks. Participants also randomized to receive one of the	Follow-up at weeks 1, 2, 4, 6, and 8	Significant improvement in Hamilton Depression Rating Scale (HRSD) scores for all three groups ($p < 0.001$ for all). HRSD mean score difference from baseline to 8 weeks: placebo = -9.4, 25 μg T3 = -9.8, 50 μg T3 = -8.3 ($F = 0.042$, $p = 0.66$)	"In conclusion, these results do not support a role for T3 addition to selective serotonin reuptake inhibitors in the treatment of nonrefractory major depressive disorder. On the contrary, more adverse reactions occurred in	Data suggest lack of efficacy of triiodothyronine to paroxetine and more adverse effects.

						following: Triiodothyronine (T3) 25 µg/day (n=30) vs. T3 50 µg/day (n=30) vs. Placebo daily (n=53)			T3-treated patients."	

Antidepressant versus Problem Solving Therapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Mynors-Wallis 1995 (score=4.5)	Problem Solving Therapy/Amitriptyline	RCT	Sponsored by the Wellcome Trust. No mention of COI.	N = 91 patients with major depression (Hamilton rating scale for depression)	Mean age: 37.1±11.4 years; 21 males, 70 females	PST Group: received problem solving treatment for 6 sessions over 3 months (n=29) vs Amitriptyline Group: received 50 mg amitriptyline for 2 nights, then increased 25	6, 12 weeks	Hamilton rating scale improved for all groups (p=0.037). PST group was superior to placebo in Ham-D score mean difference=4.69 (95% CI 0.41-8.96) but not superior to amitriptyline (M=0.94, 95% CI -3.28-5.15). Amitriptyline was superior to placebo in	"As a treatment for major depression in primary care, problem solving treatment is effective, feasible, and acceptable to patients."	At 12 weeks, there was a significant improvement for depressive scores in the PST group.

						mg per night until 150 mg total taken for 6 sessions over 3 months (n=27) vs Placebo Group: received placebo in same dosing as amitriptyline group (n=26)		HAM-D score (M=3.75, 95% CI -0.59-8.09).		

Antidepressant versus Psychotherapy or Interpersonal Psychotherapy										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Weitz 2014 (score=5.5)	Cognitive Behavioral Therapy/Interpersonal Psychotherapy	RCT	No sponsorship or COI.	N = 239 participants with current major depressive episode (RDC criteria)	Mean age: 35 years; 72 males, 167 females	CBT Group: received cognitive behavioral therapy (no specific duration or protocol mentioned) (n=33) vs IPT Group:	6, 12, 18 months	Changes in HRSD scores showed an effect size of 0.43 for CBT Group, 0.56 for IPT Group, 0.55 for Imipramine Group, and 0.34 for the placebo group. IPT	"This study demonstrates the specific effectiveness of IPT and medications in reducing suicidal ideation (relative to placebo), albeit	Data suggest medications to treat depression such as imipramine and IPT may reduce suicidal ideation.

						receiving interpersonal psychotherapy treatments consisting of 50- min sessions (n=38) vs Imipramine +CM Group: received clinical management consisting of medication management and 150-300 mg of imipramine (n=37) vs Placebo+CM Group: received clinical management consisting of medication management and placebo medication (50-60min		group and imipramine group showed the greatest reduction in suicide symptoms compared to placebo (imipramine vs placebo: b=0.47, p<0.05; IPT vs placebo: b=0.41, p<0.05).	largely as a consequence of their more general effects on depression."	

						sessions) (n=40)				
De Jonghe 2001 (score=5.0)	Insight-Oriented Psychotherapy /Fluoxetine	RCT	Sponsored by grant from Eli Lilly Nederland. No mention of COI.	N = 167 patients with major depression (DSM-III)	Mean age: 34 years; 49 males, 80 females	Pharmacotherapy Group: received fluoxetine 20 mg/d, if intolerance or inefficacy, received 50 mg/day amitriptyline—if intolerance or inefficacy, received 300 mg/day moclobemide (n=57) vs Combined Therapy: received both medication same as pharmacotherapy group and short psychodynamic supportive psychothera	8, 16, 24 weeks	Reduction in depressive symptoms was achieved at each follow-up time favoring combined therapy group in 23% at 8 weeks, 31% at 16 weeks, and 62% of patients at 24 weeks. Reduction of depressive symptoms was achieved in 40.7% of pharmacotherapy group and 59.2% in combined therapy group.	"Patients found combined treatment significantly more acceptable, they were significantly less likely to drop out of combined therapy and, ultimately, significantly more likely to recover. Combined therapy is preferable to pharmacotherapy in the treatment of ambulatory patients with major depression."	6-month efficacy evaluation. Data suggest combination psychotherapy with anti-depressants for treating depression best as patient adherence to treatment is better as well as statistically better than pharmacotherapy alone (59.2% vs 40.7%).

						py (16 45-minute sessions) consisting of focused behavioral and cognitive aspects of actual relationships (n=72)				
Reynolds 1999 (score=5.0)	Interpersonal Psychotherapy (IPT)/Nortriptyline	RCT	Sponsored by National Institute of Mental Health. No mention of COI.	N = 180 patients with recurrent non-psychotic unipolar major depression (MINI, Hamilton)	Mean age: 67.6±5.8 years; 45 males, 135 females	Nortriptyline+IPT Group: received 80-120 ng/mL nortriptyline hydrochloride and biweekly interpersonal psychotherapy (n=25) vs Nortriptyline+MC Group: received medication clinic consisting of 30 minute visits by a nonphysicia	1, 2, 3 years	The Nortriptyline+IPT group, Nortriptyline+MC group, and the IPT+Placebo group were better at preventing recurrence of depression compared to placebo (p<.001, p<.001, p=.03; respectively.)	"In geriatric patients with recurrent major depression, maintenance treatment with nortriptyline or IPT is superior to placebo in preventing or delaying recurrence. Combined treatment using both appears to be the optimal clinical strategy in preserving recovery."	Data suggest the 3 active treatment arms showed decreased time to recurrence versus placebo. Combined treatment of nortriptyline and IPT showed the lowest recurrence rates at 3 years.

						n clinician and a psychiatrist as well as 80-120 ng/mL of nortriptyline hydrochloride (n=28) vs Placebo+IPT: received placebo medication and biweekly interpersonal psychotherapy (n=25) vs Placebo+MC: received medication clinic consisting of 30 minute visits by a nonphysician clinician and a psychiatrist as well as placebo medication (n=29)				

Bastos 2015 (score=5.0)	Fluoxetine/ Psychotherapy	RCT	No mention of COI or sponsorship.	N = 272 participants meeting DSM-IV-TR criteria for major depressive disorder or depressive disorder not otherwise specified	Mean age: 29.61 years; 104 males, 168 females	Long-term psychotherapy – one weekly session (LTPP) (n=90) vs. Fluoxetine – 20-60 mg/day (n=91) vs. Combination of both treatments (n=91). All groups received treatment for 24 months.	Follow-up at 6, 12, 18, and 24 months	Mean Beck Depression Inventory (BDI) scores at the end of 24 months: LTPP = 22.08, Combination = 22.04, Fluoxetine = 12.53). Mixed analysis showed significant decrease in BDI scores among all groups(F8; 479 = 45, 96, p < 0.001)	"These findings have implications for patients with depression who may benefit from long-term psychodynamic psychotherapy or combined treatment, or for depression patients who do not wish to take medication such as fluoxetine."	Data suggest long-term psychodynamic psychotherapy (LTPP) and combination LTPP plus fluoxetine are better than fluoxetine alone.
Schatzberg 2005 (score=5.0)	Nefazodone/ Psychotherapy	Crossover trial	Sponsored by Bristol-Myers Squibb Co, New York, NY. Author Borian was associate with Bristol-Myers Squibb Co.	N = 140 patients meeting DSM-IV criteria for chronic major depressive disorder, "double depression" (current major depressive episode	Mean age: 43.1 years; 48 males, 92 females	Received nefazodone first: 100-600 mg daily, for 12 weeks (n=61) vs. Received CBASP first: cognitive behavioral analysis system of psychothera	No long term follow-up	Switching from nefazodone to CBASP and from switch from CBASP to nefazodone resulted in statistically significant improvements in symptoms (p = 0.03). Response and remission rates were not significantly	"Among chronically depressed individuals, CBASP appears to be efficacious for nonresponders to nefazodone, and nefazodone appears to be effective for CBASP nonresponders. A switch from	Data suggest in chronically depression non-responders, switching from CBASP to nefazodone or nefazodone to CBASP results in similar therapeutic efficacy in treatment of

				superimposed on antecedent dysthymic disorder), or recurrent major depressive disorder with incomplete interepisode recovery		py, twice weekly for 4 weeks, then once weekly for 8 weeks (n=79)		different between completers	an antidepressant medication to psychotherapy or vice versa appears to be useful for nonresponders to the initial treatment."	depressive symptoms.
De Jonghe 2004 (score=5.0)	Insight-Oriented Psychotherapy /Venlafaxine	RCT	Sponsored by grant from Wyeth Nederland. No mention of COI.	N = 208 patients with mild or moderate major depressive disorder (DSM-IV)	Mean age: 35.5±10.7 years; 33 males, 67 females	Psychotherapy: received short psychodynamic supportive psychotherapy (SPSP) consisting of 16 sessions within 6 months (n=106) vs Combined Therapy: received psychotherapy and pharmacotherapy consisting of 6 months of	6 months	Psychotherapy group showed a decrease in HRSD score from 18.14 to 11.35 compared to combined therapy group from 17.99 to 9.53 (F=3.04, p=0.083). Success rate was achieved in 32%-69% of psychotherapy group compared to 42%-79% in the combined group. Between group differences were observed for	"In summary, we investigated the possible advantages of combining antidepressants with psychotherapy in ambulatory patients with mild to moderate major depressive disorder. We found that psychotherapy is more acceptable than combined therapy."	Data suggest comparable efficacy.

						venlafaxine unless intolerable then changed to nortriptyline, if intolerable switched to lithium (SPSP and antidepressant medication) n=85)		HRSD scores (p<0.046).		
Burnand 2002 (score=4.5)	Insight-Oriented Psychotherapy /Clomipramine	RCT	Sponsored by grant from the Swiss National Fund for Scientific Research. No mention of COI.	N = 74 patients with a diagnosis of major depressive episode (DSM-IV)	Mean age: 36.4 years; 29 males, 45 females	Combination Group: received psychodynamic psychotherapy(n=35) vs Clomipramine Group: received 25 mg of clomipramine on the first day and increased gradually to 125 mg on fifth day (received 2 electrocardi	2, 4, 6, 8, 10 weeks	Mean HDRS scores showed a negative effect of time (8.9±7 in the combination group compared to 9.7±7.3 in the clomipramine group (F=286.4, p<.001). Nine percent of combination group showed treatment failure compared to 28% of clomipramine group (p=0.04).	"Provision of supplemental psychodynamic psychotherapy to patients with major depression who are receiving antidepressant medication is cost-effective."	Data suggest adding psychodynamic psychotherapy to antidepressant medication in the treatment of depression is associated with lower hospitalizations, lost workdays, improved global functioning, and may be cost effective.

						ograms prior to treatment) and were switched to 20-40mg of citalopram per day if patients refused or had severe adverse effects for 10 weeks (n=39)				
Zilcha-Mano 2014 (score=4.5)	Insight-Oriented Psychotherapy /Sertraline	RCT	Sponsored by a NIMH grant, grant from Pfizer Corp. and from the Fulbright Program. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 156 patients diagnosed with MDD (DSM-IV)	Mean age: 37.5±12.2 years; 64 males, 92 females	SET Group: received 20 sessions of manualized psychodynamic therapy 2 times weekly for 4 weeks, then weekly for rest of treatment (n=51) vs MED Group: received sertraline (unless don't respond then switched to	4, 6, 8, 12, 16 weeks	Depressive symptoms were reduced in all groups ($p<0.001$). No between group differences were observed ($ps \geq .09$).	"Current treatments for depression significantly improve patients' QOL and well-being. No significant differences were found between the three conditions examined in this study. The current study highlights the role of well-being in predicting subsequent	Data suggest comparable efficacy between treatment groups.

						venlafaxine after 8 weeks) no mention of dose (n=55) vs Placebo: received placebo (if no response then switched to a different placebo after 8 weeks) no mention of dosing (n=50)			symptomatic change.“	
Maina 2010 (score=4.5)	BDT /Fluvoxamine/ Sertraline	RCT	No mention of sponsorship or COI.	N = 57 patients with OCD concurrent with MDD (DSM-IV)	Mean age: 31.5 years; 24 males, 30 females	PT-alone Group received either 100 mg/day of fluvoxamine increased to a daily dose of 300 mg/day or 50 mg/day sertraline increased to a daily dose of 200 mg/day: (n=30) vs	16 weeks, 12 months	HAM-D-17 remission was not significant between groups (p=0.463). Mean HAM-D-score improved from 17.56±4.9 to 13.40±5.3 in BDT group compared to 20.48±5.1 to 15.10±5.5 in PT alone group.	“Supplemental BDT in the treatment of patients with OCD with concurrent MDD who are receiving effective medication has no significant clinical effect on both obsessive and depressive symptoms.”	Lack of efficacy of BDT. Data suggest combining BDT with either fluvoxamine or sertraline is no better than administration of either medication alone in patients with MDD and

						PT+BDT Group: received weekly 45 min sessions of brief dynamic therapy (10-16 sessions) (n=27)				concurrent OCD.
Salminen 2008 (score=4.0)	Insight-Oriented Therapy	RCT	Sponsored by the Social Insurance Institution of Finland, and the Signe and Ane Gyllenberg Foundation. No mention of COI.	N = 51 patients with major depressive disorder of mild or moderate severity (DSM-IV)	Mean age: 42.4 years; 16 males, 35 females	PSY Group: received 16 weekly psychodynamic psychotherapy sessions (n=26) vs Fluoxetine Group: received 20 mg/day of fluoxetine for 3-4 weeks then increased to 40 mg/day of fluoxetine if no response was achieved (total16 weeks) (n=25)	4 months	Both groups achieved reduction in HDRS score ($p<0.0001$), but no between group differences were found. Fluoxetine group showed 68% remission compared to 71% in the PSY group ($p=0.84$).	"Both STPP and pharmacological treatment with fluoxetine are effective in reducing symptoms and in improving functional ability of primary care patients with mild or moderate depression. This study suggests no marked differences in the therapeutic effects of these two treatment forms in a	Data suggest comparable efficacy.

									primary care setting."	
Maddux 2009 (score=4.0)	Nefazodone/CBT	RCT	Sponsored by Bristol-Myers Squibb. Author Thase serves on the Speakers Bureau and acts as a Consultant for the Bristol-Myers Squibb Company.	N = 681 participants meeting DSM-IV criteria for chronic major depressive disorder, major depressive disorder superimposed on antecedent dysthymic disorder, or recurrent major depressive disorder with incomplete remission between episodes	Mean age: 42.3 years; 236 males, 445 females	Nefazodone: 300-600 mg daily (n=227) vs. Cognitive behavioral analysis system of psychotherapy (CBASP): 16-20 sessions, 2 sessions weekly for 4 weeks, 1 session weekly for 8 weeks (n=227) vs. Combination of both treatments (n=227)	No follow-up	Patients with comorbid personality disorders (PDs) statistically lower Hamilton Depression Rating Scale scores (mean=12.2) compared to those without comorbid PDs (mean=13.5, partial n2 = 0.008).	"Comorbid Axis II disorders did not negatively affect treatment outcome and did not differentially affect response to psychotherapy versus medication. Treatment formulations for chronically depressed patients with certain PDs may not need to differ from treatment formulations of chronically depressed patients without co-occurring PDs."	Data suggest that chronic depression with comorbid personality disorders do not respond to treatment with nefazodone or psychotherapy differently than those who are chronically depressed without personality disorders.
Menchetti 2014 (score=4.0)	Sertraline/Citalopram/Counseling	RCT	No COI. Sponsored by the Italian Ministry for	N = 287 participants meetings DSM-IV	Mean age: 44.9 years, 76	Interpersonal counseling – six 30-minute	No long-term	At 2 months significantly higher percentage of	"We identified some patient characteristics predicting a	Data suggest a significantly greater number of

			University and Research as Research Program of National Interest in 2005.	criteria for major depression	males, 211 females	sessions (initial session being 60-minutes) (n=143) vs. SSRI treatment – given either sertraline or citalopram, patients met with psychiatrist every 2 to 3 week intervals, dosages not specified (n=144). Treatments given over a 2-month period	follow-up	patients who reached remission in interpersonal group compared to SSRI group (58.7%, 45.1%, p = 0.021)	differential outcome with pharmacological and psychological interventions. Should our results be confirmed in future studies, these characteristics will help clinicians to define criteria for first-line treatment of depression targeted to patients' characteristics. "	patients reached remission (58.7%) in the interpersonal counseling group compared to the SSRI group (45.1%), suggesting IP counseling better than either sertraline or citalopram.

Low Quality Evidence[69]

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Fava 1994 (score=3.5)	Fluoxetine, Desipramine, Lithium									Small sample size pilot study. Data suggest high dose fluoxetine most effective for treating partial responders to previous treatment but both high dose fluoxetine and fluoxetine plus lithium best for non-responders to previous treatment.

69 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Noorbala 2005 (score=3.5)	Fluoxetine, Crocus Sativus L.									Small sample. Pilot study. Limited baseline data. Data suggest similar efficacy between both fluoxetine and Crocus sativus L. extract.
Karp 2004 (score=3.5)	Imipramine									Data suggest risk of symptom recurrence is associated with a higher level of variability during maintenance.
Vorbach 1997 (score=3.5)	Imipramine, St. John's Wort									Data suggest there may be some benefit of Extract L1 160 for depression.

Blom 2007 (score=3.5)	Nefazodone									Data suggest combination medication and psychotherapy better than medication alone but similar to psychotherapy in the treatment of acutely depressed patients.
Schweitzer 1989 (score=3.5)	Moclobemide, Diazepam									Data suggest at 8 weeks both moclobemide and diazepam showed similar efficacy for depression.
Valiengo 2013 (score=3.5)	Sertraline, tDCS									Crossover trial. High dropout rate. Data suggest sertraline was not a

										relapse predictor.
Dunner 2007 (score=3.5)	Sertraline, Ziprasidone									Data suggest adjunctive ziprasidone was associated with a better treatment effect when added to sertraline.
Müller 2006 (score=3.5)	Reboxetine, Celecoxib									Data suggest there may be an inflammatory process involved in depression as the celecoxib group was associated with improved depression symptoms.
Coppen 1978 (score=3.5)	Mianserin, Lithium									Small sample. Data suggest

										mianserin is inferior to lithium for prophylaxis of unipolar recurrent depression.
Hoencamp 1993 (score=3.5)	Lithium, Maprotiline									Data suggest comparable efficacy.
Ather 1985 (score=3.5)	Trazodone, Diazepam, Amitriptyline									No placebo. High dropout rates in all three groups. Data suggest trazodone may be better than amitriptylin e for treating depression.
Hegerl 2010 (score=3.5)	Sertraline, CBT									Data suggest sertraline superior to placebo, cognitive behavioral therapy (CBT) superior to

										self-help groups and CBT, sertraline and patient's choice arm are similar.
Mergl 2018 (score=N/A)	Sertraline, CBT	1 year follow-up of Hegerl 2010								Data suggest sertraline and CBT have similar anti-depressive effects for mild to moderate depression but sertraline seems slightly better than CBT.
Ninan 2002 (score=3.0)	Nefazodone									Data suggest combination therapy of CBASP plus nefazodone is better than nefazodone alone or

										CBASP alone and nefazodone alone is better than CBASP for patients with symptomatic and syndromal anxiety with chronic depression.
Giannelli 1989 (score=3.0)	Trazodone, Hypothalamic Phospholipid Liposomes									Open label trial. Data suggest the addition of HPL to trazadone improved symptoms and decreased adverse events.
Elkin 1989 (score=3.0)	Cognitive Behavioral Therapy, Imipramine, Psychotherapy									High dropout rate. Data suggest lack of efficacy of all 3 treatment groups

										versus placebo.
Murphy 1985 (score=2.5)	Nortriptyline, CBT									Sparse methods. Data suggest comparable efficacy for all 4 treatment arms.
Fournier 2013 (score=2.5)	Paroxetine, CBT									Data suggest medications and CBT lead to different response patterns in symptoms.
Fournier 2015 (score=2.0)	Paroxetine, CBT									Data suggest CBT likely provides greater and sustained improvements versus medications.
Hirschfeld 2002 (score=2.0)	Nefazodone									Data suggest combination CBASP plus

										nefazodone was best for improving psychological functioning compared to treatments alone.

Amitriptyline – Altamura 1988 (3.5); Anton 1990 (3.5); Ather 1985 (3.5); Guelfi 1989 (3.5); Haider 1967 (3.5); Kuhs 1996 (3.5); Laakman 1995 (3.5); McConaghy 1968 (3.5); McNair 1984 (3.5); Mindham 1977 (3.5); O'Brien 1993 (3.5); Okasha 1976 (3.5); Ononye 2000 (3.5); Paykel 1982 (3.5); Van Amerongen 1979 (3.5); Young 1987 (3.5); Ziegler 1977 (3.5); Casper 1994 (3.0); Mihajlovic 2003 (3.0); Mihajlovic 2010 (3.0); Smith 1990 (3.0); Smith 1979 (3.0); Bersani 1994 (2.5); Kuhs 1989 (2.5); Möller 1993 (2.5); Trick 1975 (2.5); Kline 1982 (2.0)

Amineptine – Van Amerongen 1979 (3.5)

Amoxapine – Anton 1990 (3.5); McNair 1984 (3.5); Ragheb 1981 (3.5)

Brofaromine – Hoencamp 1994 (3.5)

Bupropion – Appelberg 2001 (3.5); Feighner 1984 (3.5); Gulrez 2012 (3.5); Kornstein 2011 (3.5); Lineberry 1990 (3.5); Rush 2006 (3.5); Weisler 1994 (3.5); Önder 2003 (3.0)

Citalopram – Souery 2011 (3.5); Crawford 2014 (2.5)

Clomipramine – Bech 2012 (3.5); Civeira 1990 (3.5); Danish University Antidepressant Group 1993 (3.5); Dierick 1990 (3.5); Klok 1981 (3.5); Larsen 1984 (3.5); Noguera 1991 (3.5); Stage 2005 (3.5)

Desipramine – Fava 1994 (3.5)

Desvenlafaxine – Ghosh 2015 (3.5); Maity 2014 (3.5); Rickels 2010 (3.5); Khan 2014 (3.0)

Doxepin – Mendels 1975 (3.5); Rickels 1972 (3.5)

Duloxetine – Demyttenaere 2012 (3.5); Gaynor 2011 (3.0); Martinez 2012 (2.5); Romera 2012 (2.5); Dunner 2008 (2.0)

Escitalopram – Bobo 2011 (3.5); Kornstein 2011 (3.5); Maity 2014 (3.5); Woo 2017 (3.5); Jaracz 2015 (2.5); Jeon 2014 (2.5); Romera 2012 (2.5)

Fluoxetine – Aguglia 1993 (3.5); Andreoli 2002 (3.5); Burke 2001 (3.5); De Jonghe 1991 (3.5); Fava 2000 (3.5); Fava 1994 (3.5); Hashemi 2012 (3.5); Massana 1999 (3.5); Montgomery 1994 (3.5); Noguera 1991 (3.5); Noorbala 2005 (3.5); Smith 1998 (3.5); Young 1987 (3.5); Bahramali 2016 (3.0); Önder 2003 (3.0); Tural 2003 (3.0); Diaz-Martinez 1998 (2.5); Rosenbaum 1998 (1.5)

Fluvoxamine – Itil 1983 (3.5); Kasper 1989 (3.5); Klok 1981 (3.5)

Imipramine – Baca 2003 (3.5); Casacchia 1989 (3.5); Dominguez 1984 (3.5); Dominguez 1985 (3.5); Fabre 1983 (3.5); Feighner 1992 (3.5); Itil 1983 (3.5); Karp 2004 (3.5); Kessell 1970 (3.5); Kessell 1975 (3.5); Kocsis 1989 (3.5); Koran 2001 (3.5); Mielke 1979 (3.5); Rapp 1973 (3.5); Russell 2001 (3.5); Shrivastava 1992 (3.5); Silverstone 1994 (3.5); Thase 1996 (3.5); UK Moclobemide Study Group 1994 (3.5); Vermeiden 2010 (3.5); Vorbach 1997 (3.5); Casper 1994 (3.0); Cohn 1990 (3.0); Harvey 2007 (3.0); Martin 1963 (3.0); Peselow 1989 (3.0); Abraham 1963 (2.5); Casacchia 1990 (2.5); Bhargava 2012 (2.0); Sedman 1973 (2.0)

Isocarboxazide – Young 1979 (3.5); Hays 1969 (2.5)

Maprotiline – De Jonghe 1991 (3.5); Jukes 1975 (3.5); Hoencamp 1993 (3.5); Kasper 1989 (3.5); Kessell 1975 (3.5); Mielke 1979 (3.5); Mindham 1977 (3.5); Okasha 1976 (3.5); Trick 1975 (2.5)

Mianserin – Altamura 1988 (3.5); Coppen 1978 (3.5)

Milnacipran – Chuang 2014 (2.0); Kanemoto 2004 (2.0)

Mirtazapine – Fang 2010 (3.5); Fava 2006 (3.5); Kang 2009 (3.5); Kato 2017 (3.5); Kornstein 2011 (3.5); Matreja 2012 (3.5); McGrath 2006 (3.0); Schüle 2006 (3.5); Hashimoto 2016 (3.0); Smith 1990 (3.0)

Moclobemide – Bech 2012 (3.5); Botte 1992 (3.5); Casacchia 1989 (3.5); Civeira 1990 (3.5); Danish University Antidepressant Group 1993 (3.5); Dierick 1990 (3.5); Donbak 1995 (3.5); Larsen 1984 (3.5); Ononye 2000 (3.5); Ose 1992 (3.5); Schweitzer 1989 (3.5); Silverstone 1994 (3.5); Stage 2005 (3.5); UK Moclobemide Study Group 1994 (3.5); Casacchia 1990 (2.5); Rossel 1990 (1.5)

Nefazodone – Blom 2007 (3.5); Ninan 2002 (3.0); Hirschfeld 2002 (2.0)

Nortriptyline – Fava 2006 (3.5); Hashemi 2012 (3.5); Kessell 1970 (3.5); Ziegler 1977 (3.5); Jaracz 2015 (2.5); Murphy 1985 (2.5)

Paroxetine – Claghorn 1992 (3.5); Fang 2010 (3.5); Fava 2000 (3.5); Geretsegger 2008 (3.5); Mertens 1988 (3.5); Montgomery 1993 (3.5); Rocca 2002 (3.5); Woo 2017 (3.5); Zanardi 1996 (3.5); Cohn 1990 (3.0); Peselow 1989 (3.0); Rickels 1989 (3.0); Foumier 2013 (2.5); Hwang 2004 (2.5); Kuhs 1989 (2.5); Miller 1989 (2.5); Möller 1993 (2.5); Sullivan 2003 (2.5); Chuang 2014 (2.0); Fournier 2015 (2.0); Rosenbaum 1998 (1.5)

Phenelzine – Paykel 1982 (3.5); Young 1979 (3.5); Martin 1963 (3.0)

Protriptyline – McConaghy 1968 (3.5)

Reboxetine – Andreoli 2002 (3.5); Eker 2005 (3.5); Massana 1999 (3.5); Müller 2006 (3.5); Schüle 2006 (3.5); Yazicioglu 2006 (3.5); Crawford 2014 (2.5)

Sertraline – Aguglia 1993 (3.5); Baca 2003 (3.5); Donbak 1995 (3.5); Dunner 2007 (3.5); Eker 2005 (3.5); Fava 2000 (3.5); Hegerl 2010 (3.5); Koran 2001 (3.5); Mergl 2018 (3.5); Rush 2006 (3.5); Russell 2001 (3.5); Thase 1996 (3.5); Valiengo 2013 (3.5); Yazicioglu 2006 (3.5); Zanardi 1996 (3.5); Bahramali 2016 (3.0); Kocsis 2002 (3.0); Bersani 1994 (2.5); Bhargava 2012 (2.0); Rosenbaum 1998 (1.5)

Tranylcypromine – O'Brien 1993 (3.5); McGrath 2006 (3.0); Rossel 1990 (1.5)

Trazadone – Altamura 1988 (3.5); Ather 1985 (3.5); Weisler 1994 (3.5); Giannelli 1989 (3.0); Brooks 1984 (2.0)

Trimipramine – Young 1979 (3.5); Kline 1982 (2.0)

Venlafaxine – Fang 2010 (3.5); Kornstein 2011 (3.5); Kang 2009 (3.5); Rush 2006 (3.5); Yazicioglu 2006 (3.5); Woo 2017 (3.5); McGrath 2006 (3.0); Diaz-Martinez 1998 (2.5); Hwang 2004 (2.5); Chuang 2014 (2.0)

Antipsychotics have been used to treat depression which is accompanied by psychotic features [1042-1045]. Antipsychotics have also been used to treat major unipolar depression or as adjunct therapy for treatment resistant depression [1046-1083] or for maintenance treatment [1084]. Some antipsychotics have been associated with a faster antidepressant response [1085-1089]. Risperidone has also been used to decrease suicidal ideation in MDD [1090].

Evidence for the Use of Antipsychotics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Amisulpride										
Amore 2001 (score=6.5)	Amisulpride/Sertraline	RCT	No mention of sponsorship or COI.	N = 313 patients with dysthymia with or without a superimposed episode of major depressive disorder (DSM-IV)	Mean age: 47.1 years; 100 males, 213 females	Amisulpride: received 50 mg/day of amisulpride for 12 weeks (n=157) vs Sertraline: received 50-100 mg/day of sertraline for 12 weeks (n=156)	5, 10, 15 days, 4, 8, 12 weeks	Reduction in HAM-D total score was achieved better in the amisulpride group compared to the sertraline group ($p<0.0121$). Response rate at 8 weeks for MADRS scale was 54% in amisulpride compared to 69% in sertraline.	"The tolerability of both drugs was satisfactory. Amisulpride is significantly more effective than sertraline during the first weeks of treatment in dysthymia."	Data suggest faster onset of action of amisulpride than sertraline at 4 weeks and faster time to initial improvement, but at week 12 both drugs showed comparable efficacy.
Ravizza 1999 (score=6.5)	Antipsychotic/Amisulpride/	RCT	No mention of COI or sponsorship.	N = 253 participants with a dysthymia	Mean age: 47.05 years;	Amisulpride 50 mg/day (n=166) vs. Amitriptylin	Follow-up at days 14 and 28	Montgomery and Asberg Rating	"Results of the present study in a large patient	Data suggest comparable drug efficacy in the

	Amitriptyline			or single episode of major depression in partial remission (DSM-III-R criteria)	90 males, 163 females	e 25-75 mg/day (n=87). Medications were given for six months	and months 2, 4, and 6	Scale mean total score at baseline and 6-months: amisulpride = 21.0, 10.2, amitriptyline = 21.7, 10.1 (p = 0.495)	population further confirm the safe use of amisulpride in dysthymia and support its administration upon a medium-term treatment period."	treatment of dysthymia.
Boyer 1999 (score=6.0)	Amineptine/Amisulpride	RCT	No mention of COI or sponsorship.	N = 323 participants meeting DSM-III-R for primary dysthymia	Mean age: 48 years; 81 males, 242 females	Amisulpride – 50 mg/day (n=104) vs. Amineptine – 200 mg/day (n=111) vs. Placebo (n=108). All medications given for 3 months	Follow-up at 1 week and 1, 2, and 3 months	Montgomery-Asberg Depression Rating Scale (MADRS) mean score changes: placebo = -3.8, amisulpride = -8.6, amineptide = -8.2 (p < 0.0001). Scale for the Assessment of Negative Symptoms (SANS) mean score changes: placebo = -11.2, amisulpride = -17.6,	"Results show that amisulpride can improve symptoms of chronic depression in dysthymia."	Data suggest amisulpride comparable to amineptine and both medications are superior to placebo.

								amineptide = -19.9 (p < 0.0001)		
Boyer 1996 (Study 1: score=6.0, Study 2: score=5.5)	Amisulpride/ Amineptine/ Imipramine	2 RCTs	No mention of sponsorship or COI.	Study 1: N = 323 patients with primary dysthymia with or without major depressive episode (DSM-III-R) Study 2: N = 219 patients with dysthymia or major depression (DSM-III-R)	Study 1: Mean age: 48.2 years; 81 males, 242 females Study 2: Mean age: 42.9 years; 99 males, 120 females	Study 1: Amisulpride: received 50 mg/day amisulpride for 3 months (n=104) vs Amineptine: received 200 mg/day amineptine for 3 months (n=111) vs Placebo: (n=108) Study 2: Amisulpride: received 50 mg/day amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine (n=73) vs	Study 1: 8 days, 1, 2, 3 months Study 2: 6 months	Study 1: Reduction in MADRS score was -8.63 in amisulpride and -8.21 in amineptine compared to -3.81 in placebo (p=0.0001). Study 2: MADRS score was reduced by -12.3 in amisulpride, -10.6 in imipramine, and -7.2 in placebo (placebo vs imipramine p=0.036, placebo vs amisulpride p<0.002, global p=0.007).	"Results of the intention to treat analysis and of the end-point analysis were compelling and very similar: significant differences were demonstrated for all primary criteria between amisulpride and placebo and between imipramine and placebo but not between amisulpride and imipramine. For both primary criteria and the responder rate (CGI).	Data suggest in both studies amisulpride, imipramine, and amineptine were better than placebo vis MADRS, CGI, and SANS scores. However, in study 2, the 6 month study amisulpride more efficacious than imipramine.

						Placebo: (n=73)			Statistically significant differences were evidenced between amisulpride and placebo and amineptine and placebo."	
Lecrubier 1997 (score=5.5)	Amisulpride/ Imipramine	RCT	No mention of sponsorship or COI.	N = 219 patients with primary dysthymia, dysthymia with major depression, or isolated chronic major depression (DSM-III-R)	Mean age: 42.9 years; 99 males, 120 females	Amisulpride: received 50 mg/day of amisulpride for 6 months (n=73) vs Imipramine: received 100 mg/day of imipramine for 6 months (n=73) vs Placebo: (n=73)	1, 3, 6 months	Response rate was 33.3% in the placebo group, 68.6% in the imipramine group, and 72.2% in the amisulpride group. A MADRS score reduction ≤7 was achieved in 21.9% of placebo, 32.9% in imipramine group, and 35.6% in amisulpride (placebo vs imipramine p=0.032, placebo vs amisulpride	"These results confirm the interest of a drug acting on dopaminergic transmission such as amisulpride in the treatment of depressed patients."	Data suggest comparable efficacy between amisulpride and imipramine with both drugs performing significantly better than placebo.

								p=0.004, imipramine vs amilsulpride p=0.01).		
Cassano 2002 (score=5.5)	Amisulpride/ Paroxetine	RCT	No mention of sponsorship or COI.	N = 275 patients with major depressive disorder (DSM-IV)	Mean age: 51.25 years; 63 males, 200 females	Amisulpride: received 50 mg/day amisulpride for 8 weeks (n=136) vs Paroxetine: received 20 mg/day of paroxetine for 8 weeks (n=136)	7, 14, 28, 42, and 56 days	Response rate was 76% in amisulpride compared to 84% in paroxetine. Remission in HAM-D total score was reduced in both groups, but was similar (p=0.37).	"In conclusion, in the present study, paroxetine and amisulpride were highly effective and well tolerated. We believe that statistical results of a non-inferiority trial should be carefully evaluated in the light of the overall study findings."	Data suggest therapeutic equivalence between amisulpride and paroxetine at 8 weeks with tolerability favoring amisulpride.
Smeraldi 1998 (score=5.5)	Amisulpride/ Fluoxetine	RCT	No mention of sponsorship or COI.	N = 268 patients with dysthymia or a single episode of major depression	Mean age: 49.4 years; 86 males, 182 females	Amisulpride: received 50 mg/day of amisulpride for 3 months (n=139) vs Fluoxetine:	3 months	MADRES score reduction of ≥50% was achieved in 74% in amisulpride and in 67% in fluoxetine group	"No statistically significant differences were found between the two drugs for MADRS, ERD,	Data suggest a similar response rate as measured by a decrease in MADRS score of at least 50% but the fluoxetine group was slightly (non-statistically significantly) better

				(DSM-III-R)		received 20 mg/day of fluoxetine for 3 months (n=129)		(p=0.23). Response rate was 73% in amisulpride compared to 67% in fluoxetine (p=0.316).	Sheehan Disability Scale, and CGI."	than amisulpride group in partial depressive remission.
Standish-Barry 1983 (score=4.0)	Amitriptyline/Amisulpiride	RCT	Sponsored by Chemitechna Ltd. No mention of COI.	N = 36 patients with major depressive disorder (DSM-III)	Mean age: 44 years; 22 males, 20 females	Sulpiride Group: received 200-400 mg daily sulpiride (n=18) vs Amitriptyline Group: received 50-150 mg daily of amitriptyline (n=18) All patients received medication for 24 weeks.	4, 6, 12, 24 weeks	Amitriptyline group showed a greater reduction on Hamilton and Wakefield scores compared to sulpiride group (p<0.05).	"Our results show that sulpiride appears to have antidepressant and anxiolytic properties comparable to amitriptyline up to 12 weeks of treatment."	Data suggest at 24 weeks, amitriptyline was better than sulpiride.
Aripiprazole										
Han 2015 (score=5.0)	Aripiprazole	RCT	Sponsored by grants of KOIAA and the Korean Health Technology	N = 96 patients who met the DSM-IV TR criteria for	Mean age: 49 years; 22 male, 74 female	Aripiprazole augmentation (AA) treated with a starting dose of 2 or	Follow up at baseline, 1 week, 2 weeks, 4 weeks,	The mean change from baseline to 6 weeks in MADRS score was -16.3 in	"Overall, [Aripiprazole Augmentation] yielded potentially beneficial	Data suggest aripiprazole augmentation may benefit MDD patients with inadequate ADT responses more than

			R&D Project. No COI.	Major Depressive Disorder and had an inadequate (HDRS-17 score ≥ 14) responses to their initial antidepressant in an outpatient clinic		5 mg/d aripiprazole, which was increased by 2-5 mg/day per visit to a maximum of 15 mg/day (n=50) vs Antidepressant switching (SW) discontinued previously used antidepressant and switch to a new antidepressant (Bupropion XL 300 mg/d, duloxetine 60 mg/d, escitalopram 10-20 mg/d, fluoxetine 20-40 mg/d, mirtazapine 30-45 mg/d,	and 6 weeks.	the AA group and – 7.6 in the SW group ($p<0.0001$).	clinical outcomes compared to [Antidepressant Switching]."	antidepressant switching.

						milnacipran 100 mg/d, paroxetine CR 25-62.5 mg/d, paroxetine 20-40 mg/d, sertraline 100-150 mg/d, tianeptine 25-37.5 mg/d, or venlafaxine IR or ER 112.5-225 mg/day) (n=46)				
Berman 2007 (score=4.5)	Aripiprazole	RCT	Sponsored by Bristol-Myers Squibb Co. One or more of the authors have received or will receive benefits for personal or professional use.	N = 358 Patients meeting the DSM-IV-TR criteria for a major depressive episode that had lasted ≥ 8 weeks with an inadequate response (<50% reduction	Mean age: 45.4 years; 133 male, 225 female	Assigned to adjunctive placebo in addition to antidepressant therapy (ADT) (n=176) vs. Assigned to adjunctive aripiprazole at 2-15 mg/day with fluoxetine or paroxetine	Follow-up at baseline, week 1, week 2, week 3, week 4, week 5, and week 6.	The mean change in MADRS total score was -8.8 in aripiprazole group and -5.8 in placebo group ($p<0.001$). Total rate of remission was 26.0% in aripiprazole group and 15.7% in placebo group ($p=0.011$).	"In patients with MDD who showed an incomplete response to [Antidepressant Therapy], adjunctive aripiprazole was efficacious and well tolerated."	Data suggest aripiprazole was effective for those showing inadequate response to ADT.

				in depressive system) to 1-3 antidepressant trials		2-20 mg/day with ADT (n=182). All participants participated in 8 week prospective treatment phase where they received escitalopram (10-20 mg/d), fluoxetine (20-40 mg/d), paroxetine CR (37.5-50 mg/d), sertraline (100-150 mg/d), or venlafaxine XR (150—225 mg/d) to establish ADT.		Total response rate was 33.7% in aripiprazole group and 23.8% in placebo group (p=0.027).		
Mohamed 2017 (score=4.5)	Aripiprazole, Bupropion	RCT	Sponsored by Veterans Affairs Cooperative Studies Program and Bristol-	N = 1522 US Veterans Health Administration patients	Mean age: 54.4 years; 1296 male,	Switched antidepressant medication to bupropion (starting	Follow up at baseline, 1, 2, 4, 6, 8, 10, and 12 weeks.	Remission was higher for augmented aripiprazole group at 28.9% compared with switched group	"Among a predominantly male population with major depressive disorder	Predominantly male pop. Data suggest benefit from aripiprazole augmentation in MDD patients who are unresponsive to ADT

			Myers Squibb. One or more of the authors have received or will receive benefits for personal or professional use.	with anti-depressant resistant Major Depressive Disorder diagnosis according to DSM-IV-TR criteria	226 female	dose 150 mg/d to 300-400 mg/d) (n=511) vs. Augmented current antidepressant treatment with bupropion (starting dose 150 mg/d to 300-400 mg/d) (n=506) vs. Augmented current antidepressant treatment with aripiprazole at 2mg, 5mg, 20mg, or 15mg/d (n=505)	Optional continuation phase had follow-ups at 16, 20, 24, 28, 32, and 36 weeks.	at 22.3% (p=0.02) but not significantly different than augmented bupropion group at 26.9% (p=0.47). Remission defined as a score of 5 or less on the QIDS-C16.	unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. ”	but this only resulted in a modest likelihood of remission.
Han 2013 (score=4.5)	Aripiprazole, Escitalopram	RCT	Sponsored by Korea Otsuka Pharmaceuticals. No COI.	N = 35 patients with comorbid major depression and alcohol	Mean age: 39.6 years; 23 male, 12 female	Group 1: Given flexible dose of aripiprazole (5-15 mg) and escitalopra	Follow up at baseline, and 6 weeks	Mean Beck Depression Index (BDI) scores for Group 1 was 32.1 at baseline and 16.0 at week 6	“The change of brain activity within the left anterior cingulate gyrus in all patients with	Small sample. Data suggest escitalopram plus aripiprazole decreased alcohol craving and depression scores.

				dependence according to DSM-IV criteria		m (10-20 mg) daily for 6 weeks (n=17) vs Group 2: Given 10-20 mg of escitalopram daily (n=18).		(p=0.01). Mean BDI score for Group 2 was 29.6 at baseline and 16.9 (p<0.01). There were 4 non-responders in Group 1 and 6 non-responders in Group 2 (p=0.15).	co-morbid alcohol dependence and major depressive disorder was negatively correlated with the change in craving for alcohol. These findings suggest that the effects of aripiprazole on anterior cingulate cortex might mediate the successful treatment of alcohol dependence in patients with major depressive disorder."	
Marcus 2008 (score=4.0)	Aripiprazole	RCT	Sponsored by Bristol-Myers Squibb. One or more of the authors has received	N = 381 patients experiencing a major depressive episode (criteria =	Mean age: 44.5 years; 127 male,	Adjunctive Aripiprazole group was given aripiprazole (up to 15-20mg/d) in	Follow-up at baseline, week 1, week 2, week 3, week 4,	Mean change in MADRS score was -8.5 in aripiprazole group and -5.7 in placebo group	"Aripiprazole is an effective and safe adjunctive therapy as demonstrated in this short-	Data suggest aripiprazole is effective in non-responder patients to ADT as adjunctive therapy.

			or will receive benefits for personal or professional use.	HAM-D17 score ≥ 18 and DSM-IV) who hadn't responded to antidepressant therapy (ADT)	254 female	addition to ADT (escitalopram 10-20mg/d, fluoxetine 20-40mg/d, paroxetine CR 37.5-50 mg/d, sertraline 100-150 mg/d or venlafaxine XR 150-225 mg/d) (n=191) vs. Adjunctive Placebo group was given placebo in addition to ADT (same selection as aripiprazole group) (n=190)	week 5, and week 6 of double-blind treatment phase	(p=0.001). Remission rates were 25.4% in aripiprazole group and 15.2% in placebo group (p=0.016). Response rates were 32.4% in aripiprazole group and 17.4% in placebo group (p<0.001).	term study for patients who are nonresponsive to standard [antidepressant therapy]"	
Kamijima 2013 (score=4.0)	Aripiprazole	RCT	Sponsored by Otsuka Pharmaceutical Co., Ltd. One or more of the authors has	N = 586 patients with major depressive disorder (criteria =	Mean age: 38.6 years; 340 male,	Adjunctive treatment with placebo pill (n=195) vs Fixed dose aripiprazole	Follow-up at baseline, week 1, week 2, week 3, week 4,	Mean change in MADRS score was -10.5 in fixed dose group (p<0.001), -9.6 in flexible dose	"Aripiprazole augmentation at a fixed or flexible dose was superior to ADT alone and was	Data suggest aripiprazole (3-15 mg/d) or (3 mg/d) is superior to ADT alone.

			received or will receive benefits for personal or professional use.	HAM-D17 score ≥ 18 and DSM-IV-TR) who hadn't responded to antidepressant therapy (ADT)	246 female	at 3mg/d (n=197) vs Flexible dose aripiprazole, starting at 3mg/d and increased up to 15mg/d (n=194) *all groups given placebo/ aripiprazole in addition to ADT (sertraline, fluvoxamine, paroxetine, milnacipran, or duloxetine, dosages not given).	week 5, and week 6	group (p<0.01), and -7.4 in placebo group (p>0.05). Response rates were 42.1% in fixed dose group (p<0.001), 39.2% in flexible dose group (p<0.01), and 28.2% in placebo group (p>0.05). Remission rates were 32.5% in the fixed dose group (p<0.001), 30.4% in the flexible dose group (p<0.01), and 20.5% in placebo group (p>0.05).	reasonably well tolerated in Japanese patients with inadequate response to ADT."	
Ozaki 2015 (score=NA)	Aripiprazole	Post-Hoc Analyses of Kamiji	Sponsored by Otsuka Pharmaceutical Co., Ltd. One or more	N = 586 patients with major depressive	Mean age: 38.6 years; 340	Adjunctive treatment with placebo pill (n=195) vs	Follow-up at baseline, week 1, week 2,	Mean change in MADRS score was -10.5 in fixed dose group	"[A]ripiprazole was effective for a variety of Japanese	(Post-hoc analyses of Kamijima 2013) Data suggest aripiprazole is effective for those experiencing

		ma 2013	of the authors has received or will receive benefits for personal or professional use.	disorder (criteria = HAM-D17 score ≥ 18 and DSM-IV-TR) who hadn't responded to antidepressant therapy (ADT)	male, 246 female	Fixed dose aripiprazole at 3mg/d (n=197) vs Flexible dose aripiprazole, starting at 3mg/d and increased up to 15mg/d (n=194) *all groups given placebo/ aripiprazole in addition to ADT (sertraline, fluvoxamine, paroxetine, milnacipran, or duloxetine, dosages not given).	week 3, week 4, week 5, and week 6	(p<0.001), -9.6 in flexible dose group (p<0.01), and -7.4 in placebo group (p>0.05). Effect of treatment was not related to sex, age, number of adequate ADT trials, age of MDD diagnosis, number of depressive episodes, age of first depressive episode, duration of current episode, time since first episode, type of SSRI/SNRI or severity at the end of the SSRI/SNRI treatment phase (for all, p>0.05).	patients with MDD who had exhibited inadequate responses to ADT. Additionally, we suggest that aripiprazole significantly and rapidly improved the core depressive symptoms."	inadequate response to ADT.

Berman 2009 (score=3.5)										Data support use of aripiprazole augmentation to standard ADT.70
Fava 2012 (score=3.5)										Data suggest low dose aripiprazole added to ADT is only marginally effective.
Mischoulon 2012 (score=NA)		(Follow-up to Fava 2012)								(Follow up to Fava 2010) Data suggest a slight efficacy benefit in increasing the dos to 5 mg.
Cheon 2017 (score=3.5)										Data suggest aripiprazole augmentation is comparable to bupropion augmentation.
Berman 2011 (score=2.5)										Very high attrition rate but data suggest aripiprazole is well tolerated.
Brexpiprazole										
Thase 2015a (score=5.5)	Brexpiprazole	RCT	Sponsored by Otsuka Pharmaceutical development and Commerciali	N = 379 patients with major depressive disorder and	Mean age: 44.65 years; 112 males,	Group 1: Standard antidepressant treatment (ADT) and a placebo for 6 weeks	Follow up at 8 weeks	The Brexpiprazole group score significantly better than the placebo group for MADRS	"Adjunctive brexpiprazole therapy demonstrated efficacy and was well tolerated in	Data suggest 2mg brexpiprazole demonstrated efficacy over placebo and was generally well tolerated.

70 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

			zation, Inc. COI, Dr. Thase has received grants from Agency for Healthcare Research and Quality, Alkermes, Forest, National Institute of Mental Health, Otsuka, PharmaNeuroboost and Roche.	historical inadequate response to 1-3 ADTs (DSM-IV-TR)	267 females	of treatment (n=178) vs. Group 2: Standard ADT and 2 mg of Brexpiprazole per day for 6 weeks (n=175)		score (p=.0002). Most common adverse effect was weight gain (8.0% vs 3.1%) and ankathisia (7.4% vs 1.0%) for brexpiprazole and placebo, respectively	patients with major depressive disorder and inadequate response to ADTs."	
Thase 2015b (score=5.5)	Brexpiprazole	RCT	Sponsored by Otsuka Pharmaceutical development and Commercialization, Inc. COI, Dr. Thase has received grants from Agency for Healthcare Research and Quality,	N = 677 patients with Major Depressive Disorder and historical inadequate response to 1-3 ADTs (DSM-IV-TR)	Mean age: 45.6 years; 215 males, 462 females	Group 1: allocated to standard antidepressant treatment (ADT) and a placebo for 6 weeks of treatment (n=221) vs. Group 2: Standard ADT and 1 mg of Brexpiprazole per day	Follow up at 8 weeks	Group 3 (3 mg/day) showed statistically significant difference in scores over the placebo group (p=.0079) and Group 2 (1 mg/day) did not have a great enough difference (p=.0737). The most frequent	"Brexpiprazole 3 mg demonstrated efficacy versus placebo in the efficacy population per final protocol. Both doses of brexpiprazole were well tolerated."	Data suggest Brexpiprazole 3mg demonstrated efficacy over placebo. However the 1mg dose did not show efficacy over placebo.

			Alkermes, Forest, National Institute of Mental Health, Otsuka, PharmaNeuroboost and Roche.			for 6 weeks (n=226) vs. Group 3: Standard ADT and 3 mg of Brexpiprazole per day for 6 weeks (n=230)		adverse events were akathisia (4.4%, 13.5%, 2.3 %), headache (9.3%, 6.1%, 7.7%), and weight increase (6.6%, 5.7%, 0.9%) in brexpiprazole 1-mg, 3-mg, and placebo, respectively		
Buspirone										
Trivedi 2006 (score=4.0)	Bupropion / Citalopram/Buspirone	RCT	Sponsored by the National Institute of Mental Health, National Institutes of Health. COI, one or more authors have received or will received benefits for personal or professional use.	N = 565 patients with nonpsychotic major depressive disorder without remission who had received 12 weeks of citalopram therapy, no mention of	Mean age: 41.1 years; 233 males, 332 females	Augmentation of citalopram with sustained-release bupropion. Initial dose of sustained-release bupropion = 200 mg daily for 2 weeks, 300 mg daily at week 4, 400 mg daily at week 6	Follow-up at 2, 4, 6, 9, and 12 weeks	Both treatments had similar rates for Hamilton Rating Scale for Depression remission (HRSD-17) (29.7% vs. 30.1%) and for 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR-16) remission (39.0% vs. 32.9%).	"Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings."	Data suggest similar efficacy between bupropion SR and buspirone for prevention of depression relapse.

				diagnostic criteria		(n=279) vs. Augmentation of citalopram with buspirone. Initial dose of buspirone = 15 mg daily for 1 week, 30 mg daily for 1 week, 45 mg daily for weeks 3 to 5, 60 mg daily during week 6 (n=286). All medications taken twice daily		Sustained-release bupropion had greater reduction QIDS-SR-16 scores (25.3% vs. 17.1%, p<0.04)		
Chlorpromazine										
Paykel 1968 (score=4.0)	Imipramine/Chlorpromazine	RCT	Sponsored by Geigy (UK) Ltd. No mention of COI.	N = 114 patients with a depressive illness suitable for drug treatment, no diagnostic	Mean age and gender distribution only described for those included in analysis	Imipramine – four 25mg capsules taken daily for 2 days, then four 50mg capsules taken daily for 19 days (n=57) vs.	No follow-up	No statistical difference between groups for Psychiatrists' Interview Scale scores, Nurses' Rating Scale scores, and Patients' Self-Rating	"None of the measures employed has revealed significant differences in symptom change between imipramine and	Data suggest comparable efficacy between drugs.

				criteria listed	(n=99). Mean age: 41.5 years; 24 males, 75 females	Chlorpromazine – same dosage and timing as imipramine group (n=57)		Questionnaire scores (all p>0.05).	chlorpromazine treatment in the overall groups of depressed patients in this study."	
Deanxit										
Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Wang 2015 (score=6.0)	Sertraline/ Deanxit	RCT	Sponsored by Guangdong Natural Science Foundation, Science and Technology Planning Project of Guangzhou City, and the fund of West China Psychiatric Association. No COI.	N = 75 patients diagnosed with depression by the HAM-D and anxiety with the HAM-A scales.	Mean age: 62.2 years; 28 males, 47 females.	Deanxit: Sertraline (75 mg/day) and deanxit (a combination medication of 10 mg melitracen and 0.5 mg of flupentixol- a tricyclic antidepressant and an antipsychotic) (one piece/day) (n=38) vs. Placebo: Sertraline	Follow-up at 2 weeks.	Overall, there was no distinct differences between the groups at the end point, with the exception of difference in scores between the deanxit and placebo group on day 8 (p=0.006) and day 15 (p=0.001). HAM-A scores were favoring the deanxit group on day 4, 8, and 15 (p=0.006,	"The rapid onset of sertraline plus short-term deanxit indicated that it might be an inspiring strategy to manage depression and anxiety within the first two weeks in chronic somatic diseases."	Data suggest sertraline plus short term deanxit may benefit patients with depression and anxiety.

						(75 mg/day) and placebo (on piece/day) (n=37)		p=0.001, p=0.002).		
Dixyrazine										
Feet 1985 (score=4.5)	Dixyrazine	RCT	Sponsored by CIBA-GEIGY Pharma, Apothekernes Laboratorium for Specialpræparater, and the Anders Jahres Foundation. No mention of COI.	N = 63 patients suffering from primary non-agitated depression diagnosed with the Reighner-Robins-Guze criteria.	Mean age: 45 years; 26 males, 37 females	Placebo tablet/day (n=21) vs. Diazepam 10 mg tablet/day (n=21) vs. Dixyrazine 50 mg tablet/day (n=21). All groups received imipramine —50 mg for the first two days, 75 mg for the next 2 days, 100 mg from day 5 to day 14. After two weeks, dosage was adjusted due to patients own needs. All	Follow-up at weeks 2, 4, 6, and 8	After two weeks of treatment, mean CRPS score lower in dixyrazine group when compared to diazepam and placebo groups ($p<0.05$). Throughout following weeks, same trend observed. Daily dosage of imipramine similar in all groups during first 4 weeks, after 6 weeks it was higher in diazepam group when compared to other two groups ($p<0.05$). 67%	"Our study confirmed the assumption that the combination of imipramine and dixyrazine was superior to imipramine alone as regard efficacy. The combination of imipramine and diazepam on the other hand, was not better than imipramine alone."	Short term study (8 weeks). Data suggest combining dixyrazine with imipramine led to improved symptom resolution versus either imipramine + diazepam or imipramine + placebo.

						medications given for 8 weeks		of patients in placebo and diazepam group and 86% of patients in dixyrazine group were close to symptom free		
Flupethixol										
Young 1976 (score=4.0)	Flupethixol, Amitriptyline	RCT	No mention of COI or sponsorship.	N = 60 participants with mild to moderately severe depression (no diagnostic criteria mentioned)	Age and sex data only available for 51 participants. Mean age: 37.35 years; 21 males, 30 females	Amitriptyline 75-225 mg/day (n=30) vs. Flupenthixol 1.5-4.5 mg/day (n=30). All treatments given for six weeks	Follow-up at weeks 1, 3, and 6	Mean scores of Hamilton Depression Rating Scale, Beck Depression Rating Scale, and overall severity did not statistically differ between treatment groups (p > 0.05)	"Flupenthixol, in low dosage, is a useful alternative antidepressant for depressed outpatients."	Small sample. Data suggest similar efficacy with a slight trend favoring flupenthixol.
Fluphenazine										
O'Hara 1978 (score=4.5)	Maprotiline, Fluphenazine, Nortriptyline	RCT	No mention of COI or sponsorship.	N = 75 participants with disorders on the spectrum of	Mean age: 52 years; gender distribution not	1.5 mg fluphenazine and 30 mg nortriptyline per day (n=34) vs. 75 mg	Follow-up at days 3, 10, and 28	Mean adjusted Clinical rating scale scores for depression at day 28 for combination medication =	"The greater antidepressant effect of fluphenazine/ nortriptyline after 4 weeks' treatment was	Data suggest maprotiline better than combination fluphenazine/nortriptyline (Motipress).

				depressive conditions, no formal diagnostic criteria given	specified	maprotiline daily (n=37). Both treatments given for four weeks		0.96 ($p < 0.05$), for maprotiline = 1.33 ($p > 0.05$)	the continuation of the trend already evident at day 10, and thus followed a similar time course to that expected of the antidepressant effect of tricyclic compounds."	
Haloperidol										
Klieser 1989 (score=5.5)	Trazodone /Amitriptyline/Haloperidol	RCT	No mention of COI or sponsorship.	N = 45 patients with major depressive disorder and 75 with acute schizophrenia, no diagnostic criteria listed	Mean age: 42.6 years; 49 males, 71 females	400 mg trazodone daily (n=30) vs. 20 mg haloperidol daily (n=30) vs. 150 mg amitriptyline daily (n=30) vs. Placebo daily (n=30). All treatments given for three weeks	No follow-up	Hamilton Depression Rating Scale (HAM-D) scores decreased in all drug treatments. Mean change in HAM-D scores at 3 weeks: trazodone = -3.1, amitriptyline = -12.1, haloperidol = -	"After only 7 days of trazodone treatment, a relatively reliable decision can be established as to whether a therapeutically success can be expected if treatment is continued."	Mixed population of depression and schizophrenic patients. Data suggest trazodone appears to not have antipsychotic action on schizophrenia but depression patients did respond to trazodone.

								4.0, placebo = -4.1		
Lurasidone										
Suppes 2016 (score=7.0)	Lurasidone	RCT	Sponsored by Sunovion Pharmaceuticals. COI, Dr. Suppes has received funding, medications for clinical grants, consulting fees, travel expenses from Sunovian.	N = 209 patients with a diagnosis of major depressive disorder (DSM-IV-TR)	Mean age: 44.9 years; 64 males, 145 females	Lurasidone: received 3 day washout, interactive voice/web response system, and 6 weeks of 20-40 mg of lurasidone (20 mg for 7 days, then increased to 20-60 mg/day on day 8) (n=109) vs Placebo: received 3 day washout, interactive voice/web response system, and 6 weeks of 20-40 mg of identical placebo (20 mg for 7	Follow up at 1, 2, 3, 4, 5, 6 weeks	Mean change in MADRS total score was greater in lurasidone (-20.5) compared to placebo (-13.0, $p<0.001$). Response rate was 64.8% in lurasidone group compared to 30.0% in placebo.	"Lurasidone was effective and well tolerated in this study involving patients with major depressive disorder associated with subthreshold hypomanic symptoms (mixed features)."	Short study duration (6 weeks). Population is depression plus mania. Data suggest lurasidone significantly improved depressives with subthreshold hypomania versus placebo.

						days, then increased to 20-60 mg/day on day 8) (n=100)				
Sramek 2017 (score=n/a)	Lurasidone	Post-hoc analysis of Suppes 2016	Sponsored by Sunovion Pharmaceuticals Inc. No mention of COI.	N = 145 patients with a diagnosis of major depressive disorder (DSM-IV-TR) and both pre- and post-menopausal women	Mean age: 44.5 years; 0 males, 145 females	Group 1: women aged <52 years and received 3 day washout, interactive voice/web response system, and 6 weeks of 20-40 mg of lurasidone (20 mg for 7 days, then increased to 20-60 mg/day on day 8) (n=103) vs Group 2: women aged ≥52 years and received 3 day washout, interactive voice/web response	Follow up at weeks 1, 2, 3, 4, 5 and 6	Mean MADRS score change was -6.2 in group 1 (p=0.0023) compared to -9.2 in group 2 (p=0.0056). Response rate was 69% in group 1 compared to 59% in group 2.	"In this post-hoc analysis, lurasidone was found to be effective in treating post-menopausal MDD patients with mixed features (subthreshold hypomanic symptoms)."	Data suggest Lurasidone effective in reducing symptoms of depression is post-menopausal women who also exhibit symptoms of subthreshold hypomania.

						system, and 6 weeks of 20-40 mg of identical placebo (20 mg for 7 days, then increased to 20-60 mg/day on day 8) (n=42)				
Goldberg, 2017 (score=n/a)	Lurasidone	Post-hoc analysis of Suppes 2016	Sponsored by Sunovion Pharmaceuticals Inc. No mention of COI.	N=211 patients with a diagnosis of major depressive disorder (DSM-IV-TR) and 2-3 manic symptoms	Mean age: 44.9 years; 64 males, 145 females	Lurasidone: received 3 day washout, interactive voice/web response system, and 6 weeks of 20-40 mg of lurasidone (20 mg for 7 days, then increased to 20-60 mg/day on day 8) (n=109) vs Placebo: received 3 day washout, interactive	Follow up at weeks 1, 2, 3, 4, 5 and 6	Response rate was 41.7% in lurasidone group at 3 months and 37.5% for placebo ($p<.05$). Reduction in depressive symptoms was achieved at 3 months ($p=0.006$).	"In this post-hoc analysis of a placebo-controlled study with open-label extension, involving patients with MDD and subthreshold hypomanic symptoms (mixed features), lurasidone was found to have significantly improved the rate of recovery at 6 weeks (vs.	Data suggest at 3 months lurasidone sustained treatment gains displayed at 6 weeks and improved the rate of recovery.

						voice/web response system, and 6 weeks of 20-40 mg of identical placebo (20 mg for 7 days, then increased to 20-60 mg/day on day 8) (n=100)			placebo), which was sustained after an additional 3 months of extension-study treatment."	
Olanzapine										
Meyers 2009 (score=6.0)	Sertraline/ Olanzapine	RCT	Sponsored by United States Public Health Services and the National Institute of Mental Health. No COI.	N = 259 patients with unipolar MDpsy with a score of 2 or less on the Delusional Assessment Scale (DAS) and a score 3 or less on the Schedule of	Mean age: 58.0 years; 103 males, 156 females	Sertraline + Olanzapine: 150-200 mg/day of sertraline and 15-20 mg/day of olanzapine (n=129) vs. Olanzapine + Placebo: 15-20 mg/day of olanzapine and : 150-200 mg/day of placebo (n=130)	Follow-up every week until 6 weeks, then every other week until 12 weeks.	Combination therapy was found to be superior in in young adults than older adults (p=.02, p=0.01). Olanzapine/Sertraline was seen to have higher remission rate when compared to Olanzapine/placebo (p<.001).	"Combination pharmacotherapy is efficacious for the treatment of MDpsy. Future research must determine the benefits of continuing atypical antipsychotic medications beyond twelve weeks against the associated	High attrition rate. Data suggest combination therapy in beneficial for psychotic depression.

				Affective Disorder and Schizophrenia (SADS).					metabolic effects."	
Shelton 2005 (score=4.5)	Nortriptyline/Fluoxetine/Olanzapine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 500 subjects with unipolar, nonpsychotic MDD (DSM-IV)	Mean age: 42.4 years; 160 males, 340 females	OFC: received either 6 mg/day olanzapine and 25 mg/day fluoxetine or 12 mg/day olanzapine and 50 mg/day fluoxetine (n=146) vs OLZ: received 6 mg/day of olanzapine (ranged from 6-12 mg/day (n=144) vs FLX: received 25 mg/day fluoxetine (ranged from 25-50	0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks	OFC group showed a greater decrease in MADRS scores than OLZ group (p=0.005). Remission rates were 16.9% for OFC group, 12.9% for OLZ group, 13.3% for FLX, and 18.2% for NRT group (p=0.62).	"The olanzapine/fluoxetine combination did not differ significantly from the other therapies at endpoint, although it demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization."	Data suggest comparability of all 4 treatment groups but combo olanzapine/fluoxetine resulted in a quicker response.

						mg/day) (n=142) vs NRT: received 25 mg/day nortriptyline (increased to 50 mg/day on day 2, and 75 mg/day by day 4) (n=68)				
Corya 2006 (score=4.0)	Olanzapine/Fluoxetine/Venlafaxine	RCT	Sponsored by Lilly Research Laboratories. No mention of COI.	N = 483 subjects with major depressive disorder (DSM-IV)	Mean age: 45.7±10.8 years; 133 males, 350 females	All groups received medications for 12 weeks. Group 1: received 1 mg/day of olanzapine and 5 mg/day of fluoxetine (n=59) vs Group 2: received 6 mg/day of olanzapine and 25 mg/day fluoxetine (n=63) vs Group 3:	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks	For analysis, group 1-5 were combined. Group 1-5 showed a greater improvement in MADRS mean score (-7.2) compared to group 6 (-4.8, p=0.03), group 7 (-4.7, p=0.03), and group 8 (-3.7, p=0.002). Groups 1-5 showed greater advantage to group 6 overall (-14.1 vs -7.7, p<0.001).	"In conclusion, the OFC showed a rapid and robust antidepressant effect in this sample of TRD patients, along with a safety profile comparable to its component monotherapies."	No baseline data stratified by group. Data suggest similar efficacy between olanzapine, fluoxetine, venlafaxine, and combination olanzapine/fluoxetine for the treatment of treatment resistant depression.

						received 6 mg/day of olanzapine and 50 mg/day of fluoxetine (n=63) vs Group 4: received 12 mg/day olanzapine and 25 mg/day of fluoxetine (n=60) vs Group 5: received 12 mg/day olanzapine and 50 mg/day fluoxetine (n=57) vs Group 6: received 6 or 12 mg/day olanzapine (n=62) vs Group 7: received 25 mg/day or 50 mg/day of fluoxetine				

						(n=60) vs Group 8: received 75-375 mg/day of venlafaxine (n=59)				
Brunner 2014 (score=4.0)	Olanzapine/Fluoxetine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 444 patients with single or recurrent unipolar mild depressive disorder (DSM-IV-TR)	Mean age: 44.4 years; 513 males, 1034 females	OFC Group: received an initial dose of 3 mg/day olanzapine and increased up to 18 mg/day and an initial dose of 25 mg/day fluoxetine and increased up to 50 mg/day (n=221) vs Fluoxetine Group: received 25-50 mg/day of fluoxetine (n=223) for 27 weeks	12 weeks, then weekly thereafter until week 47	Relapse time was longer in OFC group compared with fluoxetine group ($p<0.001$). Mean MADRS score change was 30.4 to 9.3.	"We believe this is the first controlled relapse-prevention study in subjects with TRD that supports continued use of a second-generation antipsychotic beyond stabilization."	High dropout rates. Data suggest time to relapse was significantly longer in the combo olanzapine/fluoxetine group.
Perphenazine										

Spiker 1985 (score=4.5)	Perphenazine, Amitriptyline	RCT	Sponsored by NIMH grants. No mention of COI.	N = 58 patients with major depressive disorder, primary type, and psychotic subtype, according to the Research Diagnostic Criteria (RDC)	Mean age: 44.1 years; 22 males, 36 females	Amitriptyline at 50 mg 4 times per day (n=19) vs. Perphenazine 16 mg 4 times per day (n=17) vs. amitriptyline at 50 mg + perphenazine at 16 mg 4 times per day (n=22)	Follow-up at days 7, 14, 21, 28 and 35	Mean HAMD score decreased from 26.0 to 13.1 in perphenazine group, from 30.6 to 11.6 in amitriptyline group, and from 28.7 to 5.6 in amitriptyline plus perphenazine group (p=0.01).	"[T]his study demonstrated that although there are clearly some patients who respond to amitriptyline alone, and to perphenazine alone, amitriptyline plus perphenazine is the treatment of choice."	Data suggest combination amitriptyline and perphenazine resulted in a better response than either amitriptyline or perphenazine alone.
Anton 1993 (score=4.5)	Amitriptyline/ Amoxapine/ Perphenazine	RCT	Sponsored by Lederle Laboratories, a division of American Cyanamid. No mention of COI.	N = 37 inpatients, 21 having mood congruent (MC) psychotic depression and 16 having mood incongruent (MI) psychotic depression, all meeting DSM-III	Mean age: 45.97 years; 32 males, 5 females	Amoxapine 100 mg four times a day (n=17) vs. Amitriptyline 50 mg + Perphenazine 8 mg daily four times a day (n=20). All treatments were given for 4 weeks	No follow-up	Through ANCOVA analysis on Hamilton Rating Scale for Depression score a main effect for treatment was present ($F = 12.13$, $p < 0.002$)	"The data suggest that classifying psychotic depression into MC versus MI subtypes may have limited acute prognostic value in pharmacotherapy response rates."	Small sample size. Data suggest comparable efficacy in the treatment of psychotic depression subtypes between amoxapine and combination amitriptyline-perphenazine.

				criteria for major depression with psychotic features						
Quetiapine										
Bauer 2009 (score=6.5)	Quetiapine	RCT	Sponsored by AstraZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 493 patients with MDD (DSM-IV-TR)	Mean age: 45.4 years; 158 males, 329 females	Quetiapine XR 150: received 150 mg/day of quetiapine XR (n=166) vs Quetiapine XR 300: received 300 mg/day of quetiapine XR (n=161) vs Placebo: (n=160)	1, 2, 4, 6 weeks	Mean MADRS total score decreased by 12.21 in placebo, 15.26 quetiapine XR 150 mg/day, and 14.94 in quetiapine XR 300 mg/day ($p<0.01$). Response rate was achieved was 55.4% in quetiapine XR 150 group, 57.8% in quetiapine XR 300 group, and 46.3% in placebo ($p=.107$).	"Adjunctive quetiapine XR (150 mg/day and 300 mg/day) was effective in patients with MDD who had shown in inadequate response to antidepressant treatment. Significant reduction of depressive symptoms occurred as early as week 1. Findings were consistent with the known safety and tolerability	Data suggest both 150 mg/day and 300 mg/day doses of quetiapine XR were effective in decreasing depressive symptoms in depressed individuals showing inadequate (partial) antidepressant response and thus occurred as early as week one.

									profile of quetiapine."	
Wijkstra 2010 (score=6.5)	Quetiapine/ Venlafaxine/ Imipramine	RCT	Sponsored by grants from AstraZeneca and Wyeth Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 122 patients with psychotic major depression (DSM-IV-TR)	Mean age: 50.6 years; 60 males, 62 females	Imipramine: received 75-450 mg/day of imipramine (n=42) vs Venlafaxine: received 75-375 mg/day of venlafaxine (n=39) vs Quetiapine: received 75-375 mg/day of venlafaxine and 100-600 mg/day of quetiapine (n=41) All patients were treated for 7 weeks.	1, 2, 3, 4, 5, 6, 7 weeks	Quetiapine group showed a better outcome of reduced HAM-D score compared to venlafaxine (OR=3.86, 95% cI 1.53-9.75). Imipramine did not show a greater improvement compared to venlafaxine group (OR=2.20, 95% CI 0.89-5.41) nor did quetiapine compared to imipramine (OR=1.75, 95% CI 0.72-4.25).	"That unipolar psychotic depression should be treated with a combination of an antidepressant and an antipsychotic and not with an antidepressant alone, can be considered evidence based with regard to venlafaxine–quetiapine vs. venlafaxine monotherapy. Whether this is also the case for imipramine monotherapy is likely, but cannot be concluded from the data.	Data suggest the addition of an antipsychotic to an antidepressant is superior to antidepressant therapy alone (venlafaxine-quetiapine).

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Cutler 2009 (score=6.0)	Quetiapine/ Duloxetine	RCT	Sponsored by AstaZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 612 patients with mild depressive disorder (DSM-IV)	Mean age: 41.3 years; 233 males, 354 females	Duloxetine: received 60 mg/day of duloxetine (n=141) vs Placebo: (n=152) vs Quetiapine XR 150: received 150 mg/day of quetiapine XR (n=147) vs Quetiapine XR 300: received 300 mg/day of quetiapine XR (n=147)	1, 2, 4, 6 weeks	Mean MADRS score was reduced by 14.81 in quetiapine XR 150 group (p<.001), 15.29 in quetiapine XR 300 group (p<.001), and 14.64 in duloxetine (p<.01), and 11.18 in placebo. Response rates were 54.4% in quetiapine XR 150, 55.1% in quetiapine XR 300, 49.6% in duloxetine, and 36.2% in placebo.	“Quetiapine XR monotherapy (150 mg/day and 300 mg/day) is effective, with safety and tolerability consistent with the known profile of quetiapine XR, in the treatment of patients with MDD, with onset of symptom improvement demonstrated at week 1.”	Data suggest at week 6 there were significantly improved MADRS scores with both doses of quetiapine and duloxetine compared to placebo. Remission rates were also improved in quetiapine 300 mg and duloxetine but not 150 mg quetiapine improvement with quetiapine occurs as early as week one.
McIntyre 2007 (score=5.5)	Quetiapine/ Venlafaxine	RCT	No mention of sponsorship or COI.	N = 58 patients with a diagnosis of major depression (DSM-IV)	Mean age: 44.5 years; 22 males,	Quetiapine: received 50-200 mg/day (n=29) vs Venlafaxine: no specific dose of	1, 2, 4, 6, 8 weeks	Response rates for HAM-D (≥50% reduction) were 48% in quetiapine and 28% in placebo	“In summary, quetiapine as an adjunct to an SSRI/SNRI was effective in reducing	Data suggest quetiapine added to SSRI/venlafaxine patients with major depression was significantly better than placebo in

					36 females	venlafaxine (n=29)		(p=0.008). HAM-A response rate (≥50% reduction) was 62% in quetiapine and 28% in placebo (p=0.002).	symptoms of major depressive disorder and comorbid anxiety in patients who had residual depressive symptoms despite having received treatment with an SSRI/SNRI."	improving depressive symptoms.
Weisler 2009 (score=5.5)	Quetiapine	RCT	Sponsored by AstraZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 723 patients with a single episode or recurrent mild depressive disorder (DSM-IV)	Mean age: 40.8 years; 285 males, 415 females	Group 1: received quetiapine XR 50 mg/day (n=178) vs Group 2: received quetiapine XR 150 mg/day (n=168) vs Group 3: received quetiapine XR 300 mg/day (n=176) vs Group 4: received	4 days, 2, 6 weeks	HAM-D total score was reduced by -10.93 in group 4, -12.35 in group 1 (p=.094), -12.84 in group 2 (p<.05), and -12.65 in group 3 (p<.05). Response in MADRS of ≥50% reduction in score was achieved in 42.7% in group 1 (p<.01), 51.2% in group	"In patients with MDD, quetiapine XR monotherapy (50/150/300 mg/day) is effective in reducing depressive symptoms, with improvement from Day 4 onwards. Safety and tolerability were consistent with the	Data suggest any of the 3 doses of quetiapine (50 mg/d, 150 mg/d, or 300 mg/d) are efficacious for treating MDD symptoms from day 4 onward.

						placebo (n=178)		2 (p<.001), 44.9% group 3 (p≤.001), and 30.3% in group 4.	known profile of quetiapine."	
Wang 2014 (score=5.5)	Quetiapine/ Escitalopram	RCT	Sponsored by AstaZeneca Pharmaceuticals. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N=471 patients with mild depressive disorder (DSM-IV)	Mean age: 40.0 years; 131 males, 328 females	Quetiapine XR: received 150 mg/day of quetiapine XR (50 mg for 2 days, then increased to 150 mg on days 3-14) if no response, increased to 300 mg/day for remainder of study (n=154) vs Escitalopram: received 10 mg/day of escitalopram (n=152) vs Placebo: (n=153)	1, 3, 5, 7, 14 days, 8 weeks	Reduction in MADRS total score was -17.21 (p=0.174) in quetiapine XR, -16.73 (p=0.346) in escitalopram, compared to -15.61 in placebo. Response rate was 44.8% (p=0.376) in quetiapine XR, 48.0% (p=0.157) in escitalopram, compared to 40.5% in placebo.	"In this study, neither quetiapine XR (150/300 mg/day) nor escitalopram (10/20 mg/day) showed significant separation from placebo. Both compounds have been shown previously to be effective in the treatment of MDD; possible reasons for this failed study are discussed. Quetiapine XR was generally well tolerated, with a profile	Data suggest lack of efficacy as neither quetiapine XR at 150 mg/d or 300 mg/d nor escitalopram 10 mg/d were significantly better than placebo in treating patients with MDD.

									similar to that reported previously."	
El-Khalili 2010 (score=5.5)	Quetiapine	RCT	Sponsored by AstaZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 446 patients with a diagnosis of mild depressive disorder (DSM-IV)	Mean age: 45.5 years; 119 males, 313 females	Group 1: received quetiapine XR 150 mg/day in (3x50 mg tablets) (n=143) vs Group 2: quetiapine XR 300 mg/day (1x300 mg tablet) (n=146) vs Group 3: received placebo (n=143) All patients maintained dose of their current antidepressant.	1, 2, 4, 6, 8 weeks	Mean MADRS score reduction was greater in group 2 compared to group 3 (-14.70 vs -11.70, $p<0.01$) and also greater in group 1 compared to group 3 (-13.6, $p=0.067$). Remission rate was 35.0% (MADRS total score≤8) in group 1 ($p=0.059$), 42.5% in group 2 ($p<0.01$), compared to 24.5% in group 3.	"In this study, quetiapine XR 300 mg/d as adjunctive therapy in patients with MDD with an inadequate response to ongoing antidepressant treatment was effective at week 6. However, the difference from placebo for quetiapine XR 150 mg/d at week 6 was not statistically significant. Both doses studied (150 and 300 mg/d) were effective at week 1 and generally well tolerated."	Data suggest at week 6 there was a significant positive response with adjunctive 300 mg quetiapine XR but the result was not significantly better than placebo for the 150 mg dose.

McIntyre 2014 (score=5.0)	Quetiapine	RCT	Sponsored by AstraZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 120 patients with a diagnosis of mild depressive disorder (DSM-IV)	Mean age: 51±10 years; 4 males, 116 females	Quetiapine: received 50 mg/day of quetiapine XR on day 1 then increased to 150 mg/day on day 3 for remaining 2 weeks, then if no response increased to 300 mg/day to week 8 (n=61) vs Placebo: received 50-300 mg/day of placebo (n=59)	1, 2, 4, 6, 8 weeks	Mean HAM-D scores were better in quetiapine (-10.0±0.9) compared to placebo (-5.8±0.8) at week 8 (p=0.001). Response rate was 25.9% (95% CI 9.9-41.9, p=0.002) in quetiapine compared to 18.0% in placebo (95% CI 5.8-30.1, p=0.004).	"This study is the first to demonstrate that measures of depression, pain, and quality of life are significantly improved with quetiapine XR compared with placebo in patients with a dual diagnosis of MDD and fibromyalgia. "	Population of MDD and fibromyalgia. Data suggest a significant improvement in HAM-D scores in the quetiapine XR group over placebo.
Bortnick 2011 (score=5.0)	Quetiapine	RCT	Sponsored by AstraZeneca. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 310 patients with a diagnosis of mild depressive disorder (DSM-IV)	Mean age: 42.9 years; 106 males, 193 females	Quetiapine: received 50 mg/day of quetiapine XR on day 1 then increased to 150 mg/day on day 3 for remaining 2 weeks, then if no response	2, 8 weeks	Mean MADRS score was reduced by -16.49 in quetiapine XR compared to -13.10 in placebo (p<0.01). Response rates were 61.9% in quetiapine compared to	"In summary, the results of this large-scale, randomized, double-blind, placebo-controlled study demonstrate that quetiapine XR monotherapy	Data suggest quetiapine XR monotherapy is effective in MDD compared to placebo and improvements may occur as easily as week one.

						increased to 300 mg/day to week 8 (n=154) vs Placebo: received 50-300 mg/day of placebo (n=156) Patients were given medication for insomnia (lorazepam, zolpidem tartrate, zaleplon, zopiclone, or chloral hydrate) if needed		48.0% in placebo ($p<0.05$).	is effective in patients with MDD, with an improvement in symptoms seen as early as Week 1. Furthermore, overall tolerability and safety were consistent with the known profile of quetiapine."	
Liebowitz 2010 (score=3.5)										Open label study. Data suggest depression recurrence was significantly less in quetiapine XR versus placebo.71
Risperidone										
Mahmoud 2007	Risperidone	RCT	Sponsored by Ortho-McNeil	N = 274 outpatients adults	Mean age: 46.1	Risperidone: received 0.25 mg/day	4, 6 weeks	Reduced HRSD-17 score improved	"In conclusion, we found that	Data suggest risperidone augmentation results

71 Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

(score=6.5)			Janssen Scientific Affairs. COI: One or more of the authors have received or will receive benefits for personal or professional use.	with major depressive disorder (DSM-IV)	years; 71 males, 197 females	of risperidone for the first 3 days, 0.5 mg/day for days 4-15, then 1.0 mg/day for days 16-28, if insufficient response, increased to 2 mg/day on day 29 (n=137) vs Placebo: received same dosing as risperidone of identical tablet placebo (n= 131)		greater in risperidone compared to placebo (15.4±0.52 vs 17.3±0.52, 95% CI -3.3 to -0.5, p=0.006) at week 4 and also in week 6 (13.4±0.54 vs 16.2±0.53, 95% CI -4.2 to -1.4, p<0.001). Remission rates were 24.5% in risperidone compared to 10.7% in placebo (p=0.004).	risperidone augmentation was associated with improvements in clinician-rated depressive symptoms and patients' perception of those symptoms, reduced disability, and increased response and remission rates in patients with suboptimal response to standard antidepressant monotherapy. "	in statistically significant improvement in depressive symptoms, increased remission, and response rates and improved clinician and patients measures.
Rapaport 2006 (score=5.5)	Risperidone	RCT	Sponsored by Medical Affairs, Janssen Pharmaceutica. No mention of COI.	N = 243 patients with major depressive disorder, single or recurrent	Mean age: 46.3±12.6 years; 87 males, 154 females	Risperidone: received 0.5-2.0 mg/day risperidone and 20-6 mg/day citalopram	4 days, 1, 2, 4, 6, 8, 12, 16, 20, 24 weeks	Relapse in decrease HAM-D score occurred in 56.1% in risperidone compared to 64.1% in	"In conclusion, treatment-resistant depression is a common challenge that clinicians and	Double blind phase with high dropout rate. Data suggest risperidone augmentation in treatment resistant depression may benefit some patients

				episode, with or without psychotic features (DSM-IV)		(n=123) vs Placebo: received placebo and escitalopram (20-60 mg/day) (n=120) All patients were given an open label monotherapy of 20-60 mg/day of citalopram for 6 weeks, then given 4-6 weeks of 0.5-2.0 mg/day risperidone for 4-6 weeks, then randomized again.		placebo ($p \leq 0.05$). Citalopram monotherapy group showed <50% HAM-D-17 reduction in 434 patients.	patients must face. In this large international multicenter study, two-thirds of the patients responded rapidly and robustly to open-label risperidone augmentation. "	as approximately 50% did not relapse during double blind phase. However, not all patients with treatment resistant depression respond to risperidone augmentation suggesting the complexities of the disease.
Reeves 2008 (score=5.5)	Risperidone	RCT	Sponsored by Ortho-McNeil Janssen Scientific Affaird, LLC. COI: One or more authors have	N = 24 patients with mild depressive disorder (DSM-IV)	Mean age: 44.0 years; 7 males, 16 females	Risperidone: received 0.25-2mg/day of risperidone for 8 weeks (n=12) vs Placebo: (n=11)	1, 2, 3, 4, 6, 8 weeks	Risperidone was more effective than placebo at reducing suicide ideation ($p<0.005$), and in MADRS	"Data from this pilot study suggest that risperidone is beneficial as an augmenting treatment in	Pilot study population is MDD plus suicidality. Data suggest risperidone augmented treatment and decreased suicidal ideation during depressive episodes.

			received or will receive benefits for personal or professional use.					score reduction at week 8 (p=0.1822).	MDD patients who have developed high-risk suicidal ideation during a depressive episode. The antisuicidality effect of risperidone is especially valuable in the acute management of severe depressive symptoms."	
Keitner 2009 (score=5.0)	Risperidone	RCT	Sponsored by Investigator Initiated Grant from Janssen Pharmaceutica. COI: One or more of the authors have received or will receive benefits from personal or	N = 97 outpatients with unipolar non-psychotic major depression (DSM-IV)	Mean age: 45.2 years; 42 males, 55 females	Risperidone: received 0.5 mg/day from day 1-21, then increased to 2 mg/day, if no response then increased to 3 mg/day for 4 weeks (n=64) vs Placebo: (n=30)	1, 2, 3, 4 weeks	Remission rate for MADRS score was 51.6% in risperidone compared to 24.2% of placebo (p=0.011).	"Augmentation of an antidepressant with risperidone for patients with difficult-to-treat depression leads to more rapid response and a higher remission rate and better quality-of-life."	Data suggest risperidone augmentation of antidepressants resulted in improved and more rapid response, higher remission rates and improved quality of life in treatment resistant non-psychotic major depressives.

			professional use.							
Sulpiride										
Uchida 2005 (score=4.5)	Sulpiride, Paroxetine	RCT	No mention of COI or sponsorship.	N = 41 participants meeting DSM-IV criteria for major depressive disorder without psychotic features	Mean age: 38.94 years; 25 males, 16 females	Paroxetine 10-40 mg/day plus Sulpiride 100 mg/day (n=20) vs. Paroxetine 10-40 mg/day alone (n=21)	Follow-up at weeks 1, 2, 4, 6, 8, and 12	Mean change in Montgomery-Asberg Depression Rating Scale: Paroxetine + sulpiride group = 34.4 to 5.6, Paroxetine alone group = 32.2 to 10.4 ($p < 0.001$). Combined group had greater reduction in Hamilton Rating Scale for Depression and Zung Depression Scale scores between week 1 and 12 ($p < 0.05$)	"The combination treatment may be a safe and effective strategy for accelerating antidepressant response."	Small study sample. Open label trial. Data suggest addition of sulpiride to paroxetine resulted in significant improved depression scores.
Thioridazine										
Stabl 1995	Moclobemide/Thioridazine	RCT	No mention of	N = 78 patients with	Mean age: 52.0	Group 1: received 150 mg	3, 7, 14, 21, 28 days, 4	Improvement in depression of at least 50%	"[T]he study shows a remarkable	Small sample size per group. Data suggest addition of

(score=6.0)			sponsorship or COI.	severe depression (DSM-III-R)	years; 34 males, 44 females	moclobemide 3 times daily and 100 mg placebo for 4 weeks (n=40) vs Group 2: received 150 mg moclobemide and 100 mg thioridazine 3 times daily for 4 weeks (n=38)	weeks, 6 months	was observed in 77% of group 1 compared to 74% in group 2 (p>0.2).	antidepressant effect of moclobemide in severe refractory depression, even in patients with an existing depressive episode of long duration. The addition of thioridazine did not further increase efficacy or speed of onset. Moclobemide was well tolerated, and the addition of thioridazine did not significantly impair its tolerability."	thioridazine did not increase efficacy of moclobemide.
Ziprasidone										
Papakostas 2015 (score=7.5)	Ziprasidone, Escitalopram	RCT	Sponsored by the NIMH, Pfizer and	N = 139 participants who had 8 weeks	Mean age: 44.46 years;	Escitalopram 10-30 mg/day plus Ziprasidone	Follow-up at weeks 1, 2, 3, 4,	Mean improvement in Hamilton Depression	"Ziprasidone as an adjunct to escitalopram	Data suggest ziprasidone as adjunctive therapy to escitalopram shows

			Forest Laboratories. COI, one or more of the authors have received or will receive benefits for personal or professional use	of open-label escitalopram and still met DSM-IV criteria for major depressive disorder	41 males, 98 females	dosage range of 20–80 mg twice daily (n=71) vs. Escitalopram 10-30 mg/day plus placebo of 20–80 mg twice daily (n=68). All treatments were given for 8 weeks	5, 6, 7 and 8	Rating Scale scores at 8 weeks: ziprasidone group = -6.4, placebo group = -3.3 (p=0.04)	demonstrated antidepressant efficacy in adult patients with major depressive disorder experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram."	efficacy in patients with MDD who have persistent symptoms after 8 weeks of escitalopram monotherapy.
Papakostas 2012 (score=5.5)	Ziprasidone	RCT	Sponsored by Pfizer, Inc. COI, one or more of the authors have received or will receive benefits for personal or professional use	N = 120 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 43.7 years; 67 males, 53 females	Study divided into two 6-week phases. Group 1 – given placebo during phase I and II (n=43) vs. Group 2 – given placebo during phase I and ziprasidone during phase II (n=48) vs. Group 3 –	Follow-up weekly for 12 weeks	Mean score reduction in Hamilton Depression Rating Scale scores: Pooled ziprasidone groups = -5.4, placebo group = -5.7 (p = 0.96)	"In conclusion, treatment with ziprasidone monotherapy was not associated with any statistically significant advantage in efficacy over placebo. Although studies involving larger sample size would be required to have adequate	Data suggest lack of efficacy as ziprasidone was not much better than placebo.

						given ziprasidone during phases I and II (n=29). Ziprasidone given as 20-80 mg twice daily, placebo given in same dosage and frequency			statistical power to detect treatment differences smaller than 2.5 points on the HDRS-17, such differences would be of questionable clinical relevance."	
Jeon 2014 (score=NA)	Ziprasidone	Post-hoc analysis of Papakostas 2012	Sponsored by Pfizer Inc., the Ministry of Education, Science and Technology and the Samsung Medical Center Clinical Research Development Program. COI, one or more of the authors have received or will receive	N = 106 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 44.0 years; 60 males, 46 females	Study divided into two 6-week phases. Group 1 – given placebo during phase I and II (n=41) vs. Group 2 – given placebo during phase I and ziprasidone during phase II (n=41) vs. Group 3 – given	Follow-up weekly for 12 weeks	Quick Inventory of Depressive Symptomatology Scale, Self-Rated (QIDS-SR) mean score reduction significantly lower in ziprasidone pooled group compared to placebo group (Z = 2, p = 0.046) but not in Hamilton Depression Rating Scale scores (HDRS-	"Ziprasidone monotherapy may produce significant improvement compared with placebo in MDD patients with psychomotor symptoms."	Data suggest ziprasidone may improve MDD patients with psychomotor symptoms.

			benefits for personal or professional use			ziprasidone during phases I and II (n=24). Ziprasidone given as 20-80 mg twice daily, placebo given in same dosage and frequency		17) (Z = 1.66, p = 0.10)		
Heo 2015 (score=NA)	Ziprasidone	Post-hoc analysis of Papakostas 2012	Sponsored by Pfizer Inc., the Ministry of Education, Science and Technology and the Samsung Medical Center Clinical Research Development Program. COI, one or more of the authors have received or will receive benefits for	N = 120 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 43.7 years; 67 males, 53 females	Study divided into two 6-week phases. Group 1 – given placebo during phase I and II (n=43) vs. Group 2 – given placebo during phase I and ziprasidone during phase II (n=48) vs. Group 3 – given ziprasidone	Follow-up weekly for 12 weeks	No significant difference in score reduction of Hamilton Depression Rating Scale (HDRS) and Quick Inventory of Depressive Symptomatology Scale, Self-Rated (QIDS-SR) in pooled analysis of ziprasidone and placebo groups (HDRS: Z = 0.25, p = 0.08; QIDS-SR: Z = 0.43, p = 0.67)	"In conclusion, treatment with ziprasidone monotherapy may produce no significant improvement compared with placebo in patients with in anxious depression."	Data suggest lack of efficacy compared to placebo for ziprasidone monotherapy in the treatment anxious and non-anxious depression.

			personal or professional use			during phases I and II (n=29). Ziprasidone given as 20-80 mg twice daily, placebo given in same dosage and frequency				
Patkar 2012 (score=5.5)	Ziprasidone	RCT	Sponsored by Pfizer. COI, one or more of the authors have received or will receive benefits for personal or professional use	N = 73 participants meeting DSM-IV criteria for major depressive episode (MDE) and 2-3 manic criteria	Mean age: 38.89 years; 34 females, 39 males	Ziprasidone 40-160 mg/day (n=35) vs. Placebo 40-160 mg/day (n=38). All treatments given for six weeks	Follow-up at weeks 1, 2, 3, 4, 5, and 6	Montgomery-Asberg Depression Rating Scale (MADRS) mean difference between ziprasidone and placebo groups = 5.4 ($F = 8.273$, $p < 0.05$)	"There was a statistically significant benefit with ziprasidone versus placebo in this first RCT of any medication for the provisional diagnostic concept of the depressive mixed state."	Mixed population of MDD and bipolar disorder. Short study duration. Data suggest ziprasidone was effective for both MDD and bipolar disorders but most effective for bipolar disorder.

Evidence for the Use of Symbyax

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Rothschild 2004 (score=5.5)	Olanzapine/ Fluoxetine	RCT	Sponsored by Eli Lilly and Company. No mention of COI.	Trial 1: N = 124 patients with unipolar major depression with psychotic features* Trial 2: N = 125 patients with unipolar major depression with psychotic features* *diagnosis according to DSM-IV criteria	Trial 1: Mean age 40.7 years; 60 males, 64 females Trial 2: Mean age: 41.1 years; 62 males, 63 females	Trial 1: Olanzapine (OLZ) at 5-20 mg/d (n=48) vs. Placebo group (PLA) (n=51) vs. Olanzapine 5-20 mg/d and fluoxetine 20-80 mg/d (OFC) (n=25) Trial 2: Olanzapine at 5-20 mg/d (OLZ) (n=53) vs. Placebo group (PLA) (n=49) vs. Olanzapine 5-20 mg/d and fluoxetine 20-80 mg/d (OFC) (n=23)	Follow-up at baseline, week 1, 2, 3 4, 5, 6, 7, & 8	Trial 1: The mean change in HAMD-24 scores was -14.9 in OLZ group, -10.4 in PLA group, and -20.9 in OFC group. OLZ vs PLA (p=0.088). OFC vs PLA (p=0.001).OLZ vs OFC (p=0.057). Trial 2: The mean change in HAMD-24 scores was -13.9 in OLZ group, -12.5 in PLA group, and -15.8 in OFC group. OLZ vs PLA (p=0.517). OFC vs PLA (p=0.220). OFC vs OLZ (0.481).	"[A]n olanzapine/fluoxetine combination was associated with significant improvement compared with placebo in one trial and was well tolerated."	High dropout rates in both studies (53-59%) Data suggest olanzapine monotherapy was not significantly superior to placebo but combination olanzapine/fluoxetine therapy was associated with significant improvement in depression symptoms in Trial 1 (i.e. not in both trials).
Shelton 2005 (score=4.5)	Nortriptyline/Fluoxetine /Olanzapine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or	N = 500 subjects with unipolar, nonpsychotic MDD (DSM-IV)	Mean age: 42.4 years; 160 males, 340 females	OFC: received either 6 mg/day olanzapine and 25 mg/day fluoxetine or 12 mg/day olanzapine and 50 mg/day fluoxetine	0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks	OFC group showed a greater decrease in MADRS scores than OLZ group (p=0.005). Remission rates were 16.9% for OFC group, 12.9%	"The olanzapine/fluoxetine combination did not differ significantly from the other therapies at endpoint,	Data suggest comparability of all 4 treatment groups but combo olanzapine/fluoxetine resulted in a faster response.

			professional use.			(n=146) vs OLZ: received 6 mg/day of olanzapine (ranged from 6-12 mg/day (n=144) vs FLX: received 25 mg/day fluoxetine (ranged from 25-50 mg/day) (n=142) vs NRT: received 25 mg/day nortriptyline (increased to 50 mg/day on day 2, and 75 mg/day by day 4) (n=68)		for OLZ group, 13.3% for FLX, and 18.2% for NRT group (p=0.62).	although it demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization."	
Corya 2006 (score=4.0)	Olanzapine/ Fluoxetine/ Venlafaxine	RCT	Sponsored by Lilly Research Laboratories. No mention of COI.	N = 483 subjects with major depressive disorder (DSM-IV)	Mean age: 45.7±10.8 years; 133 males, 350 females	All groups received medications for 12 weeks. Group 1: received 1 mg/day of olanzapine and 5 mg/day of fluoxetine (n=59) vs Group 2: received 6 mg/day of olanzapine and 25 mg/day fluoxetine (n=63) vs	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks	For analysis, group 1-5 were combined. Group 1-5 showed a greater improvement in MADRS mean score (-7.2) compared to group 6 (-4.8, p=0.03), group 7 (-4.7, p=0.03), and group 8 (-3.7, p=0.002). Groups 1-5 showed greater advantage to group 6 overall (-14.1 vs -7.7, p<0.001).	"[T]he OFC showed a rapid and robust antidepressant effect in this sample of TRD patients, along with a safety profile comparable to its component monotherapies. "	No baseline data stratified by group. Data suggest similar efficacy between olanzapine, fluoxetine, venlafaxine, and combination olanzapine/fluoxetine for the treatment of treatment resistant depression.

						Group 3: received 6 mg/day of olanzapine and 50 mg/day of fluoxetine (n=63) vs Group 4: received 12 mg/day olanzapine and 25 mg/day of fluoxetine (n=60) vs Group 5: received 12 mg/day olanzapine and 50 mg/day fluoxetine (n=57) vs Group 6: received 6 or 12 mg/day olanzapine (n=62) vs Group 7: received 25 mg/day or 50 mg/day of fluoxetine (n=60) vs Group 8: received 75-375 mg/day of venlafaxine (n=59)				

Brunner 2014 (score=4.0)	Olanzapine/ Fluoxetine	RCT	Sponsored by Eli Lilly and Company. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 444 patients with single or recurrent unipolar mild depressive disorder (DSM-IV-TR)	Mean age: 44.4 years; 513 males, 1034 females	OFC Group: received an initial dose of 3 mg/day olanzapine and increased up to 18 mg/day and an initial dose of 25 mg/day fluoxetine and increased up to 50 mg/day (n=221) vs Fluoxetine Group: received 25-50 mg/day of fluoxetine (n=223) for 27 weeks	12 weeks, then weekly thereafter until week 47	Relapse time was longer in OFC group compared with fluoxetine group ($p<0.001$). Mean MADRS score change was 30.4 to 9.3.	"We believe this is the first controlled relapse-prevention study in subjects with TRD that supports continued use of a second-generation antipsychotic beyond stabilization."	High dropout rates. Data suggest time to relapse was significantly longer in the combo olanzapine/fluoxetine group.

Evidence for the Use of Ketamine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Murrough 2013 (score = 9.0)	IV Ketamine	RCT	Sponsored by NIMH, NIH National Center for Advancing Translational Sciences, the Department of Veterans Affairs (VA), the Brown Foundation, Inc., the Michael E. DeBakey VA Medical Center. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 73 participants with a primary diagnosis of major depressive disorder via DSM-IV criteria	Mean age: 44.82 years; 36 males, 37 females	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) (n=47) vs. Single intravenous infusion of midazolam (0.045 mg/kg) (n=25). Both treatments were infused over 40 minutes	Follow-up at 24, 48, and 72 hours and 7 days. Responders were followed biweekly for up to 4 weeks	Ketamine showed significantly greater Montgomery–Asberg Depression Rating Scale score improvement at 24 hours versus midazolam group - adjusted mean MADRS score lower in ketamine group by 7.95 points (95% CI [3.2, 12.71], $p \leq 0.002$)	"Ketamine demonstrated rapid antidepressant effects in an optimized study design, further supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression."	Short term follow-up. Data suggest a single IV infusion of ketamine hydrochloride (0.5 mg/kg) showed a rapid antidepressant effect in patients with moderate to severe treatment resistant depression and MADRS scores improved compared to placebo (midazolam).
Price 2014 (score=N/A)	IV Ketamine	Secondary Analysis of Morroug h 2013	Sponsored by Evotec, Janssen Pharmaceuticals, Avanir, NIMH, NIH National Center for Advancing Translational Sciences, AstraZeneca, Brainsway, Euthymics, Neosync, and Roche and CNS Response,	N = 57 participants with a primary diagnosis of major depressive disorder via DSM-IV criteria	Mean age: 46.83 years; 27 males, 30 females	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) (n=36) vs. Single intravenous infusion of midazolam (0.045 mg/kg) (n=21). Both treatments were infused	Follow-up at 24, 48, and 72 hours and 7 days. Responders were followed biweekly for up to 4 weeks	Ketamine group had 53% of patients score zero on all three explicit suicide measures at 24 hours. Midazolam had 24% ($\chi 2 = 4.6$, $p = 0.03$)	"Intravenous ketamine produces rapid reductions in suicidal cognition over and above active placebo. Further study is warranted to test ketamine's antisuicidal effects in higher risk samples."	Data suggest IV ketamine was associated with rapid and significant reduction of suicidal ideation in moderate to severely treatment depressed individuals as reflected in all 3 suicide measures.

			Otsuka, Servier, and Sunovion, NARSAD, and USAMRAA, Bristol-Myers Squibb, Naurex, Roche, Genentech, and the Department of Veterans Affairs (VA), and the Brown Foundation, Inc. COI, one or more of the authors have received or will receive benefits for personal or professional use.			over 40 minutes				
Murrough 2015 (score = N/A)	IV Ketamine	Secondary Analysis of Murrough 2013	Sponsored by NIH, NIMH, NIH National Center for Advancing Translational Sciences, Department of Veterans Affairs, and a NARSAD Independent Investigator Award. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 62 participants with a primary diagnosis of major depressive disorder via DSM-IV criteria, with treatment-resistant depression and free of concomitant antidepressant medication	Mean age: 46.2 years; 28 males, 34 females	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) (n=43) vs. Single intravenous infusion of midazolam (0.045 mg/kg) (n=19). Both treatments were infused over 40 minutes	Follow-up at 24, 48, and 72 hours and 7 days. Responders were followed biweekly for up to 4 weeks	No difference in neurocognitive performance between treatments ($p > 0.05$) as well as no associated with antidepressant response ($p > 0.05$)	"In the current study, we found that ketamine was devoid of adverse neurocognitive effects at 7 days post treatment and that slower baseline processing speed was associated with greater antidepressant response."	Data suggest ketamine was not associated with adverse neurocognitive effects 7 days post infusion in treatment resistant depressives and slower baseline processing speed was associated with a larger antidepressant response.

Singh 2016 (score = 7.5)	IV Ketamine	RCT	Sponsored by Janssen Research and Development. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 68 participants satisfying DSM-IV-TR criteria for recurrent major depressive disorder without psychotic features	Mean age: 43.9 years; 23 males, 45 females	Intravenous ketamine (0.5 mg/kg of body weight) two times weekly (n=18) vs. Intravenous placebo (0.5 mg/kg of body weight) two times weekly (n=17) vs. Intravenous ketamine (0.5 mg/kg of body weight) three times weekly (n=17) vs. Intravenous placebo (0.5 mg/kg of body weight) three times weekly (n=16). All treatments given over 40 minutes and treatments lasted up to 4 weeks	Follow-up at days 1, 4, 8, 11, and 15	Mean difference in Montgomery–Asberg Depression Rating Scale (MADRS) scores at day 15: ketamine twice weekly = -18.4, placebo twice weekly = -5.7 ($p < 0.001$), ketamine thrice weekly = -17.7, placebo thrice weekly = -3.1 ($p < 0.001$). Mean difference in MADRS scores did not different between ketamine groups	"Twice-weekly and thrice-weekly administration of ketamine at 0.5 mg/kg similarly maintained antidepressant efficacy over 15 days."	Data suggest either twice weekly or three times weekly infusions of IV ketamine (0.5mg/kg) were similar in maintaining antidepressant efficacy in the treatment of treatment resistant depression.
Lapidus 2014 (score = 6.5)	IV Ketamine	RCT	Sponsored by NIH and the Brain and Behavior Research Foundation. COI, one or more of the authors have received or will receive benefits for personal or	N = 20 participants meeting DSM-IV criteria for major depressive disorder (chronic or recurrent) without	Mean age: 48.0 years; 10 males, 10 females	Crossover design – all participants received both treatments. First received 50 mg of racemic ketamine hydrochloride (n=10) vs. First received	Follow-up at 40, 120, and 240 minutes, 24, 48, and 72 hours, and 7 days	Mean difference in Montgomery–Asberg Depression Rating Scale (MADRS) scores at 24 hours between ketamine and placebo groups = 7.6 (95% CI [3.9, 11.3]). Via repeated measures mixed	"This study provides the first controlled evidence for the rapid antidepressant effects of intranasal ketamine. Treatment was associated with minimal adverse	Double blind crossover study. Data suggest 50 mg of racemic ketamine may be appropriate for treatment of treatment resistant depression as symptoms were significantly

			professional use.	psychotic features		placebo (0.9% saline solution) (n=10)		linear model ketamine has greater improvement compared to placebo over seven day follow-up ($F_{1,18}$=28.1, p < 0.001)	effects. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with major depression.	reduced in MADRS scores compared to placebo.
Jafarinia 2016 (score = 6.5)	Oral Ketamine	RCT	No COI. Sponsored by Tehran University of Medical Sciences.	N = 46 participants meeting DSM-IV-TR criteria for major depression	Age and gender data only available for 40 participants. Mean age: 39.83 years; 10 males, 30 females	Ketamine 50 mg three times daily (n=23) vs. Diclofenac 50 mg three times daily (n=23). Both treatments given for six weeks	Follow-up at 3, 6 weeks	Hamilton Depression Rating Scale (HADS) scores at week 3: ketamine = 6.95, diclofenac = 8.4 (p = 0.005), at week 6: ketamine = 6.2, diclofenac = 7.35 (p = 0.003)	"Oral ketamine appears to be a safe and effective option in improving depressive symptoms of patients with chronic pain with mild-to-moderate depression."	Small sample. 6 week follow-up. Data suggest oral ketamine significantly reduced depression scores in mild to moderate chronically depressed patients.
Zarate 2006 (score = 6.5)	Ketamine	RCT	Sponsored by the Intramural Research Program at the National Institute of Mental Health, National Institutes of EHealth, and Department of Health and Human Services. No mention of COI.	N = 18 participants meeting DSM-IV major depression criteria	Mean age: 46.7 years; 6 males, 12 females	Crossover design – all groups received both treatments. First received single intravenous infusion of saline solution (n=9) vs. First received single intravenous infusion of ketamine hydrochloride 0.5 mg/kg	Follow-up at 40, 80, 110, and 230 minutes, 1, 2, 3, and 7 days	Ketamine group showed decreased Hamilton Depression Rating Scale scores at 110 minutes through 7 days. Effect size for drug difference (d) = 1.46 (95% CI [0.91, 2.01]), after 24 hours, d = 0.68 [0.13, 1.23] after 24 hours to 1 week	"Robust and rapid antidepressant effects resulted from a single intravenous dose of an N-methyl-Daspartate antagonist; onset occurred within 2 hours postinfusion and continued to remain significant for 1 week."	Data suggest a rapid antidepressant response from a single dose of ketamine 2 hours post infusion and gains were sustained up to 7 days in treatment resistant major depression.
Li 2016 (score = 5.0)	IV Ketamine	RCT	No mention of COI. Sponsored by the Ministry of Science and	N = 48 participants meeting DSM-IV-TR	Mean age: 45.87 years; 13	Single dose of intravenous ketamine 0.5 kg/mg (n=16)	Follow-up at 40, 80, 120, and	Both ketamine groups showed through ROI analysis had	"Ketamine's rapid antidepressant effects involved	Data suggest both ketamine groups responded better than

			Technology and Taipei veterans general hospital.	criteria for major depressive disorder	males, 35 females	vs. Single dose of intravenous ketamine 0.2 kg/mg (n=16) vs. Single dose intravenous normal saline (n=16). All treatments given over 40 minutes	240 minutes	increased standardized uptake values (SUV) of glucose metabolism (group by time interaction: F = 7.373, p = 0.002). All three groups had decreases in SUV of amygdala (p < 0.001)	the facilitation of glutamatergic neurotransmissio n in the PFC."	placebo and the lowest dose (0.2 mg/kg) group exhibited rapid antidepressant response. Data support ketamine facilitation of glutamatergic transmission in the prefrontal cortex.

Evidence for the Use of Esketamine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Canuso 2018 (score=6.5)	Esketamine	RCT	Sponsored by Janssen Research and Development, LLC. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 68 participants meeting DSM-IV-TR criteria for major depressive disorder without psychotic features	Age and sex data only available for 66 participants. Mean age: 35.8 years; 25 males, 43 females	Intranasal esketamine (84 mg) twice weekly (n=32) vs. Placebo (84 mg) (n=36). All treatments were given for 4 weeks	Twice weekly until day 25, then weekly until day 52, and then biweekly through day 81	Mean MADRS scores decreased significantly more in esketamine group at 4 hours after initial dose ($p = 0.015$). Esketamine had greater mean reduction in depressive symptoms during four weeks of treatment (significant at 1, 2, 3 hours and day 11, $p < 0.05$). During follow-up there was no significant difference between groups ($p = 0.211$)	"These preliminary findings indicate that intranasal esketamine compared with placebo, given in addition to comprehensive standard-of-care treatment, may result in significantly rapid improvement in depressive symptoms, including some measures of suicidal ideation, among depressed patients at imminent risk for suicide."	Data suggest intranasal esketamine may benefit depressed patients when given in addition to standard antidepressant therapy as MADRS scores significantly improved in the interventional group.
Daly 2017 (score=6.0)	Esketamine	RCT	Sponsored by Janssen Research and Development, LLC. COI, one or more of the authors have received or will receive benefits for personal or	N = 67 participants meeting DSM-IV-TR criteria for major depressive disorder and have a history of	Mean age: 44.7 years; 29 males, 38 females	Placebo Nasal Spray (n=33) vs. Esketamine 28 mg Nasal Spray (n=11) vs. Esketamine 56 mg Nasal Spray (n=11) vs. Esketamine 84 mg Nasal	Follow-up at 2 hours, 24 hours, and day 15, 18, 22, 25, 32, 39, 46, 60, 74 with an additional follow-up	Mean MADRS total score in all three esketamine groups superior to placebo (28 mg $p = 0.02$, 56 mg $p = 0.001$, 84 mg $p < 0.001$). There was a significant ascending dose-	"In this first clinical study to date of intranasal esketamine for TRD, antidepressant effect was rapid in onset and dose related.	Data suggest a rapid and dose-related response of adjunct esketamine to standard oral antidepressant therapy

			professional use.	inadequate response to two or more antidepressants		Spray (n=12). All treatments were given twice in one week (days 1 and 4). After day 8 those within the placebo group were randomized to all treatments (placebo n=10, esketamine 28mg n=8, esketamine 56mg n=9, esketamine 84mg n=5)	at 1, 2, 4 and 8 weeks	response among esketamine groups ($p < 0.001$)	Response appeared to persist for more than 2 months with a lower dosing frequency. Results support further investigation in larger trials."	compared to placebo.

Evidence for the Use of Anti-inflammatory Agents

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Dean 2017 (score=7.0)	Anti-inflammatory	RCT	COI, one or more of the authors have received or will receive benefits for personal and professional use. Sponsored by the Brain and Behavior Foundation, the Australasian Society of Bipolar and Depressive Disorders/Servier and the Mental Health Research Institute.	N = 71 participants with major depressive disorder meeting DSM-IV criteria	Mean age: 49.42 years; 24 males, 47 females	Minocycline – 200 mg/day (n=36) vs. Placebo – 200 mg/day (n=35). Each treatment given for 12 weeks	Follow-up at weeks 2, 4, 8, 12, and 16	At weeks 12 and 16 there was no significant difference in mean Montgomery-Asberg Depression Rating Scale scores between groups (week 12 p = 0.624, week 16 p = 0.761)	"While the primary outcome was not significant, the improvements in other comprehensive clinical measures suggest that minocycline may be a useful adjunct to improve global experience, functioning, and quality of life in people with major depressive disorder. Further studies are warranted to confirm the potential of this accessible agent to optimise treatment outcomes."	Data suggest no difference between groups at conclusion of 12 week trial for primary outcome with respect to changes in depression via Montgomery-Asberg Rating Scale.
Müller 2006 (score=6.5)	Anti-inflammatory	RCT	No mention of COI. Sponsored by Pharmacia GmbH, Erlangen, Germany.	N = 40 patients with major depression meeting DSM-IV criteria	Mean age: 44.4 years; 20 males, 20 females	Celecoxib – 400 mg/day (n=20) vs. Placebo – 400 mg/day (n=20). Both groups also received reboxetine – 4-10 mg/day. Treatments	Follow-up at weeks 1, 2, 3, 4, 5 and 6	Mean Hamilton Depression Rating Scale scores at week 6: celecoxib group = 7.9, placebo = 12.1. Mean difference between week 12 and baseline scores significantly	"Moreover, the fact that treatment with an anti-inflammatory drug showed beneficial effects on MD indicates that inflammation is related to the pathomechanism	High dropout rate. Both celecoxib and placebo groups improved significantly but the celecoxib group showed more improvement

						were given for 6 weeks		greater in reboxetine group (F = 3.22, p = 0.035)	of the disorder, although the exact mechanisms remain to be elucidated."	compared to placebo.
Akhondzadeh 2009 (score=6.5)	Anti-inflammatory	RCT	No mention of COI. Sponsored by Tehran University of Medical Sciences.	N = 40 patients with major depression meeting DSM-IV criteria	Mean age: 34.43 years; 15 males, 25 females	Fluoxetine 20 mg/day plus celecoxib 400 mg/day (n=20) vs. Fluoxetine 20 mg/day plus placebo 400 mg/day (n=20). All treatments given for six weeks	Follow-up at weeks 2, 4, and 6	Mean Hamilton Depression Rating Scale scores were significantly lower in the celecoxib group versus the placebo group at 6 weeks ($p \geq 0.001$)	"The results of this study suggest that celecoxib may be an effective adjuvant agent in the management of patients with major depression and anti-inflammatory therapies should be further investigated."	Data suggest fluoxetine plus celecoxib group was better than placebo in improving symptoms of major depression although both interventional and placebo groups improved. Baseline data do not depict length or duration of depression symptoms in groups.
Abbasi 2012 (score=6.5)	Anti-inflammatory	RCT	No COI. Sponsored by Tehran University of Medical Sciences.	N = 40 patients with major depression meeting DSM-IV criteria	Mean age: 34.65 years; 27 males, 13 females	Sertraline 200 mg/day plus celecoxib 200 mg/day (n=20) vs. Sertraline 200 mg/day plus placebo 200 mg/day (n=20)	Follow-up at weeks 1, 2, 4, and 6	Mean Hamilton Depression Rating Scale scores by week 6: Celecoxib group = 13.4, Placebo group = 10.05 (mean difference = 3.35, t = 2.994, p = 0.005)	"We showed that the antidepressant activity of celecoxib might be linked to its capability of reducing IL-6 concentrations. Moreover, supporting previous studies we showed that celecoxib is both safe and effective as an adjunctive antidepressant."	Data suggest celecoxib's antidepressant effect may be associated with serum IL-6 reduction.

Sepanjnia 2012 (score=6.5)	Anti-inflammatory	RCT	No COI. Sponsored by Tehran University of Medical Sciences.	N = 40 patients with major depression meeting DSM-IV criteria	Mean age: 32.05 years; 11 males, 29 females	Pioglitazone 15 mg / 12 hours for 6 weeks (n=20) vs. Placebo 15 mg / 12 hours for 6 weeks (n=20). All participants were given 20 mg/day for one week, 30 mg/day for 5 weeks	Follow-up at weeks 2, 4, and 6	Mean Hamilton Depression Rating Scale scores by week 6: Pioglitazone group = 8.6, Placebo group = 12.0 (mean difference = -3.4, F = 9.6, p = 0.004)	"Pioglitazone is a safe and effective adjunctive short-term treatment in patients with moderate-to-severe MDD even in the absence of metabolic syndrome and diabetes."	Study does not disclose duration of depression at baseline between groups. Data suggest no dropouts. Data suggest more symptom remission and earlier response in pioglitazone plus citalopram group.
Gougol 2015 (score=6.5)	Anti-inflammatory	RCT	No COI. Sponsored by Tehran University of Medical Sciences.	N = 44 participants meeting DSM-IV-TR criteria for major depressive disorder	Mean age: 35.3 years; 15 males, 29 females	Fluoxetine 20 mg/day plus Simvastatin 20 mg/day (n=22) vs. Fluoxetine 20 mg/day plus Placebo 20 mg/day (n=22). All treatments were given for six weeks	Follow-up at weeks 2, 4, and 6	Mean Hamilton Depression Rating Scale score reduction by week 6: Simvastatin group = 18.5, Placebo group = 13.68 (mean difference = 4.81, F = 3.78, p = 0.02)	"In conclusion, simvastatin seems to be a safe and effective adjunct therapy for patients suffering from major depression disorder."	Study suggests no dropouts. Data suggest simvastatin plus fluoxetine group showed earlier symptom improvement, but remission rates were similar between both the simvastatin and placebo groups.
Husain 2017 (score=6.0)	Anti-inflammatory	RCT	COI, one or more of the authors have received or will receive benefits for personal and professional use. Sponsored by the Pakistan Institute of Living and Learning (PILL).	N = 41 participants meeting DSM-5 criteria for major depressive disorder with a current episode and failed to respond to at least two	Mean age not reported. Median age: 35 for minocycline group, 40 for placebo group; 20 males, 21 females	Minocycline 100 mg/day for two weeks, then 200 mg/day for ten weeks, plus treatment as usual (TAU) (n=21) vs. Placebo 100 mg/day for two weeks, then 200 mg/day for ten weeks, plus TAU (n=20)	Follow-up at 2, 4, 8 and 12 weeks	Hamilton Depression Rating Scale scores at baseline and 12 weeks: Placebo = 32.6, 32.0 (mean difference = -0.2), Minocycline = 34.5, 15.1 (-18.3). There was a significant difference between groups (p < 0.001)	"The findings indicate that adjunctive minocycline leads to improvement in symptoms of treatment-resistant depression. However, our findings require replication in a larger sample."	No dropouts. Data suggest minocycline may benefit patients with treatment resistant depression as reflected in proved HAM-D scores.

				antidepressants						
Block 2017 (score=5.0)	Anti-inflammatory	RCT	COI, one or more of the authors have received or will receive benefits for personal and professional use. Sponsored by Corcept Therapeutics.	N = 34 participants meeting DSM-IV criteria for severe major depressive disorder with psychotic features	Mean age: 46.2 years; 131 males, 161 females	Mifepristone 1200 mg/day for 1 week, followed by antidepressant treatment for days 8 to 56 (n=141) vs. Placebo 1200 mg/day for 1 week, followed by antidepressant treatment for days 8 to 56 (n=151)	Follow-up at days 7, 14, 28, 42, and 56	Study stopped early – primary efficacy end point unlikely to be met. No statistical difference between groups with proportion with greater than 50% reduction in Brief Psychiatric Rating Scale – Positive Symptom Subscale (BPRS-PSS)	"Mifepristone 1200 mg daily for 7 days was safe and well tolerated, allowing most treated patients to achieve the a priori defined therapeutic plasma level of 1637 ng/mL, the mifepristone level associated with biological effect and clinical benefit."	Study terminated early before desired enrollment achieved.
El-Haggar 2018 (score=4.5)	Anti-inflammatory	RCT	No COI or sponsorship.	N = 80 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 32.91 years; 39 males, 41 females	Escitalopram 20 mg/day plus 2 placebo tablets (n=40) vs. Escitalopram 20 mg/day plus phosphodiesterase inhibitor pentoxifylline (PTX) 800 mg/day (n=40). All treatments given for 12 weeks	Follow-up at weeks 4, 8, and 12	85% of PTX group and 41% of placebo group remitted based on Hamilton Depression Rating Scales scores (p = 0.023)	"The findings of this study suggest that PTX could be a promising adjunct to antidepressants in the treatment of MDD patients."	Duration of depression not mentioned at baseline. Data suggest at 8 and 12 weeks the pentoxifylline plus escitalopram group showed greater improvement in HAM-D scores.
Majd 2015 (score=4.0)	Anti-inflammatory	RCT	No mention of COI or sponsorship.	N = 30 female participants meeting DSM-IV-TR criteria for	Mean age: 35.45 years; 0 males, 30 females	Sertraline plus celecoxib 100 mg/day twice daily (n=15) vs. Sertraline plus placebo	Follow-up at weeks 4 and 8	Mean Hamilton Depression Rating Scale scores at week 4: placebo group = 17.3, celecoxib group =	"The results suggested that celecoxib may hasten the onset of therapeutic action of	Study population comprised of females only. Small sample size (n=30) with high dropout rate.

				major depression		100 mg/day twice daily (n=15). All treatments given for 8 weeks		12.4 (p=0.021). Mean Hamilton Depression Rating Scale scores at week 8: placebo group = 10.4, celecoxib group = 7.9 (p>0.05)	sertraline and increase response and remission rate in depressive disorders."	Data states depression severity at baseline did not differ between groups but no data available to analyze. Data suggest remission rate better in celecoxib plus sertraline group versus placebo group.
Moreira 2015 (score=3.0)										Sparse methods with limited baseline data. High dropout rate.[72]

Evidence for the Use of Tumor Necrosis Factor Inhibitors

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Raison 2013 (Score=7.5)	Tumor Necrosis Factor (TNF) Inhibitors	RCT	Sponsored by the National Institute of Mental Health and Centocor OrthoBiotec Services. One or more of the authors have received or will receive benefits	N = 60 medically-stable outpatients with major depression meeting DSM-IV criteria	Mean age: 43.4 years; 20 male, 40 female	Group 1: Received infusion of infliximab at 5 mg/kg over 120 minutes at baseline, 2 weeks, and 6 weeks (n=30) vs. Group 2:	Follow-up at 1, 2, 4, 6, 8, 10, and 12 weeks	Mean decrease in HAM-D score in infliximab group was 7 from baseline to 12 weeks (P<0.05). Mean decrease in HAM-D score in placebo group was 9 from baseline to 12 weeks	"This proof-of-concept study suggests that TNF antagonism does not have generalized efficacy in treatment-resistant depression but may improve	Duration of MDD significantly less in infliximab group. Data suggest lack of efficacy of Infliximab versus placebo for treatment

[72] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

			for personal or professional use.			Received an infusion of placebo (saline) over 120 minutes at baseline, 2 weeks, and 6 weeks (n=30)		(P<0.05). The difference in HAM-D scores over baseline to 12 weeks between group was not significant (P=0.92).	depressive symptoms in patients with high baseline inflammatory biomarkers."	resistant depression as reflected in HAM-D scores.
Mehta 2013 (Score=NA)	Tumor Necrosis Factor (TNF) Inhibitors	Post-hoc analysis	Sponsored by the National Institute of Mental Health and Centocor OrthoBiotec Services. No COI.	N = 57 of the 60 medically-stable outpatients with major depression from Raison 2013	Mean age: 43.4 years; 20 male, 37 female	Group 1: Responder to infliximab treatment (n=13) vs. Group 2: Non-responders to infliximab treatment (n=14) vs. Group 3: Responders to placebo (n=15) vs. Group 4: Non-responders to placebo (n=15) *Treatment response was defined as a 50% reduction in depressive symptoms over the 12 week study period.	Follow-up at 6h, 24h, and 2 weeks after the first infliximab infusion	Expression levels of 148 different transcripts were found to have a significant association with response to infliximab treatment (1.2-fold change, adjusted P≤ 0.01). None of the 148 transcripts overlapped with the transcripts associated with response in the placebo group (n=12).	"Thus, baseline transcriptional signatures reflective of alterations in glucose and lipid metabolism predicted antidepressant response to infliximab, and infliximab response involved regulation of metabolic genes and inhibition of genes related to innate immune activation."	(Post-hoc analysis of Raison 2103). Data suggest that antidepressant response may be associated with markers of glucose and lipid metabolism (inflammation) .
Weinberger 2015 (Score=NA)	Tumor Necrosis Factor (TNF) Inhibitors	Post-hoc analysis	Sponsored from the National Institute of Mental Health and the National Center for Advancing	N = 36 of the 60 medically-stable outpatients with major depression	Mean age: 43.4 years; 11 male, 25 female	Group 1: Received infusion of infliximab at 5 mg/kg over 120 minutes at baseline, 2	Follow-up at 1, 2, 4, 6, 8, 10, and 12 weeks	In the infliximab group, a significant relationship was found between inflammation and sleep period time	"These data suggest that inhibition of inflammation may be a viable strategy to improve sleep	(Post-hoc analysis of Raison 2013). Data suggest suppression of inflammation may improve

			Translational Sciences of the National Institutes of Health.	from Raison 2013 who had complete polysomnography data		weeks, and 6 weeks (n=19) vs. Group 2: Received an infusion of placebo (saline) over 120 minutes at baseline, 2 weeks, and 6 weeks (n=17)		(P=0.037, wake after sleep onset (WASO, P=0.024), sleep efficiency (P=0.05), spontaneous arousal index (P=0.005), and Stage 2 sleep (P=0.018).	alterations in patients with depression and other disorders associated with increased inflammation."	sleep in patients with treatment resistant depression.

Evidence for the Use of Cumin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lopresti 2014 (score=7.0)	Cumin	RCT	No COI. Sponsored by Arjuna Natural Extracts Limited.	N = 56 participants meeting DSM-IV criteria for current major depressive disorder	Mean age: 46.29 years; 16 males, 40 females	Cellulose (placebo) capsules (n=28) vs. Curcumin capsules 500mg – containing total curcuminoids 88% (curcumin, bisdemethoxycurcumin, desmethoxycurcumin) and volatile oils (7% for rhizomes of Curcuman longa Linn). Each treatment was taken one capsule at a time twice daily for 8 weeks (n=28)	Follow-up at 4 and 8 weeks	There were no significant differences between treatments at any time point in Spielberger State-Trait Anxiety Inventory (STAI) means scores ($p > 0.05$). The curcumin group had significantly better mean Inventory of Depressive Symptomatology self-rated version (IDS) total scores and mean IDS mood scores when comparing week 4 scores to week 8 scores (total: $p = 0.045$, mood: $p = 0.014$)	"Partial support is provided for the antidepressant effects of curcumin in people with major depressive disorder, evidenced by benefits occurring 4 to 8 weeks after treatment."	Data suggest both placebo and curcumin groups improved in the first 4 weeks but from week 4 to week 8 there was more improvement in mood associated with the curcumin group. Placebo group had significantly more medical illnesses at baseline than curcumin group.
Bergman 2013 (score=6.5)	Cumin	RCT	No COI. No mention of sponsorship.	N = 40 participants meeting DSM-IV criteria for major depressive episode	Mean age: 63.55 years; 17 males, 23 females	Curcumin – 500 mg/day (Curcumin Forte Balance, Extracts H. Plant, each capsule contains 330 mg curcumin, 120 mg of ellagic acid)	Follow-up at weeks 1, 2, 3, 4, and 5	Mean MADRS scores at week 5: placebo = 15.4, curcumin = 14.0 (treatment effect $F = 1.0$, $p = 0.3$). Mean HDRS scores at week 5: placebo = 16.5, curcumin = 14.7	"Although there is no definitive proof that curcumin can induce an earlier beneficial effect of antidepressive agents, it seems like an extended study is needed to prove it, using	Data suggest lack of efficacy. There was however a trend for more rapid depression symptom relief in the curcumin group.

						(n=20) vs. Placebo in identical capsules 500 mg/day (n=20). Both treatments given for 5 weeks		(treatment effect F = 1.4, p = 0.3)	higher therapeutic doses of curcumin."	
Sanmukhani 2014 (score=5.0)	Cumin	RCT	No COI. Sponsored by the Ministry of Health and Family Welfare, Government of Gujarat, India.	N = 60 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 37.27 years; 21 males, 39 females	Fluoxetine – 20 mg/day (n=20) vs. Curcumin – 1000 mg/day, 88% curcuminoids, 7% volatile oils (n=20) vs. Fluoxetine and Curcumin – both treatments (n=20). All treatments given for six weeks	Follow-up at weeks 2, 4, and 6	Mean change in HAM-D scores at six weeks compared to baseline: fluoxetine = -14, curcumin = -12.6, combined = -14.8 (ANOVA p = 0.33). No difference in response rates using HAM-D scores between groups (p = 0.58)	"This study provides first clinical evidence that curcumin may be used as an effective and safe modality for treatment in patients with MDD without concurrent suicidal ideation or other psychotic disorders."	Data suggest a trend towards combination group being associated with a higher number of responders but results are not statistically significant.

Evidence for the Use of St. John's Wort

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Shelton 2001 (score=7.0)	St. John's Wort	RCT	Sponsored by grants from the C.D. Smithers Foundation, Solvay Pharmaceuticals Inc., the Italian Association for Cancer Research, the	N = 200 outpatients diagnosed with major depression (DSM-IV criteria)	Mean age: 42.4 years; 72 males, 128 females	St John's Wort Group: received 300 mg tablet extract of st john's wort 1 tablet 3 times per day equivalent to 900 mg/day for	1, 2, 4, 6, 8 weeks	No significant treatment effect was observed for HAM-D scores ($F_{1,188}$=2.0, p=0.16). Remission rate was 20.3% (95% CI 12.7-30.7%) in St John's Wort	"In this study, St John's wort was not effective for treatment of major depression."	Data suggest lack of efficacy.

			National Institute of Health, the German Research Council, and the Interdisciplinary Center for Clinical Research. COI: One or more of the authors have received or will receive benefits for personal or professional use.			at least 4 weeks and could be increased to 4 tablets or 1200 mg/day for remainder of trial (n=98) vs Placebo: received identically matched placebo for 8 weeks (n=102)		group compared to 10.3% (95% CI 5.4-18.8%) in the placebo group (p=0.07)		
Vorbach 1994 (score=6.5)	St. John's Wort/Imipramine	RCT	No mention of sponsorship or COI.	N = 135 depressed patients (DSM-III-R criteria)	Mean age: 53.4 years; 71 males, 64 females	LI 160 Group: received hypericum extract (3x300 mg) (n=67) vs Imipramine Group: received imipramine (3x25 mg) (n=68)	1, 2, 4, 6 weeks	Hamilton depression scale decreased from 20.2 to 8.8 in LI 160 group compared to imipramine group from 19.4 to 10.7 ($p<0.001$).	"The analysis of CGI revealed comparable results in both treatment groups. Clinically relevant changes of the safety parameters were not found. In the LI 160 group fewer and milder side effects were found as compared to imipramine."	Data suggest comparable efficacy to imipramine.
Szegedi 2005 (score=6.5)	St. John's Wort/Paroxetine	RCT	Sponsored by Dr Willmar Schwabe Pharmaceuticals. COI: AS has received consultancy fees from Dr Willmar	N = 251 patients with acute major depression (DSM-IV criteria)	Mean age: 47.3 years; 76 males, 168 females	Hypericum Group: received hydroalcoholic extract from herba hyperici with 3-6% hyperiforin and 0.12-0.28%	7, 14, 28, 42 days	Hamilton depression scores decreased by an average of 14.4±8.8 points for hypericum group compared to 11.4±8.6 points in the paroxetine	"In the treatment of moderate to severe major depression, hypericum extract WS 5570 is at least as effective as	Data suggest comparable efficacy to paroxetine and may be slightly better.

			Schwabe Pharmaceuticals . RK is head of a contract research organization. AD and MK are employees of Dr. Willmar Schwabe Pharmaceuticals .			hypericin (300-600 mg) (n=122) vs Paroxetine Group: received 20 mg tablets of paroxetine (40 mg per day) (n=122)		group. Hypericum group showed better improvement in remission compared to paroxetine group (p=0.02).	paroxetine and is better tolerated."	
Woelk 2000 (score=6.5)	St. John's Wort/Imipramine	RCT	Sponsored by Bayer AG. No COI.	N = 324 patients with mild to moderate depression (ICD-10 criteria)	Mean age: 45.9 years; 93 males, 231 females	Hypericum Group: received 0.2% hypericin extracted in ethanol 50% (250 mg film coated tablet 2 times daily) (n=157) vs Imipramine Group: received 75 mg tablet of imipramine 2 times daily (dose increased form 25 mg twice daily for 3 days to 50 mg twice daily for 4 days) (n=167)	6 weeks	Hamilton depression scale decreased from 12 to 11.53 for hypericum group compared to 12.75 to 11.21 in the imipramine group and neither were statistically significant. Patients tolerated hypericum better than imipramine (p<0.01).	"This Hypericum perforatum extract is therapeutically equivalent to imipramine in treating mild to moderate depression, but patients tolerate hypericum better."	Data suggest comparable efficacy but patients appeared to tolerate hypericum perforatum better.
Hypericum Depression Trial Study Group 2002 (score=6.0)	St. John's Wort/Sertraline	RCT	Sponsored by National Center for Complementary and Alternative Medicine and the National	N = 340 patients with major depressive disorder (DSM-IV)	Mean age: 42.3 years; 116 males, 224 females	Hypericum Group: received 900 mg/day hypericum (n=113) vs Placebo:	1, 8, 18 weeks	HAM-D scores were reduced by -9.20 (95% CI-10.51 to -7.89) for placebo compared to -8.68 (95% CI -10.01 to -7.35) for	"This study fails to support the efficacy of H perforatum in moderately severe major depression. The	Data suggest lack of efficacy as Hypericum perforatum not superior to placebo for

			Institute of Mental Health to Duke University Medical Center. No mention of COI.			received equivalent placebo (n=116) vs Sertraline: received 50mg/day sertraline (n=111)		H perforatum (p=0.59) and -10.53 (95% CI –11.94 to -9.12) for sertraline (p=0.18).	result may be due to low assay sensitivity of the trial, but the complete absence of trends suggestive of efficacy for H perforatum is noteworthy."	treatment of major depression.
Harrer 1994 (score=5.5)	St. John's Wort/ Maprotiline	RCT	No mention of COI or sponsorship.	N = 102 participants meeting ICD-10 depression criteria	Mean age: 45.7 years; 29 males, 73 females	300 mg of hypericum extract LI 160 three times a day (n=51) vs. 25 mg of maprotiline three times a day (n=51). All treatments given for a total of 4 weeks	Follow-up at 2 and 4 weeks	At four weeks the mean score of Hamilton Depression Rating Scale (HAMD) for hypericum group went from 20.5 to 12.2 and for maprotiline group went from 21.5 to 10.5 (different not significant, p > 0.05)	"Statistical evaluation of the results in the three psychometric scales used in this study (HAMD, D-S, and CGI) demonstrated a roughly equal efficacy for maprotiline and hypericum after 4 weeks of treatment."	Data suggest maprotiline and Hypericum Extract LI 160 have similar efficacy but maprotiline effects are observed earlier.
Gastpar 2005 (score=5.5)	St. John's Wort/Citalopram	RCT	No mention of sponsorship or COI.	N = 388 patients with major depressive episode and recurrent major depression (DSM-IV and ICD-10)	Mean age: 49.8 years; 125 males, 263 females	Hypericum Group: received 900 mg of hypericum perforatum extract/tablet (n=131) vs Citalopram Group: received 20 mg of citalopram (n=127) vs Placebo group: (n=130)	7, 21, 42 days	HAM-D scores decreased by 11.6 points in hypericum group compared to 11.5 points in citalopram group and 9.0 points in the placebo group. Superiority of citalopram to placebo (p<0.0001) as well as the comparison of hypericum	"The non-inferiority of hypericum extract as compared to citalopram and the superiority of both active compounds to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in	Data suggest comparable efficacy of hypericum extract STW3-C1 and citalopram and both are only slightly better than placebo group.

								group compared to placebo.	comparison to citalopram. These results revealed that hypericum extract STW2-VI is a good alternative to chemically defined antidepressants in the treatment of outpatients with moderate depression."	
Brenner 2000 (score=5.5)	St. John's Wort/Sertraline	RCT	Sponsored by Lichtwer Pharma AG, Berlin, Germany. No mention of COI.	N = 30 patients diagnosed with major depression (recurrent, or single episode) (DSM-IV)	Mean age: 45 years; 11 males, 19 females	Hypericum Group: received LI 160 H. perforatum 600 mg/day during week 1, and 900 mg/day for remainder of trial (n=15) vs Sertraline: received 50 mg/day for week 1, and 75 mg/day for the rest of the trial (n=15)	2, 4, 7 weeks	HAM-D scores reduced by 40±30% in hypericum group compared to 42±24% in the placebo group.	"In a controlled, randomized comparison of hypericum extract (LI 160) and sertraline in the treatment of mild to moderate depression, hypericum was found to be at least as efficacious as the SSRI antidepressant. Both drugs were well tolerated."	Small sample. Data suggest comparable efficacy and may be slightly better.
Van Gurp 2002 (Score=5.0)	St. John's Wort/Sertraline/Fluoxetine	RCT	Sponsored by grant from St. Mary's Hospital Centre, grant from Pfizer Canada. No COI.	N = 87 patients diagnosed with major depression (DSM-IV)	Mean age: 40.1 years; 33 males, 52 females	St John's Wort: received 900 mg of st john's wort (3-300 mg tablets daily) (n=44) vs Sertraline: received 50 mg sertraline (16.67 mg	2, 4, 8, 12 weeks, 6 months	Mean HAM-D and BDI scores were decreased for both groups (p=0.582, p=0.808, respectively).	"The more benign side effects of SJW make it a good first choice for this patient population."	Data suggest comparable efficacy with less adverse events than SJW.

						tablets 3 times daily) (n=34)				
Harrer 1999 (score=5.0)	St. John's Wort	RCT	No mention of sponsorship or COI.	N = 149 patients with mild to moderate depressive episodes (ICD-10)	Mean age: 68.8 years; 20 males, 129 females	SJW Group: received 2 coated tablets twice daily of 200 mg St John's Wort extract LoHyp-57 (Ze 117) (n=69) vs Fluoxetine Group: received 2 coated tablets twice daily of 5.6 mg fluoxetine-HCl (n=68)	1, 2, 4, 6 weeks	HAM-D score reduced for both groups; however, neither were statistically significant. Response rate was 71.4% in SJW group and 72.2% in fluoxetine group.	"There was a trend towards somewhat better results with Hypericum in mild depressive episodes, and with fluoxetine in moderate depressive episodes, but these differences were not statistically significant."	Data suggest comparable efficacy but there was a trend for St. John's Wort to be better in mild depression and fluoxetine better for moderate depression.
Schrader 2000 (score=5.0)	St. John's Wort/Fluoxetine	RCT	No mention of sponsorship or COI.	N = 252 patients with depressive episode or recurrent depressive disorder (ICD-10)	Mean age: 46.5 years; 83 males, 157 females	Fluoxetine: received 20 mg once daily of fluoxetine (n=114) vs Hypericum: received 250 mg 2 times daily of hypericum (n=126)	6 weeks	Overall HAM-D scores were decreased for both groups ($p<0.09$). Mean CGI score was superior in hypericum compared to fluoxetine ($p<0.03$).	"We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is safety. Hypericum was superior to	Data suggest comparable efficacy but fewer adverse events with Ze 117.

									fluoxetine in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported."	
Sarris 2012 (score=5.0)	St. John's Wort/Sertraline	RCT	No sponsorship or COI.	N = 124 participants with major depressive disorder (DSM-IV)	Mean age: 44.4 years; 43 males, 77 females	SJW Group: received 900 mg/day hypericum (n=35) vs Placebo: received equivalent placebo (n=40) vs Sertraline: received 50mg/day sertraline (n=49)	8, 10, 14, 18, 22, 26 weeks	HAM-D scores were 6.6±4.5 in SJW group, 7.1±5.4 in the sertraline group, and 5.7±5.4 in the placebo group (p=0.036). Remission rates were 58% for sertraline, 63% for SJW group, and 74% for placebo (p=0.20).	"In conclusion, while the results of the continuation phase of this large RCT revealed similar findings to the acute phase, the surprising outcome that a placebo response was maintained, and the questions of why this occurred, are of considerable interest."	Placebo controlled. Data suggest comparable efficacy between all treatments at 26 weeks.
Gastpar 2005 (score=4.5)	Sertraline/St. John's Wort	RCT	No mention of COI or sponsorship.	N = 241 participants meeting ICD-10 criteria for moderate depressive disorder	Mean age: 48.89 years; 61 males, 180 females	Hypericum – ethanolic hypericum extract STW3 (Laif 600), 612 mg/day (n=123) vs. Sertraline – 50 mg/day (n=118). Treatments were given for 24 weeks	Follow-up at weeks 1, 12 and 24	Hamilton Depression Rating Scale scores at 12 weeks: hypericum = 22.0, sertraline = 22.1) and at 24 weeks: hypericum = 5.7, sertraline = 7.1. Covariance analysis with respect to non-inferiority was significant ($p < 0.0001$) – hypericum was not inferior	"The results indicate that hypericum extract STW 3 is not inferior to sertraline and that it is a well-tolerated drug for the treatment of moderate depression. These favorable effects were achieved with a once-daily dose of 612 mg of	Data suggest hypericum extract STW3 is not inferior to sertraline and is well tolerated.

									hypericum extract given for up to 24 weeks."	
Kalb 2001 (score=4.5)	St. John's Wort	RCT	Sponsored by Dr. Willmar Schwabe Pharmaceuticals. No mention of COI.	N = 72 patients with a diagnosis of mild to moderate major depressive disorder (DSM-IV)	Mean age: 48.5 years; 24 males, 48 females	Hypericum Group: received 3x300 mg/day Hypericum extract WS 5572 (n=37) vs Placebo Group: (n=35)	7, 14, 28, 42 days	HAM-D scored average reduction was 54.8% in Hypericum group compared to 29.2% in the placebo group ($p<0.001$).	"The results of the present study demonstrate that the standardized hypericum extract WS 5572 has superior efficacy compared to placebo and very good tolerability in the acute treatment of mildly to moderately depressed patients."	Data suggest hypericum extract WS 5572 better than placebo.
Lecrubier 2002 (score=4.5)	St. John's Wort	RCT	Sponsored by Dr. Willmar Schwabe Pharmaceuticals. No mention of COI.	N = 375 participants with mild to moderate major depression (DSM-IV)	Mean age: 40.7 years; 88 males, 287 females	Hypericum Group: received WS 5570 H. perforatum extract 300 mg tablets (n=186) vs Placebo Group: (n=189)	1, 2, 4, 6 weeks	Hamilton depression score decreased by an average of 9.9±6.8 points in the hypericum group compared to 8.1±7.1 points in the placebo group.	"In conclusion, this study demonstrates the existence of an antidepressant effect of H. perforatum in mildly and moderately depressed patients."	Data suggests WS 5570 better than placebo.
Philipp 1999 (score=4.5)	St. John's Wort/Imipramine	RCT	Sponsored by Steiner Arzneimittel, Berlin, Germany. COI: KOH is an employee of	N = 263 patients with moderate depression (ICD-10)	Mean age: 47±12 years; 66 males, 197 females	Hypericum Extract: received 350 mg per capsule (total daily dose of 1050 mg) of	1, 2, 4, 6, 8 weeks	Hamilton depression score improved in 74% of hypericum group, 71% in the imipramine group,	"In summary, this trial adds to the growing evidence on the effectiveness of hypericum in mildly and	Data suggest comparable efficacy between hypericum extract and imipramine in

			Steiner Arzneimittel. RK is a head of a contract research organization involved with hypericum extract for different pharmaceutical companies.			hypericum extract (n=106) vs Imipramine: received 50 mg imipramine on the 1st day, 75 mg on days 2-4, and 100 mg (50mg, 25mg, 25 mg, thereafter) (n=110) vs Placebo: (n=47)		and 50% in the placebo group.	moderately depressed patients."	the treatment of mild to moderate depression.
Sommer 1994 (score=3.5)										Sparse methods. Data suggest hypericum better than placebo.[73]
Randløv 2006 (score=3.5)										Data suggest improvements occurred most frequently in non-dysthymic patients treated with PM 235.
Fava 2005 (score=3.5)										Data suggest St John's Wort trended to be slightly better than placebo and better than fluoxetine.[74]

[73] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

[74] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Vorbach 1997 (score=3.5)										Data suggest there may be some benefit of Extract L1 160 for depression.
Pakseresht 2012 (score=3.0)										Data suggest improvement in both groups with combination therapy of SJW and TCA being better than TCA therapy alone.

Evidence for the Use of Omega-3 Fatty Acids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Rogers, 2008 (score=6.5)	Omega-3 fatty acid	RCT	Sponsored by a grant (NO5038) form the standards agency. No mention of COI	N = 190 with low dietary omega-3 intake, and mild to low score on DASS-d (10-24)	Mean age: 38.1 ± 13.6 years; 50 males, 168 females	Intervention group: received 630 mg EPA, 850 mg DHA, 870 mg olive oil, 7.5 mg mixed tocopherols and 12 mg of orange oil three times daily (n = 109) vs Placebo group: received 2360 mg olive oil, 7.5 mg mixed tocopherols and 12 mg of orange oil (n = 109)	4, 12 weeks	No evidence of a significant difference between intervention group and placebo groups in depression subscale of depression and stress scales at 12 weeks. Mean depression scores for intervention group (8.4) and the placebo group at (9.6) [(95% CI – 2.8, 0.8; p = 0.27)	"In conclusion, substantially increasing EPA þ DHA intake for 3 months was found not to have beneficial or harmful effects on mood in mild to moderate depression. Adding the present result to a meta-analysis of previous relevant randomized controlled trial results confirmed an overall negligible benefit of n-3 LCPUFA supplementation for depressed mood."	Data suggest lack of efficacy.
Antypa, 2012 (Score=6.0)	Omega-3 fatty acid	RCT	Sponsored by N.W.O.-VICI (grant no. 453-06-005) to AJWVD. No COI	N = 71 participants had a BMI between 18-27 kg/m^2 and history of at least 1 major depressive episode. Exclusions criteria BDI-2 > 19.	Mean Age: 24.67 ± 8.94 years; 13 males, 58 females	Intervention group: received daily dose of fish oil [2.3 g of n-3 PUFA (including 1.74 g e icosapentaenoic acid [EPA] + 0.25g DHA)] for 4 weeks (n = 36) vs Placebo group: Received olive oil (n = 35)	None	No significant effects were found on the BD-2 and LEIDS-R. Post-test difference were significant for both depression [t(69) = 2.45, p = 0.006],and tension [t(69) = 2.45,. p = 0.02] with moderate effect size (depression: d = 0.47; tension; d = 0.48)	"No significant effects were observed on memory, attention, cognitive reactivity and depressive symptoms. While inconclusive, the present findings may indicate that omega-3 supplementation has selective effects on emotional cognition and mood in recovered depressed participants."	Data suggests minimal trend of improved self-report depressive symptoms.
Mischoulon, 2015 (score=5.5)	Omega-3 fatty acid	RCT	Sponsored by a NIH grant 5R01MH74085. No COI	N = 177 out patients with MDD by DSM-IV, CGI-S score >	Mean age: 45.8 ± 12.5 years; 72 males,	EPA- Enriched group: received 1000 mg/d of EPA-enriched mix for 8 weeks (n =	None	No statistical significant difference between groups. All 3 groups experienced statistically significant	"In the first head-to-head comparison of EPA- versus DHA-enriched monotherapy for MDD, a	Data suggest both EPA and DHA no better than placebo

				3, and baseline HDRS-17 score > 15	105 females	60) vs DHA-Enriched group: received 1000 mg/d of DHA-enriched mix for 8 weeks (n = 58) vs Placebo group (n = 59)		improvements in HDRS-17, QIDS-SR-16, CGI-S, Q-LES-Q and 6 WBS scales.	heterogeneous sample of outpatients improved equally both on n-3 preparations and on placebo."	(lack of efficacy).
Duffy, 2015, (score=5.5)	Omega-3 fatty acid	RCT	Sponsored by a grant received from the Bupa Health Foundation. No mention of COI	N = 51 participants from a larger Beyond Ageing (BA) Project that met the criteria and were at risk for MD determined form a score of 16-30 on the K10.	Mean age: 71.75 ± 3.94 years; 32 males, 19 females	Intervention group: participants took 4 1000-mg omega-3 tablets plus 800 mg docosahexaenoic acid (DHA) and 1 microcrystalline cellulose. Participants received intervention in 5 capsules every day for 12 weeks. (n = 28) vs Placebo Group: received 4 1000 mg paraffin oil capsules and 1 microcrystalline cellulose tablet (n =23)	12 weeks	Statistically significant results were found in the patient health questionnaire when comparing groups (r = 0.43, p = 0.043). Placebo group had greater change In GSH-to-creatine ration in the Thalamus (t = 2.00; p = 0.049).	"To our knowledge, this study demonstrates for the first time that u-3 FA supplementation is associated with the attenuation of GSH change in the thalamus of older adults at risk for depression."	Data suggest high levels of GSH appears to be a Matter of stress and omega-3 FA supplementatio n may attenuate this stress, thus benefiting depressed patients
Gertsik, 2012 (score=5.0)	Omega-3 fatty acid	RCT	Sponsored by the National Institutes of Health's National Center for Complement ary and Alternative Medicine (R21-AT001077)	N = 42 subjects who met the DSM-IV criteria for major depression (score >17)	Mean age 40.5 ± 10.2 years; No mention of sex	Treatment Group: received omega-3 + citalopram 2 times daily (n = 20) vs Placebo Group: Received placebo + citalopram (n = 22)	None	Significant greater improvements over time in HAM_D scores among subjects in treatment group compared to the other group (Group x time interactions= 7.32, p = 0.008). Significant difference were noted at 4 weeks (t= -2.48, 38df, p= 0.018) , 6 weeks, (t= -2.83,38df,	"Data suggest that initiation of treatment with an SSRI and PUFA simultaneously is advantageous in terms of efficacy when compared with treatment with SSRI as a monotherapy."	Data suggest there may be some benefit of omega -3 fatty acids in augmenting citalopram for treating depression

			and the National Center for Research Resources (M01-RR000425). No mention of COI					p= 0.007)and at study completion (t= -2.92,38df, p = 0.006).		
Park, 2014 (score=5.0)	Omega 3 fatty acids	RCT	No Sponsorship or COI.	N = 35 Patients diagnosed with depression by a psychiatrist (no specific diagnostic criteria)	Mean age: 41.46 years; 8 males; 27 females	Patients with confirmed depression treated with 3 capsules a day of 380 mg EPA + 200 mg DHA for 12 weeks of n-3 polyunsaturated fatty acids (PUFA) (n=18) vs Patients with depression given a placebo of olive oil and safflower oil for the same period (n=17)	Follow up at 12 weeks	Scores were significantly reduced ($p < 0.001$) within each group during the 12 weeks. Supplementation with n-3PUFAs significantly ($p = 0.041$) reduced Clinical Global Impression scale score after adjustment for energy, fat, and fish intake as compared with the placebo group over the intervention period, but did not improve standardized test scores.	"N-3 PUFAs demonstrated an advantage over placebo that did not reach clinical significance, although CGI-I score was significantly decreased in the n-3 PUFA group as compared with the placebo group."	Small Sample size. Data suggest slight trend of n-3 PUFAs over placebo. Placebo group consumed more fish during study period.
Silver, 2005 (score=4.5)	Omega 3 Fatty acids	RCT	Sponsored by the Foundation for Research, Science and Technology New Zealand. No COI.	N = 77 patients with current depressive episode and no co-existing psychiatric disorders using HDRS-SF.	Mean age: 38.75 years; 36 males, 41 females	Depression patients given placebo 80mg olive oil pills for 12 weeks (n=37) vs Depression patients given 80 mg fish oil pills for 12 weeks (n=40)	Assessments at 2, 4, 8 and 12 weeks	Findings show that there was no significant difference for the results of the two groups. There was a significant improvement in the mood of both groups within the first 2 weeks of entering the study ($P<0.001$ for HDRS-SF and BDI-II scores). Improvement sustained throughout	"In conclusion, DHA enriched fish oil was no more effective than the placebo oil as add-on therapy for depression in this setting, despite an increase in circulating levels of o-3 PUFAs.	Data suggests lack of efficacy.

								and it was proportional to baseline mood.		
Marangell, 2003 (score=4.5)	Omega 3 fatty-acids	RCT	No mention of sponsorship or COI.	N = 36 depressed patients (DSM-IV)	Mean age: 47.45 years; 12 males, 23 females	Depressed patients given placebo pills twice a day for 6 weeks (n=17) vs Depressed patients given 2g Omega-3 Fatty Acid Docosahexaenoic Acid (DHA) pills twice a day for 6 weeks (n=18)	Follow up at 6 weeks	There was a 27.8% response rate in the DHA Group and a 23.5% response in the placebo. This means that there was not a statistically significant difference in the two.	"This trial failed to show a significant effect of DHA monotherapy in subjects with major depression."	Data suggest the lack of efficacy.
Jazayeri, 2008 (score=4.5)	Omega 3 fatty-acids	RCT	Sponsored by Vice-Chancellor for Research, Tehran University of Medical Sciences, Tehran, Iran. No mention of COI.	N = 60 outpatients with a diagnosis of major depressive disorder (DSM-IV)	Mean age: 34.8 years; 15 males, 45 females	Depressed patients given 1000 mg Eicosapentaenoic acid (EPA) daily for 8 weeks (n=16) vs 20 mg Fluoxetine daily for 8 weeks (n=16) vs 20 mg Fluoxetine + 1000 mg EPA daily for 8 weeks (n=16)	Follow up at 4, 6, and 8 weeks	The fluoxetine and EPA combination is significantly better than fluoxetine or EPA alone. Fluoxetine and EPA appear to be equally effective in controlling depressive symptoms. Response rates were 50%, 56% and 81% in the fluoxetine, EPA and combination groups, respectively.	"In the present 8 week trial EPA and fluoxetine had equal therapeutic effects in major depressive disorder. EPA and fluoxetine combination was superior to either of them alone."	Data suggest EPA + fluoxetine better than either fluoxetine or EPA alone.
Tajalizadekhoob 2011 (score=3.5)										Data suggest low dose omega 3 FAs had some efficacy for treatment of mild to moderate depression.[75]

[75] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Vitamin D

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Frandsen 2014 (score=8.0)	Vitamin D	RCT	No COI. Sponsored by the Psychiatric Research Foundation in Southern Denmark.	N = 43 healthcare professionals employed in psychiatric and somatic hospitals, with score ≥ 8 points on question #2 on the Seasonal Pattern Assessment Questionnaire (SPAQ-SAD)	Mean age: 44.30 years; 11 males, 32 females	70 µm of vitamin D daily for 12 weeks (n=22) vs. 70 µm of placebo daily for 12 weeks (n=21)	Follow-up at 12 weeks	No significant between-group difference in decrease of the sum of the self-reported questionnaire Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders score (SIGH-SAD) over time: vitamin D group mean decrease = -6.4, control group mean decrease = -6.8 (p = 0.7)	"Thus, the study failed to demonstrate an effect of vitamin D on SAD symptoms, but our findings may be limited by confounders. Furthermore, the study was underpowered and did not allow us to assess the ability of vitamin D to improve mood in those with low 25(OH)D."	Data suggest lack of efficacy.
Kjærgaard 2012 (score=8.0)	Vitamin D	RCT	No COI. Sponsored by the Northern Norway Regional Health Authority.	N = 243 participants with serum 25(OH)D levels below 55 nmol/l Depressive symptoms evaluated with BDI, HADS, SPAQ, MADRS and SCID-CV	Mean age: 53.6 years; 110 males, 123 females	High-dose vitamin D, two vitamin D_3 capsules per week for 12 weeks (n=122) vs. Placebo, two placebo capsules per week for 12 weeks (n=121)	Follow-up at 6 months	Comparison of placebo versus Vitamin D group mean differences from baseline to 6 months, respectively – serum calcium: -0.01 vs. 0.02 (p = 0.016), Plasma PTH: 0.2 vs. - 0.8 (p < 0.001), Serum 25(OH)D3: 4.7 vs. 100.3 (p < 0.001)	"Low levels of serum 25(OH)D are associated with depressive symptoms, but no effect was found with vitamin D supplementation. "	Data suggest lack of efficacy although there is an association between low vitamin D levels and higher depression scores.

				from DSM-IV.						
Sepehrmanesh 2016 (score=7.0)	Vitamin D	RCT	No COI. Sponsored by the Kashan University of Medical Sciences.	N = 40 patients diagnosed with major depression disorder via the Diagnostic and Statistical Manual of Mental Disorders via BDI.	Mean age: 36.3 years; 6 males, 34 females	Single capsule of 50 kIU vitamin D weekly for 8 weeks (n=20) vs. Single capsule of placebo weekly for 8 weeks (n=20)	Follow-up at 2, 4, 6, and 8 weeks during intervention	Beck Depression Inventory (BDI) change in scores from baseline to 8 weeks – Placebo group: -3.3, Vitamin D group: -8.0 (mean change between groups not statistically significant, p = 0.06). When adjusting for baseline values, age, and baseline BMI the mean change becomes significant (p = 0.04)	"Overall, vitamin D supplementation of patients with MDD for 8 wk had beneficial effects on the BDI, indicators of glucose homeostasis, and oxidative stress."	Data suggest benefits on depression glucose metabolism markers and stress were associated with vitamin D supplementation.
Khoraminya 2012 (score=6.5)	Vitamin D	RCT	No COI or sponsorship.	N = 42 patients (minus 2 dropouts) with diagnosis of major depressive disorder via DSM-IV.	Mean age: 38.88 years; 6 males, 34 females	1500 IU vitamin D_3 plus 20 mg fluoxetine daily for 8 weeks (n=20) vs. 20 mg fluoxetine daily for 8 weeks (n=20)	Follow-up at 2, 4, 6 and 8 weeks during treatment	Hamilton Depression Rating Scale (HDRS) scores at base, week 2, week 4, week 6, and week 8, respectively: Fluoxetine only – 30.2, 25.23, 21.35, 19.00, 17.2, Vitamin D and Fluoxetine – 29.4, 23.94, 18.5, 14.6, 11.7 (Repeated measure analysis of variance on time: F = 9.29, p = 0.004, Analysis of covariance adjusted for	"In the present 8-week trial, the vitamin D + fluoxetine combination was superior to fluoxetine alone in controlling depressive symptoms."	Data suggest vitamin D plus fluoxetine was better than fluoxetine alone for decreasing symptoms of depression.

								baseline values: F = 8.54, p = 0.006)		
Mozaffari-Khosravi 2013 (score=4.5)	Vitamin D	RCT	Sponsored by Shahid Sadoughi University of Medical Sciences (SSUMS). All authors except Barzegar work for SSUMS.	N = 120 participants who had a Beck Depression Inventory II score of 17+ and had vitamin D deficiency, however only 109 included in analysis due to drop outs	Mean age: 38.88 years; 31 males, 78 females	G300 – Intramuscular single dose of 300,000 IU of vitamin D (n=39) vs. G150 – Intramuscular single dose of 150,000 IU of vitamin D (n=36) vs. NTG – No intramuscular injection (n=34). All groups originally had 40 participants allocated	Follow-up at 3 months	BDI-II scores before intervention for NTG, G150, and G300, respectively: 26.4, 27.5, 26.7 (p=0.82). BDI-II scores after intervention: 24.3, 20.6, 17.4 (p=0.01). Mean difference in BDI-II scores: 2.1 (p=0.003), 6.8 (p<0.001), 9.3 (p<0.001) (comparing all mean difference, p<0.001)	"The results of the study revealed that first, the correction of vitamin D deficiency improved the depression state, and second, a single injection dose of 300,000 IU of vitamin D was safe and more effective than a 150,000-IU dose."	Data suggest one to two injections of high dose vitamin D improves vitamin D deficiency and improves depressive symptoms.

Evidence for the Use of B Vitamins

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Hvas 2001 (score=8.5)	B Vitamins	RCT	Sponsored by the Danish Medical Research Council, the Health Found of "danmark's" Sygeforsiking, EU Biomed, The Institute of Experimental	N = 140 participants with mild to moderate increased plasma methylmalonic acid (P-MMA) (0.4-2.0 μmol/L)	No mention of mean age, median age for Vitamin B_{12} group: 75 years, median age for placebo group: 74	Intramuscular injections of 1 mg of cyanocobalamin (Betolvex), 1 injection per week for 4 weeks (n=70) vs. Intramuscular injections of 1 mL of isotonic	Follow-up at 3 months	Decreased P-MMA and plasma total homocysteine in treatment group ($p < 0.001$, $p < 0.001$). No significant difference found in blood hemoglobin change ($p = 0.18$) or mean cell	"Treatment with vitamin B_{12} reduces PMMA and plasma total homocysteine, but individuals with a mild to modest increase in P-MMA may have only limited clinical benefit from vitamin B_{12}	Data suggest small benefit (if any) from vitamin B_{12} treatment on reducing plasma methylmalonic acid (P-MMA).

			Clinical Research, Aarhus University, the E. Danielsen and Wife Foundation, The Novo Nordisk Foundation, the Hans and Nora Buchard Foundation, the Mogens Svarre Mogensen Foundation, the Velux Foundation, and The Family Hede Nielsen Foundation. All authors worked for the Aarhus University Hospital.		years; 42 males, 98 females	sodium chloride (placebo), 1 injection per week for 4 weeks (n=70)		volume (p = 0.71). Symptoms of anemia (p = 0.63), neurologic symptoms (p = 0.21), gastroenterological symptoms (p = 0.32), or neurological disability score (p = 0.85) did not change between groups.	treatment, at least in the short term."	
Hvas 2004 (score= 8.5)	B Vitamins	Secondary Analysis of Hvas 2001	Sponsored by the Danish Medical Research Council, the Health Found of "danmark's" Sygeforsiking, EU Biomed, The Institute of Experimental Clinical Research, Aarhus University,	N = 140 participants with mild to moderate increased plasma methylmalonic acid (P-MMA) (0.4-2.0 µmol/L) The MDI, a self-rating tool was used to measure depression	No mention of mean age, median age for Vitamin B_{12} group: 75 years, median age for placebo group: 74 years; 42 males, 98 females	Intramuscular injections of 1 mg of cyanocobalamin (Betolvex), 1 injection per week for 4 weeks (n=70) vs. Intramuscular injections of 1 mL of isotonic sodium chloride (placebo), 1 injection per	Follow-up at 3 months	78 individuals at baseline had cognitive impairment via Cambridge Cognitive Examination (CAMCOG), 40 based on Mini-Mental State Examination (MMSE), and 18 had symptoms of depression. Treatment did not improve cognitive	"A high proportion of individuals with an increased plasma methylmalonic acid had impaired cognitive function, and a rather high prevalence of depression was observed. However, vitamin B-12	Data suggest lack of efficacy for either cognitive function or depressive symptoms.

			the E. Danielsen and Wife Foundation, The Novo Nordisk Foundation, the Hans and Nora Buchard Foundation, the Mogens Svarre Mogensen Foundation, the Velux Foundation, and The Family Hede Nielsen Foundation. All authors except Nexø worked for the Aarhus University Hospital.	based on DSM-IV and ICD-10.		week for 4 weeks (n=70)		function between groups via CAMCOG score (p = 0.43). Depression scores did not differ between groups either (p = 0.18)	treatment did not improve cognitive function or symptoms of depression within the 3-months study period."	
Almeida 2014 (score=7.0)	B Vitamins	RCT	No COI. Sponsored by the National Health and Medical Council of Australia.	N = 153 participants with a major depressive episode in the context of a major depressive disorder (single episode or recurrent) per DSM-IV-TR.	No mention of mean age, all participants were aged ≥50 with a majority of participants being between 50 and 69 years; 67 males, 86 females	Citalopram plus 0.5mg of vitamin B12, 2mg of folic acid and 25mg of vitamin B6 (n=77) vs. Citalopram plus placebo (n=76). Citalopram daily dosages were 10 mg, and then 2 weeks later increased to 20 mg and could be maximized to 40 mg	Follow-up at 12, 26, and 52 weeks	At 12 weeks remission of depressive episode symptoms reached by 78.1% of those treated by placebo and 79.4% of those treated with vitamins (p = 0.84). At 26 weeks remission reached by 76.5% and 85.3%. At 52 weeks remission reached by 75.8% and 85.5% (effect of intervention over 52 weeks,	"B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Replication of these findings would mandate that treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to	Data suggest 12 weeks of added B-vitamins did not enhance antidepressant response but maintained antidepressant response over one-year.

						between 4 and 8 weeks. Vitamins and placebos were in capsules and were taken daily.		odds ratio OR = 2.49).	manage major depression in middle-aged and older adults."	
Ghaleiha 2016 (score=6.5)	B Vitamins	RCT	No COI or sponsorship.	N = 51 inpatients with major depressive disorder diagnosed via the Diagnostic and Statistical Manual of Mental Disorders 5 using Hamilton Depression Rating Scale (HDRS).	Mean age: 35.2 years; 24 males, 27 females	Thiamine (300 mg per day) (n = 25) vs. Placebo (300 mg per day) (n=24). After washout phase participants treated with fluoxetine (20 mg per day) for at least 12 consecutive weeks	Follow-up at 3, 6, and 12 weeks	Hamilton Depression Rating Scale (HDRS) scores for Thiamine and placebo groups, respectively: at baseline – 31.40, 32.77 (mean difference p = 0.25, d = 0.33), at 3 weeks – 21.52, 22.12 (p = 0.68, d = 0.12), at 6 weeks – 13.96, 18.50 (p = 0.0001, d = 1.29), at 12 weeks – 10.52, 12.64 (p = 0.04, d = 0.59)	"Among a sample of inpatients with MDD treated with a standard SSRI, compared to placebo, adjuvant thiamine produces improvements in symptoms of depression 6 weeks after medication intake. Adjuvant thiamine may have the potential to increase treatment adherence."	Data suggest at 6 weeks thiamine improved symptoms of depression.
Coppen 2000 (score=6.0)	B Vitamins	RCT	Sponsored by Scotia Pharmaceuticals . No mention of COI.	N = 127 with a new episode of depression and diagnosed with MDD via DSM-III-R	Mean age: 43.13 years; 45 males, 82 females	500 µm of folic acid daily (n=62) vs. 500 µm of placebo daily (n=65). All participants were also prescribed 20 mg of fluoxetine	Follow-up at 2, 4, 6, and 10 weeks	Patients receiving fluoxetine and folic acid had significantly better response to 10 weeks compared to placebo (Hamilton rating scale scores: 8.1 vs. 10.7, p < 0.05). Difference in scores greater in women (6.8 vs. 11.4, p < 0.005) at	"Folic acid is a simple method of greatly improving the antidepressant action of fluoxetine and probably other antidepressants. Folic acid should be given in doses sufficient to decrease plasma homocysteine.	Data suggest folic acid augments the antidepressant effects of fluoxetine.

								10 weeks compared to men (10.9 vs. 9.7, p > 0.05)	Men require a higher dose of folic acid to achieve this than women, but more work is required to ascertain the optimum dose of folic acid."	

Evidence for the Use of Transcranial Magnetic Stimulation & Repetitive Transcranial Magnetic Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Bares 2009 (score=7.5)	TMS	RCT	Supported by a grant from Ministry of Education of Czech Republic MSMT 1M0517. No COI.	N = 60 inpatients with DSM-IV criteria depressive disorder who did not respond to at least one antidepressant treatment before	Mean age: 44.7 years; 12 males, 48 females	1Hz rTMS (Magstim Super Rapid stimulator), every weekday at 100% of MT with 600 pulses/session, sessions being 600 s. Coil placed 45° *from midline of scalp. Given* placebo capsule (n=29) vs Receiving venlafaxine ER (75mg) on days 1-5 with dose increasing to 150mg/day. Sham treatment of rTMS, but with coil rotated 90° away from scalp. Voltage reduced to 70% (n=31)	Follow up at baseline and weekly up to week 4	Regarding MADRS score, there was no significant difference between the two groups (time x group interaction, F=1.01, df=4,224, p=0.38). Regarding the rating scale BDI-SF, there was no significant differences (F=0.73, df=4,224, p=0.56). Regarding rating scale CGI, there was also no significant difference (F=1.73, df=4,224, p=0.17). Response rates also were not statistically significant, as rTMS was 33% and venlafaxine was 39%	"The findings of this study suggest that, at least in the acute treatment, the right sided rTMS produces clinically relevant reduction of depressive symptomatology in patients with resistant depression comparable to venlafaxine ER. Larger sample sizes are required to confirm these results."	Both groups showed significant reduction of depressive symptoms. Data suggest right side rTMS reduces symptoms of depression equivalent efficacy to venlafaxine ER (comparable efficacy).
Fitzgerald 2006 (a) (score=7.5)	TMS	RCT	Sponsored by a grant from the Australian National	N = 50 patients with treatment-resistant	Mean age: 45.3 years; 19 males, 21 females.	rTMS (Medtronic Magpro30 magnetic stimulator), given at right side (110% of resting motor threshold,	Follow up weekly with a maximum of 6 weeks	Mean improvement on the MADRS of active group (7.7, SD=7.1) and sham group (3.2, SD=7.7) (F=25.5, df=1,	"Sequentially applying both high-frequency left-side rTMS and low-frequency rTMS to	Data suggest application of sequential high frequency left sided rTMS and

			Health and Medical Research Council and by Constance and Stephen Lieber. No mention of COI.	depression of DSM-IV.		1Hz in three trains of 140 seconds with 30 seconds interval between) and then left side (100% of resting motor threshold, 10HZ in 15 trains of 5 seconds with 25 seconds intervals) (n=25) vs Sham rTMS, same application as active treatment but coil was angled at 45-degrees off the head (n=25)		25, p<0.001) during the first two weeks. There was a greater reduction in MADRS scores in the active group than the sham group due to the significant group by time interaction (F=3.9, df=5, 44, p=0.005) and significant effect of time (F=4.8, df=5, 44, p=0.001)	the right prefrontal ortex, has substantial treatment efficacy in patients with treatment-resistant major depression. The treatment response accumulates to a clinically meaningful level over 4 to 6 weeks of active treatment."	low frequency rTMS to the right pre-frontal cortex leads to improved depressive symptoms at 4 to 6 weeks of active treatment.
Schutter 2009 (score=7.5)	TMS	RCT	Sponsored by Innovational Research Grants (451-04-070, 452-07-012) from The Netherlands Organization for Scientific Research (NWO).No COI.	N = 34 patients with a primary diagnosis of depressive disorder on the DSM-IV-TR criteria and a score of greater than or equal to 15 on the HAMD.	Mean age: 44.1 years; 17 males, 17 females	Active rTMS (Magpro Dantec), ten sessions at 20 minutes each, 2Hz rTMS at 90% MT of 2400 pulses (n=17) vs Sham rTMS, figure of eight coil used to mimic active treatment (n=17). Both treatments done on ten consecutive business days	Follow up at week 2	Percentage change from baseline on the HAMD was not statistically significant from active ($mean_{real}$ S.D., - 19.9) and sham treatments (mean real S.D. – 5.6) [F(1,31)=1.75, p=0.20, n^2=0.06]. There were more partial clinical responders in the real (43.8%) than sham (6.3%)	"…In spite of the above noted limitations this study provides the first direct evidence for beneficial effects of rTMS treatment over the right parietal cortex in the treatment of depression and warrants further research."	Data suggest an observed partial clinical response in active treatment group but HAMD score changes were not significant.
Rossini 2005 (score=7.5)	rTMS/Escitalopram	RCT	No sponsorship or COI.	N = 99 patients with major depressive episode (DSM-IV)	Mean age: 47.4±12.9 years; 20 males, 79 females	Active Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225 mg venlafaxine (n=17 and 10 consecutive days of active repetitive transcranial magnetic stimulation (15 hz, 30 trains of 30 pulses 2 seconds each with 28	5 weeks	Active group showed greater favor in HAM-D score reduction compared to sham group (F=7.6, p=0.0073). Response rates were greater in active group (p=0.002). HAM-D score reduction was not significant among medications in	"These findings support the efficacy of rTMS in hastening the response to antidepressant drugs in patients with major depressive disorder. The effect of rTMS seems to be unaffected by the specific	Data suggest rTMS accelerates patient response to escitalopram, sertraline or venlafaxine in patients with MDD.

						second inter-train interval (n=50) vs Sham Group: received either 5-15 mg escitalopram (n=17), 50-150 mg sertraline (n=16), or 75-225 mg venlafaxine (n=16) and sham rTMS (n=49)		either the active or sham group.	concomitantly administered drug."	
Brunelin 2014 (score=7.0)	TMS	RCT	Sponsored by the French Ministry of Health, PHRC 2007 (Dr. Poulet). No COI.	N = 170 patients who experienced a single episode or recurrent unipolar non-psychotic MDD that is confirmed on the DSM-IV criteria and the MINI 5.0 and had to be present with an $HDRS_{17}$ > 20.	Mean age: 54.5 years; 52 males, 105 females	rTMS stimulations (Magpro x 100/Magstim Super Rapid) at 120%, electrical intensity of 0.5 mA, stimulation of 6 1-minute trains with 30 second intervals (1 Hz), one daily session for 5 consecutive days for at least 2-6 weeks, took venlafaxine ER (75 mg) for 3 days (n = 55) vs. rTMS stimulations with placebo capsules (n = 60) vs. sham rTMS procedure but stimulation given over ipsilateral supraorbital area with 2 disposable 30-mm EMG electrodes, electrical intensity of 2 mA, also received venlafaxine (75 mg) (n=55)	Follow up monthly	No difference in patients who went in remission ($HDRS_{17}$ < 18) between the rTMS group (41%), venlafaxine group (43%) and the combination group (28%) (P=0.59). Results from ANOVA indicated that the continuous efficacy outcome measures were not different between the three groups regarding HDRS17 (F(12,912) = 0.36; P = 0.97), MADRS10 (F(12,912) =0.47; P = 0.93) or BDI13 (F(12,912= 0.52; P =0.90).	"Low frequency rTMS appears to be as effective as venlafaxine and as effective as the combination of both treatments for TRD. Because of its short session duration (the duration of one session was 8.5 min) and its safety, slow rTMS might be a useful alternative treatment for patients with TRD."	Data suggest comparable efficacy between low frequency rTMS and venlafaxine or the combination compared to sham.
Fitzgerald 2010 (score=6.5)	TMS	RCT	Sponsored by a Practitioner Fellowship grant from the National Health and	N = 219 patients with treatment resistant depression and a score	Mean age: 47.2 years; 71 males, 148 females.	Group 1: rTMS (Medtronic Magori30) with coils positioned at 45° angle, low freq right (1Hz), high freq left (10 Hz) (n=71) vs Group 2: bilateral low	Follow up at baseline, and 2 and 4 weeks	Clinical response achieved in 53.4% of the subjects and 31.5% achieved remission. There was a significant overall improvement in HAMD (p<0.001), BDI	"There is no substantial difference in efficacy between unilateral right-sided rTMS and the two forms of bilateral rTMS assessed in the	Data suggest similar response between unilateral and bilateral rTMS.

			Medical Research Council (NHMRC) and an NHMRC project grant (4367120). COI, P.B.F. received equipment for research from MagVenture A/S and Brainsway Ltd.	of > 13 on the HAM-D scale.		freq. (1 Hz) stimulation applied to right hemisphere and then to left (n=76) vs Group 3: sham stimulation in right unilateral side (n=71). All patients received 5 weekly sessions for 4 weeks		(p<0.001), response over time (p<0.001), and effect of time (p<0.001) between the groups.	study. Furthermore, our results call into question the specificity between frequency and laterality and rTMS response."	
Rossini 2005 (score=6.5)	TMS	RCT	No mention of sponsorship or COI.	N = 54 patients with severe and drug-resistant major depression with a score of 26 or higher on the HAM-D scale	Mean age: 55.9 years; 16 males, 38 females.	rTMS (Magstim rapid stimulator) with motor threshold of 80% (n=19) or 100% (n=18). Consisted of 10 sessions for 5 consecutive days for 2 weeks vs Sham rTMS, received same parameters but intensity was at 90% but subjects did not receive any stimulation (n=17)	Follow up weekly for 5 weeks	Response rate in the 100% rTMS group was 61.1%, 27.8% in the 80% l rTMS, and 6.2% in the sham group. There is a significant difference between the 100% rTMS and sham, according to the pearson x^2 test, but not between the 80% rTMS and sham group.	"The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients."	Data suggest the 100% MY group better than 80% MT group did not differ significantly from sham group suggesting rTMS may be beneficial in drug-resistant patients with depression.
Fitzgerald 2003 (score=6.5)	TMS	RCT	Sponsored by grant 143561 from the National Health and Medical Research Council and by a grant from The Stanley Medical	N = 60 patients with treatment resistant depression (DSM-IV) who failed to respond to therapy with multiple	Mean age: 45.6 years; 34 males, 26 females.	High-frequency left-sided rTMS (HFL-TM): (Magstim Super) twenty 5 seconds of 10 Hz at 100% RMT. 25-second intervals. (n=20) vs Low-frequency rTMS: 60 seconds trains of 1Hz and 100% RMT. 1-minute interval. (n=20) vs Sham: same positions as other	Follow up at end of treatment	Response between the groups were significant ($F_{56,2}$=6.2). It was significantly different between HFL-TMS and sham and LFR-TMS and sham (P<0.005) but not between HFL-TMS and LFR-TMS.	"In conclusion, our results support the efficacy of HFL-TMS and LFR-TMS in the treatment of TRD and suggest equivalence of these treatments. Treatment for at least 4 weeks seems to be necessary for clinically meaningful	Data suggest comparable efficacy between the 2 treatment groups compared to sham and the 2 treatment groups were better than sham.

			Research Institute. No mention of COI.	antidepressant medications		groups but received scalp sensation (n=20). All received 10 sessions for 5 d/wk			benefits to be achieved with the parameters applied in this study. Further evaluation of whether alterations in stimulation parameters can increase the response or the rapidity of response to rTMS is required."	
Avery 2006 (score=6.5)	TMS	RCT	No mention of sponsorship or COI.	N = 68 met DSM-IV requirements for major depressive disorder	Mean age: 44.25 ± 10.00 years; 31 males, 37 females.	TMS group: received 15 Transcranial Magnetic Stimulation sessions of TMS, only on the weekdays, within 4 weeks. (n = 35) Vs Sham group: receive sham TMS (n =33).	1, 2 weeks	TMS group had significantly greater response when compared to sham group. (Fisher's p = 0.008, effect size = 0.69). TMS group had a greater remission rate, 20% compared to the sham group 3% (fisher's p = 0.033, effect size = 0.58).	"Transcranial magnetic stimulation can produce statistically and clinically significant antidepressant effects in patients with medication-resistant major depression."	Data suggest rTMS can result in statistically significant antidepressant effects in those patients with treatment resultant MDD.
O'Readon 2007 (score=6.5)	TMS	RCT	Sponsored by multiple different grants. No mention of COI.	N = 301 subject were antidepressants medication-free outpatients with a DSM-IV diagnosis of MDD.	Mean age: 44.72 ± 10.01 years; 166 males 159 females.	TMS group: receives Transcranial Magnetic Stimulation Sessions were scheduled daily in a 5-day sequence, for a max of 30 sessions (6 weeks) (n=155) vs Sham group: (n=146)	None	When comparing baseline to 4 weeks MADRS scores in the TMS group the results showed a trend toward significance (p =0.057).	"In conclusion, TMS administered over the left DLPFC using the parameters reported here for a period of up to 6 weeks was effective in treating major depression and with a good tolerability profile. These results indicate that TMS offers clinicians a novel alternative in the treatment of this disorder."	Data suggest TMS appears effective in the treatment of depression as active TMS was significantly better then sham at 4 weeks via the MADRS.

Lisanby 2009 (score= N/A)	TMS	Secondary analysis of O'reardor, 2007	Sponsored by multiple grants no COI.	N = 301 that met DSM-IV diagnostic criteria for unipolar, nonpsychotic major depressive disorder	Mean age: 48.28 ± 10.81 years; 141 males, 160 females.	Active group: receives Transcranial Magnetic Stimulation, a total of 75 pulse trains, or about 3000 pulses (10Hz) to the left dorsolateral prefrontal cortex (n=155) vs. Sham group: (n=146)	None	In the Sham to TMS group a reduced incidence of comorbid anxiety disorder (p = 0.005), less treatment resistance in current episode (p = 0.051).	" Shorter duration of current illness and lack of anxiety comorbidity may also confer an increased likelihood of good antidepressant response to TMS."	Data suggest it appears that in unipolar depressed patients those who have several treatment failures and have shorter duration of illness are more likely to respond to 10 hertz TMS delivered to DLPFC.
Solvason 2013 (score= N/A)	TMS	6 month follow - up of O'reardon, 2007	Sponsored by a grant by Neuribetics Inc. No mention of COI.	N = 301 subject were antidepressants medication-free outpatients with a DSM-IV diagnosis of MDD.	Mean age: 44.72 ± 10.01 years; 166 males 159 females.	TMS group: Transcranial Magnetic Stimulation Sessions were scheduled daily in a 5-day sequence, for a max of 30 sessions (6 weeks) (n=155) vs Sham group: (n=146)	4, 6 week	Statistically significant improvement in both functional status and QOL outcomes was observed in patients treated with active TMS compared with sham TMS during the acute phase of the randomized, sham-controlled trial. (4 week TMS p <0.001, sham p < 0.001; 6 week TMS p < 0.001, sham p < 0.001) Similar benefits were observed in patients who entered the open-label extension study. These improvements were sustained across the 24-week follow up study(6 month TMS p = 0.124, Sham p = 0.165)	"This study has contributed to the growing literature showing that TMS is a safe and effective treatment for patients with major depression who have failed to receive adequate benefit from prior pharmacotherapy."	Data suggest at 6 months post-acute THS treatment, functional improvement and QOL improvement was observed.
Wang 2017 (score=6.5)	TMS	RCT	No mention of sponsorship. No COI.	N = 43 patients who reported no history of taking any	Mean age: 37.21 ± 8.95 years; 23 males, 20 females.	rTMS group: Phase 1; five times a week received Transcranial Magnetic Stimulation with paroxetine for 4 weeks, Phase 2 received	None	HDRS scores in the rTMS group were lower than the Sham group (Repeated-measures ANOVA, F(1,41)= 4.18, P=0.047)	"This randomized controlled trial provided evidence that 10 Hz rTMS at 80% MT effectively accelerates and	Data suggest rTMS may accelerate the paroxetine response compared to sham in 1st

				antidepressants and met DSM-IV criteria for major depression.		only paroxetine treatment alone for an additional 4 weeks (n=22) Vs Sham group: received Sham TMS instead of TMS (n=21)			augments the therapeutic response to paroxetine and is safe and well tolerated in Chinese patients with first-episode depression."	episode depressed patients.
George 2010 (score=6.5)	TMS	RCT	Sponsored by National institute of mental health as the optimization of tms for the treatment of depression study (OPT-TMS) grants 5R01MH069929, 5R01MH069887, 6R01MH069896, 5R01MH069886. COI: Neuronetics Inc. was selected and loaned the TMS devices, head holders, and coils for the Trial and allowed used of the safety Investigational Devices Exemption	N = 199 anti-depression medication-free outpatients, Hamilton scale for depression ≥ 20	Mean age: 47.1 ± 11.5 years; 82 males, 117 females.	rTMS group: received Transcranial Magnetic Stimulation Intervention to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil (n=92) Vs Sham group: used a similar coil (n=98).	6 months	There was significant effect of treatment when compared between groups (odds ratio, 4.2%; 95% CI. 1.32-13.24; P = 0.02)	"Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham."	Small sample. Data suggest younger age is predictive for a positive treatment response to TMS for MDD.

			for their device.							
Borckardt 2013 (score=N/A)	TMS	Secondary analysis of George 2010	Sponsored by OPT-TMS involving grants 5R01MH069929 PI. COI: Neuronetics was selected and loaned the TMS device, head-holder and coils used In the trial and allowed to use safety IDE of their device.	N = 142 anti-depression medication-free outpatients, Hamilton scale for depression ≥ 20.	Mean age and gender data not reported.	rTMS group: received Transcranial Magnetic Stimulation Intervention to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil (n=68) Vs Sham group: used a similar coil (n=74)	None	Statistical difference between means painfulness in the rTMS (73.66 ± 31.31) group and the Sham group (28.91 ± 31.43). The slope/time main effect was also found significant $F(1,136) = 23.39$, $P < 0.0001$	"We have found that the painfulness of prefrontal rTMS diminishes steadily over the course of 3 weeks in depressed patients undergoing a double-blind treatment trial and that this only occurs in patients getting active treatment."	Data suggest that the pain associated with the prefrontal delivery of rTMS steadily decreases over 3 weeks and thus pain appears to only occurs In those receiving active treatment.
Aguirre 2011 (score=6.5)	TMS	RCT	Sponsored by IUNICS Research Institute and Mateu Orfila Foundation. No COI	N = 34 Unipolar Major Depression fulfilling DSM-IV criteria.	No mention of mean age; 8 males 11 females.	Active-TMS group: received 20 Transcranial Magnetic Stimulation treatments with the coil held flat on the scalp, and the handle 45 degrees laterally with respect to the midsagittal line (n= 13) vs. Sham group: coil was placed perpendicularly to the cranium at the calculated stimulation point (n=8)	2, 4, 8 weeks	No difference in Hamilton scale sores between groups. One variable correlated with the lower Hamilton score at the end of 20 sessions (r= -0.683, p = 0.002) and four weeks later (r=-0.0631, p=0.005)	"Only younger patients benefited from LF-rTMS as adjuvant treatment to antidepressants in this study."	Small sample Data suggest younger age is predictive for a positive treatment response to TMD for MDD.
Huang 2012 (score=6.5)	TMS	RCT	Sponsored by the Department of Health	N = 60 patients with major depressive	Mean age: 32.1 years; 17	Active rTMS: received repetitive transcranial magnetic stimulation therapy on 10	2 weeks	Active rTMS group showed 57% of the group improved compared to 29% in the	"rTMS accelerated the rapidity of the antidepressant response in first-	Data suggest rTMS accelerated the effects of citalopram.

			Foundation of Zhejiang Province, the Department of Traditional Chinese Medicine Science Foundation of Zhejiang Province, and the Education Bureau of Zhejiang Province. No COI.	episode (DSM-IV)	males, 39 females	consecutive workdays for 2 weeks, each session with 20 mg of citalopram (n=28) vs Sham rTMS: received sham treatment (n=28)		sham group (p=0.031). HAMD-17 scores were reduced more in the Active group (f=575.24, p=0.000) compared to the sham group (F=374.02, p=0.000).	episode young depressive patients. Our results call for future rTMS studies with larger sample sizes, high intensity of stimuli, and longer duration to draw more definitive conclusions."	
McLoughlin 2007 (score=6.0)	Electrocon vulsive Therapy (ECT)/rTM S	RCT	Sponsored by the NHS HTA Programme. It was also supported in part by the Guy's and St Thomas' Charitable Foundation (R001126) and a 2003 Ritter Independent Investigator Award from the National Alliance for Research on Schizophreni a and Depression (NARSAD,	N = 46 patients with major depressive disorder diagnosed with DSM-IV.	Mean age: 65.82 years; 14 males, 32 females.	rTMS group – participants received a 15 day course of rTMS of the left dorsolateral prefrontal cortex (n=24) vs. ECT group – participants received a 15 day course of ECT (n=22).	6 months.	The end-of-treatment HRSD scores were lower for ECT, with 13 (59%) achieving remission compared with four (17%) in the rTMS group.	"ECT is a more effective and potentially cost-effective antidepressant treatment than 3 weeks of rTMS as administered in this study."	Data suggest ECT was more cost effective than rTMS and at 6 months, more patients in the ECT group achieved remission compared to rTMS.

			USA). No COI.							
Chistyakov 2005 (score=6.0)	Clomipramine/rTMS	RCT	No COI. Sponsored by the Stanley Research Institute.	N = 59 participants meeting DSM-IV criteria for major depression	Mean age: 60.46 years; 15 males, 44 females	3 Hz left prefrontal repetitive transcranial magnetic stimulation (rTMS) with placebo medication (n=12) vs. 3 Hz right prefrontal rTMS with placebo medication (n=12) vs. 10 Hz left prefrontal rTMS with placebo medication (n=10) vs. 10 Hz prefrontal rTMS with placebo medication (n=9) vs. sham rTMS with clomipramine 150 mg/day (n=16). rTMS given in 10 daily sessions over a 2 week period	Follow-up at 1 and 2 weeks	Percentage of participants that had at least 50% reduction in the Hamilton Depression Rating Scale after treatment: 3 Hz left active rTMS = 54.5% ($p < 0.05$), 3 Hz right active rTMS = 16.7%, 10 Hz left active rTMS = 16.7%, 10 Hz right active rTMS = 33.3%, clomipramine and sham rTMS = 13.3% (all other groups had non-significant percentages)	"Our results suggest that 3 Hz left rTMS has a higher therapeutic efficacy and tolerability in patients with MD. "	Small group sizes. Data suggest administration of 3 Hz left rTMS was associated with better therapeutic efficacy than either 3 Hz right rTMS or 2 weeks of clomipramine.
Theleritis 2017 (score=6.0)	TMS	RCT	No mention of sponsorship. No COI.	N = 98 patients with current nonpsychotic MDD (DSM-IV)	Mean age: 38.9 years; 50 males, 48 females	Group A1: received once daily active high frequency repetitive transcranial magnetic stimulation (HF-rTMS) (15 sessions over 3 weeks) 20 HZ at 100% motor threshold for train duration of 2 seconds and intertrain interval of 1 min yielding 1600 pulses per session (n=27) vs Group A2: received twice-daily active HF-rTMS stimulation (30 session over 3 weeks) (n=27) vs Group S1: received once-daily	1, 2, 3, 5 weeks	Group A1 showed a higher HDRS score than Group A2 ($p=0.026$) and a lower score than both S1 ($p<0.001$) and S2 groups ($p<0.001$).	"Twice per day active HF-rTMS might be more effective than once per day active HF-rTMS or sham stimulation."	Data suggest two per day HFrTMS sessions may be more effective than either one session per day or sham in treating treatment-resistant depression.

						sham stimulation (15 sessions over 3 weeks) (n=20) vs Group S2: received twice-daily sham stimulation (30 session over 3 weeks) (n=24)				
Fitzgerald 2012 (score=6.0)	TMS	RCT	Sponsored by National Health and Medical Research Council. No COI.	N = 67 patients with treatment resistant depression (MINI)	Mean age: 42.9±14.4 years; 36 males, 31 females	Group 1: received bilateral rTMS (single 15 minute train at 1 Hz) (n=22) vs Group 2: received unilateral rTMS (30 trains at 10 Hz for 5 seconds) and sham on the right side(n=24) vs Group 3: received sham stimulation on both the right and left side of the cranium (n=20)	3, 6 weeks	Group 2 showed a greater reduction in HAMD scores than sham group (p=0.02). There were no differences HAMD scores between group 3 and group 1 or between group 2 and group 1.	"This study does not support the hypothesis that sequential bilateral rTMS is more effective than unilateral high-frequency left-sided rTMS."	Data suggest comparable efficacy between both groups.
Fitzgerald 2006 (b) (score=6.0)	TMS	RCT	Sponsored by a grant from the National Health and Medical Research Council and a NARSAD Young Investigator award. COI: P.F. and J.Z.D. have received support for research conducted with Neuronetics Inc., a TMS equipment	N = 130 patients with treatment resistant depression (DSM-IV)	Mean age: 49.4±13.9 years; 47 males, 83 females	Right rTMS Group: received 1 Hz of right-sided repetitive transcranial magnetic stimulation (rTMS) for 15 min train (n=31) vs Left rTMS Group: received either 2 Hz of right-sided repetitive transcranial magnetic stimulation (rTMS) (n=37) All patients received 10 sessions of rTMS on daily basis, 5 days per week, then randomized.	2, 4 weeks	HAMD scores changed by a mean of 26.1±31.1% in the 1 Hz group compared to 30.1±36.4% in the 2 Hz group. Response criteria was achieved by 42% of 1 Hz group compared to 53% in the 2 Hz group (p>0.05).	"In conclusion, low-frequency right-sided rTMS produced a clinically relevant response rate in a large representative sample of patients with TRD. There was no difference in response between 1- and 2-Hz stimulation. Finally, a moderate but significant percentage of patients who failed to respond subsequently responded to high-frequency left-sided rTMS at either 5 or 10 Hz."	Data suggest 50% of study sample achieved response and 27% met remission criteria. There was no difference in outcome of the two different pulses such that 2 Hz offers no advantage over 1 Hz.

			manufacturer.							
Grunhaus 2002 (score=5.5)	Electroconvulsive Therapy (ECT)/TMS	RCT	Sponsored by an Established Investigator Award of the National Association for Research in Schizophrenia and Affective Disorders (NARSAD) and by a Stanley Foundation Research Grant to Leon Grunhaus. No mention of COI.	N = 40 patients with major depression disorder diagnosed by the DSM-IV.	Mean age: 59.5 years; 11 males, 19 females.	ECT group – patients received at least 6 sessions of right unilateral or bilateral ECT (n=20) vs. TMS group – repetitive TMS was performed over the left dorsolateral prefrontal cortex at 90% motor threshold. Patients treated with 20 sessions (five times per week for 4 weeks) of 10-Hz treatments (1200 pulses per treatment-day) at 90% motor threshold. (n=30).	No follow up.	The overall response rate was 58% (23 out of 40 patients responded to treatment). In the ECT group, 12 responded and eight did not; in the rTMS group, 11 responded and nine did not (X^2 = .10, ns).	"This study adds to the growing literature supporting an antidepressant effect for rTMS. This study is particularly relevant because it suggests that rTMS and ECT reach similar results in nonpsychotic major depressive disorder."	Data suggest comparable efficacy but TMS less invasive than ECT.
Prasser 2015 (score=5.5)	TMS	RCT	No mention of sponsorship. No COI.	N = 56 patients diagnosed with a moderate to severe depressive episode (ICD-10)	Mean age: 47.1 years; 27 males, 27 females	rTMS Group: received repetitive transcranial magnetic stimulation at 110% motor threshold (1000 stimuli at 1 Hz to the right dorsolateral prefrontal cortex (DLPFC) and 1000 stimuli to the left DLPFC at 10 Hz for 20 trains with 25 s intervals) (n=17) vs TBS Group: received bilateral theta-burst stimulation of 1200 stimulation to the right	1, 2, 3, 7, 11 weeks	HAMD score changes were greater in the TBS group compared to sham (d=0.359) and the rTMS group (d=0.406). Effect size between rTMS group and sham group was d=0.088.	"In summary, our data confirm the potential of bilateral TBS as a non-invasive, safe and well tolerated method of brain stimulation in the treatment of major depression."	Data suggest lack of efficacy of both treatments over sham for add-on treatment of depression in terms of changes In the HRDS as there were no significant differences over sham, rather, only a trend towards improvement.

						DLPFC and 1200 to the left DLPFC (n=20) vs Sham Group: received TBS protocol with a sham coil (n=17)				
Mogg 2008 (score=5.5)	TMS	RCT	Sponsored by the Guy's and St Thomas' Charitable Foundation, the National Health Service Research and Developmen t National Coordinating Centre for Health Technology Assessment, National Alliance for Research on Schizophreni a and Depression, and the Psychiatry Research Trust. No COI.	N = 59 patients with a diagnosis of major depressive episode (DSM-IV)	Mean age: 53.5 years; 22 males, 37 females	Active rTMS: received repetitive transcranial magnetic stimulation at 110% motor threshold at 10 Hz in 5 s trains (20 trains each session with intertrain intervals of 55 seconds, 1000 TMS pulses per session) (n=29) vs Placebo rTMS Group: received sham coil rTMS protocol (n=30)	6 weeks, 4 months	Active group showed a mean 2.9 point reduction in HAMD scores compared to sham group (95% CI -0.7-6.5). Remission rate was 25% in the active group compared to 10% in the sham group (p=0.2).	"Adjunctive rTMS of the left DLPFC could not be shown to be more effective than sham rTMS for treating depression."	Blinding of both patients and assessors challenging so only "partially blinded". Data suggest modest trend of improvement in both groups suggesting lack of efficacy.
Blumberger 2016 (score=5.5)	TMS	RCT	Sponsored by a grant from the Ontario Mental Health Foundation. COI: One or	N = 121 patients with a diagnosis of MDD (DSM-IV)	Mean age: 47.0 years; 44 males, 77 females	Bilateral rTMS: received bilateral repetitive transcranial magnetic stimulation (rTMS-1-10 Hz) (n=40) vs Unilateral rTMS: received unilateral rTMS (10 Hz) (n=40)	3, 6 weeks	Remission rate was 20% in the bilateral group compared to 7.5% in the unilateral group and 2.4% in the sham group (p=0.027). Remission was higher in the bilateral group	"Our findings suggest that sequential Bilateral rTMS is superior to sham rTMS; however, adjusting for coil-to-cortex distance did	Data suggest numbers of pulses dissimilar between groups and sham group did not employ an active stimulation

			more of the authors have received or will receive benefits for personal or professional use.			vs Sham Control: received sham stimulation (n=41)		compared to the sham group (p=0.014) and a similar observation was made between the bilateral group and the sham group (p=0.028). Remission rate did not different between bilateral or unilateral groups (p=0.19).	not yield enhanced efficacy rates."	therefor results are indeterminant.
Pallanti 2010 (score=5.5)	TMS	RCT	Sponsored by the Italian Department of Health. No mention of COI.	N = 60 participants meeting DSM-IV criteria for non-psychotic major depression	Mean age: 48.88 years; 35 males, 25 females	Low-frequency repetitive transcranial magnetic stimulation (rTMS) over the right dorsolateral prefrontal cortex (DLPFC) (140 s X 1 Hz) with contralateral sham (unilateral) (n=20) vs. Low-frequency right DLPFC rTMS followed by left DLPFC high frequency rTMS (5 s X 10 Hz) (bilateral) (n=20) vs. Bilateral sham. All treatments were given for 3 weeks, with 15 daily sessions on weekdays	Follow-up at 1, 2, and 3 weeks	ANCOVA analysis resulted in significant effect of stimulation conditions between subjects factor (F = 8.01, p = 0.001). Significance was seen at week 1 (F = 6.32, p = 0.004)	"These findings constitute the first comparison of sequential bilateral left high-frequency/right low-frequency, and unilateral low frequency right-sided rTMS. Both techniques showed efficacy in a sample of treatment resistant depression patients with only unilateral rTMS significantly more effective of sham."	Data suggest right sided low frequency TMS may be appropriate treatment for treatment-resistant depression.
Rosa 2006 (score=5.0)	TMS/Electroconvulsive Therapy	RCT	No mention of sponsorship. No COI.	N = 42 patients with unipolar depressive disorder (DSM-IV)	Mean age: 43.6±10.5 years; 22 males, 20 females	ECT Group: received right unilateral electric convulsive therapy, then 2 weeks later received bilateral ECT (n=15) vs rTMS Group: received repetitive transcranial magnetic stimulation (20 sessions 5x per week for 4 weeks) (n=20)	2, 4 weeks	No group effect was observed (p=0.495) or group time interaction (p=0.949). Between group VAS score did not differ (p=0.388) or time interaction (p=0.942). Response rates were 20% for ECT group and 10% for the rTMS group (p=0.631).	"Both treatments were associated with a degree of improvement in refractory depression and therefore add to the literature that rTMS can be an effective option to ECT as it is a less costly treatment and is not associated with	Data suggest comparable efficacy between rTMS and ECT.

									anaesthetic and other ECT risks."	
Loo 2007 (score=5.0)	TMS	RCT	Sponsored by a grant from National Health and Medical Research Council Program. No COI.	N = 38 patients with major depressive episode (DSM-IV)	Mean age: 47.8 years; 20 males, 18 females	Active Group: received rTMS of 10 Hz, 30 trains of 5 s each, 25 s between trains at 110% motor threshold (2 session each week (n=19) vs Sham Group: received sham rTMS with an inactive coil (n=19)	2, 6 weeks	Active group showed greater improvement in MADRS scores compared to sham group ($p<0.05$).	"rTMS given twice daily was effective and safe, with no adverse neuropsychological effects."	Data suggest 2 weeks of twice per day treatment of rTMS more effective than sham in improving symptoms of depression.
Wajdik 2014 (score=5.0)	TMS	RCT	Sponsored by grants from the National Institute of Mental Health. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 68 participants with major depressive disorder (DSM-IV)	No mention of mean age, range 21-65 years; no mention of sex.	rTMS Group: received repetitive transcranial magnetic stimulation 10 Hz in 5 s trains, (25-30 s intertrain interval) for 1600 pulses per session for 3-4 weeks (n=32) vs Sham Group: received sham treatment (n=31)	4 weeks, 6 weeks	Active rTMS group showed a greater decrease in depression symptoms compared to sham group. rTMS group showed 30.6% response rate compared to 6.1% in sham group ($p=0.033$).	"Using a higher TMS intensity as well as a greater number of pulses and having a larger sample size compared with most previous studies, this study found no negative neuropsychological effects of TMS. Changes in neuropsychological function were unrelated to changes in depression."	Data suggest the changes in neuropsychological function post rTMS did not result or correlate to changes in depressive symptoms but TMS was somewhat better than sham in decreasing HDRS depression symptoms. No long term follow-up.
Galletly 2012 (score=5.0)	TMS	RCT	No mention of sponsorship. COI: P.B.F. is supported by a NHMRC Practitioner fellowship and has received equipment	N = 77 participants with major depression (MINI)	Mean age: 48.6±13.42 years; 26 males, 51 females	Spaced Group: received spaced rTMS 3 days/week for 6 weeks (18 total treatments) (n=42) vs Daily Group: received daily rTMS 5 days/week for 4 weeks (20 total treatments) (n=35)	4 weeks, 6 weeks	All participants showed a reduction in HAMD, HAMA, MADRS, and Zung SDS scores ($p<0.001$, for all scores). Group interactions were observed for HAMD ($p=0.01$) and for Zung SDS ($p=0.04$). Participants in daily group showed more	"Our study indicates that the efficacy of rTMS is related to the number of treatments given and that spacing the treatments neither improves nor reduces efficacy."	Data suggest more improved symptoms in daily TMS group versus spaced group by week 4. However, there were similar results (comparable efficacy) at the end of 6 weeks.

			for research from MagVenture, Medtronic Ltd and Brainsway Ltd.					improvement compared to the spaced group.		
Eranti 2007 (score=4.5)	Electroconvulsive Therapy/TMS	RCT	Sponsored by National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment, Guy's and St. Thomas's Charitable Foundation, and the National Alliance for Research on Schizophrenia and Depression. No COI.	N = 46 patients referred to ECT and diagnosed with major depressive disorder using Structured Clinical Interview for DSM-IV Axis 1 Disorders	Mean age: 65.8 years; 14 males, 32 females.	Group 1 – repetitive transcranial magnetic stimulation (rTMS) (magstim super rapid stimulator) to left of lateral prefrontal cortex at 110% motor threshold, 15 daily sessions with 20 trains in 55 sec intervals of 10 Hz for 5 seconds (n=24) vs Group 2 – ECT twice a week with 0.75-1.0 mg/kg methohexitone, 0.5–1.0 mg/kg suxamethonium. For bilateral frontotemporal ECT given at 1.5 times seizure threshold while right unilateral ECT given at 2.5 times seizure threshold (n=22)	2-3 days after treatment and at 6 months	Hamilton Depression Rating Scale (HAM-D) scores were lower for group 2 at the end of treatment (p=0.002). No difference in HAM-D scores at 6 months (p=0.93). 13 patients in group 2 had a HAM-D score of 8 or lower vs 4 in group 1 after treatments (p=0.006). No difference between time and group on the Beck scale (p=0.25). No evidence that HAM-D score would change due to psychosis (p=0.06).	"rTMS was not as effective as ECT, and ECT was substantially more effective for the short-term treatment of depression."	Data suggest although ECT was initially better for depressive symptoms, at 6 months there was no difference between TMS and ECT.
Hansen 2011 (score=4.5)	Electroconvulsive Therapy/TMS	RCT	Sponsored by Danish Council for Medical Research, Einar Geert-Jorgensen and Ellen Geert-Jorgensen	N = 60 patients diagnosed with moderate to severe depression using ICD-10 criteria and major	Mean age: 49 years; 18 males, 42 females.	Group 1 – rTMS (magstim rapid stimulator) over right dorsolateral prefrontal cortex, received 2 60 sec 1 Hz trains at 110% intensity in a 180 sec intertrain interval for 15 consecutive week days (n=30) vs Group 2 –	4 weeks.	Both groups had HAM-D scores reduced (ACT and rTMS, p<0.001). There was a rate difference between the two methods at week 3 (p=0.035) and remission (p=0.003). The rate of success between the two groups	"Low-frequency rTMS was significantly less effective than ECT, but ECT had more adverse effects on cognitive function. However, the outcome does not point to right frontal	Data suggest TMS less effective than ECT for depression treatment but has less adverse effects.

			Research Foundation, a Butcher Worzner and wife Inger Worzner grant, Aarhus University Foundation for Research in Mental Diseases, and the Foundation of Psychiatric Research. No COI.	depressive disorder using DSM-IV criteria.		given 2-6 mg/kg sodium thiopental, 0.5-1 mg/kg suxamethonium chloride, and 4-8 µg/kg Atropine, electrodes placed unilaterally over right hemisphere, intensity determined by age. Treatment given 3 times a week for 3 weeks (n=30).		was not significant at 4 weeks (p=0.2)	low-frequency rTMS in the present stimulus design as a first-line substitute for ECT, but rather as a treatment option for patients with depression who are intolerant to other types of treatment or not accepting ECT."	
Koerselman 2004 (score=4.5)	TMS	RCT	No mention of sponsorship. No COI.	N = 55 patients with moderate or severe major depressive episode (DSM-IV)	Mean age: 51.5 years; 23 males, 29 females	rTMS Group: received repetitive transcranial magnetic stimulation daily (5 sessions per week) of 20 Hz, 20 trains of 2 seconds, 30 second intervals, and 80% motor threshold (n=26) vs Sham Group: received sham treatment (n=26)	1, 2, 4, 8, 14 weeks	Mean HAM-D scores decreased in both groups by 2.5 points, but never more than 20%. At 12 weeks, the HAM-D scores showed improvement in favor of rTMS group (p=.006).	"Decrease of depressive symptoms may continue after the cessation of rTMS stimulation."	High dropout rate in both groups. At 2 weeks there were only modest changes observed between groups favoring active treatment but at 3 months the rTMS group increased gains.
Levkovitz 2009 (score=4.5)	TMS	RCT	Sponsored by Rosenzweig-Coopersmith Fund and Brainsway Inc. COI: Drs. Levkovitz, Roth, and Zangen have financial	N = 65 patients with treatment resistant depression	Mean age: 48±12.6 years; no mention of sex.	H1-Coil Group: (n=24) vs H2-Coil Group: (n=22) vs H1L-110% Group: (n=8) vs H1L-120% Group: (n=11). All groups received 20 Hz at either 110 or 120% of the motor threshold of transcranial magnetic stimulation (42 s trains with a 20 s interval, total of 180	4 weeks, 3 months	Decrease in HDRS-24 score of 50% or more was observed in 47% of the H1-coil group, 30% in the H2-coil group, 60% in the H1L-120% coil group, and 0% of the H1L-110%-coil group (p=0.0331). Remission rate was 42% for H1 group, 10% in H2 group, 50% in the	"DTMS over the PFC was found safe and effective in alleviating depression. The results accentuate the significance of deep, high-intensity stimulation over low, and serve as the first study to indicate the potential of DTMS in	Sparse methods limited demographic data. Data suggest improved cognitive and antidepressant effects from high TMS as evidenced by HDRS scores.

			interest in Brainsway Inc.			pulses during 15-minute daily session)		H1L-120% group, and 0% in the H1L-110% group (p=0.0092).	psychiatric and neurologic disorders."	
Herbsman 2009 (score=4.0)	TMS	RCT	Sponsored by National Institute of Mental Health, NIMH Optimization of TMS for the Treatment of Depression, and Brain Stimulation Laboratory, the Center for Advanced Imaging Research, and the South Carolina Research Authority. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 54 subjects with current major depressive disorder (MDD) (DSM-IV)	Mean age: 43.2 years; 23 males, 31 females	Active TMS: received repetitive transcranial magnetic stimulation (rTMS) of 10 Hz in 5 second trains (32 trains each session, 1600 pulses per session for 15 sessions over 4 weeks) (n=28) vs Sham TMS: received sham rTMS (n=26)	4 weeks	Active group showed a greater reduction in HDRS score compared to sham group (p=.017).	"These results suggest that within the general anatomical area targeted by the 5-cm rule, placing the TMS coil more laterally and anteriorly is associated with improved response rates in TMS depression studies. Controlled studies testing this anatomical hypothesis are needed."	Data suggest a more anterio-lateral coil placement may improve TMS response.
Keshtkar 2011 (score= 3.5)	Electrocon vulsive Therapy/T MS									Data suggest both interventions improved symptoms of depression as well as improving the

										suicidal subscale score but the antidepressant effects of ECT were greater than TMS.[76]
Philip 2016 (score=3.0)										A pilot feasibility study. Data suggest some depressed patients may be able to be maintained with periodic TMS with no medications, high attrition rate.
Triggs 2010 (score=3.0)										Data suggest lack of efficacy. Data suggest stimulation of the left hemisphere via rTMS may be associated with achieving a therapeutic effect but rTMS compared to sham not statistically significant.

[76] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Deep Brain Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Bergfeld 2016 (score=7.0)	Deep brain Stimulation	RCT	Sponsored by an unrestricted grant from Medtronic Inc. Authors get occasional education payments from Medtronic.	N = 25 patients with MDD for more than 2 years (Hamilton Depression Rating Scale score ≥18).	Mean age: 53.2±8.4 years; 8 males, 17 females	Group 1 (n = 9) received active deep brain stimulation (DBS) then crossed over to sham treatment vs Group 2 (n =7) received sham first then crossed over to active DBS treatment.	Baseline, Optimization period (4 to 52 weeks), 3, 9 and 15 weeks.	During active DBS, patients HAM-D17 scored 13.6 (95% CI, 9.8 – 17.4) vs sham 23.1 (95% CI, 20.6-25.6 (p<0.001). Baseline vs optimization end (4-52 weeks) HAM-D 17 score: 22.2 (95% CI, 20.3-24.1) vs 15.9 (95% CI, 12.3-19.5) (p=0.001).	"This trial shows efficacy of DBS in patients with TRD and supports the possible benefits of DBS despite a previous disappointing randomized clinical trial."	Crossover RCT. No baseline comparability data by individual groups. Small sample size. Data suggest DBS for TRD patients reduced depressive symptoms via HAM-D 17.
Dougherty 2014 (score=5.0)	Deep brain Stimulation	RCT	Sponsored by Medtronic. All authors received compensation and support from Medtronic.	N = 30 patients with DSM – IV criteria for MDD lasting for 2 or more years.	Mean age: 47.7±12.0 years; 17 males, 13 females.	Active Group (n=16) received programmed voltage to the device for greatest antidepressant effect vs. Control (n=14) had the programmed device on but was set to 0 volts.	Baseline, 2, 4, 6, 8, 12, 16 weeks, 1, 2, 3 years.	Baseline to week 16, Montgomery-Åsberg Depression Rating Scale improvement and percentage improvement, Active vs Control: 8.0±13.7 (19.6% ±34.9%) vs 9.1±10.6 (24.6%±28.8%) (NS). More adverse health effects happened in the active group vs control group.	"The results of this first randomized controlled study of DBS for the treatment of TRD did not demonstrate a significant difference in response rates between the active and control groups at the end of the 16-week controlled phase. However, a range of 20% to 26.7% of patients did achieve response at any time during the open-label continuation phase."	Data suggest lack of efficacy. No significant difference between active versus control (sham) groups at end of 16 weeks.

Evidence for the Use of Vagal Nerve Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Aaronson 2013 (score=7.5)	Vagus Nerve Stimulation	RCT	Sponsored by Cyberonics, Inc. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 331 patients diagnosed with chronic or recurrent MDD or bipolar disorder (BP) and a recurrent diagnosis of major depressive episode (MDE) defined by Diagnostic and Statistical Manual of Mental Disorders, Mini-International Neuropsychiatric Interview, MADRS scale	Mean age: 47.9±10.8 years; 100 males, 210 females	High Group: received high dose vagus nerve stimulation of 1.25-1.5 mA, pulse width 250 µs (n=107) vs Medium Group: received medium dose vagus nerve stimulation of 0.5-1.0 mA, pulse width of 250 µs (n=101) vs Low Group: received low dose vagus nerve stimulation of 0.25 mA, pulse width of 130 µs (n=102) All groups received same duty cycles (30 s ON and 5 min OFF) and pulse frequencies (20 Hz)	7 days, 10, 14, 18, 22, 26, 32, 38, 44, 50 weeks	ICD-C scores were reduced from baseline to follow-up for all stimulation dose groups (p=0.0023). Treatment group effects were not significantly different comparing low vs medium (p=0.8131), low vs high (p=0.8027), or medium vs high (p=0.9921).	"TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. Higher electrical dose parameters were associated with response durability."	Data suggest individuals with treatment-resistant depression showed improvement compared to baseline when administered VNS as all 3 treatment groups improved, but differences between groups were not significant.
Rush 2005 (score=6.5)	Vagus Nerve Stimulation	RCT	Sponsored by Cyberonics, Inc. COI: One or more of the authors have	N = 235 participants with primary diagnosis of major	Mean age: 46.5±9.0 years; 82 males, 140 females	Treatment Group: received vagus nerve stimulation at	6, 12, 18 months	Primary outcome of response rate to $HRSD_{24}$ scores was 15.2% for treatment group	"In sum, VNS was safe and well tolerated. This study did not	Data suggest lack of or inconclusive efficacy.

			received or will receive benefits for personal or professional use.	depressive disorder (MDD) or bipolar 1 or 2 disorder as criteria of DSM-IV		20 Hz, 500 µs pulse width, and on/off cycle of 30 sec on and 5 min off for 2 week stimulation, output was 0.25 mA-3.5 mA increase in 0.25 mA increments (n=112) vs Control Group: (n=110)		compared to 10% in control group (p=0.251). Response to IDS-SR_{30} score was 17% in the treatment group compared to 7% in the control group (p=0.032).	yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression. By all measures, VNS was associated with greater symptom reduction."	
Nierenberg 2008 (score= N/A)	Vagus Nerve Stimulation	Post-hoc analysis of Rush 2005.	Sponsored by Cyberonics, Inc. COI: One or more of the authors have received or will receive benefits for personal or professional use.	N = 235 participants with primary diagnosis of major depressive disorder (MDD) or bipolar 1 or 2 disorder as criteria of DSM-IV	Mean age: 46.5±9.0 years; 82 males, 140 females	Treatment Group: received vagus nerve stimulation at 20 Hz, 500 µs pulse width, and on/off cycle of 30 sec on and 5 min off for 2 week stimulation, output was 0.25 mA-3.5 mA increase in 0.25 mA increments (n=112) vs Control Group: (n=95)	3, 6, 9, 12 months	Bipolar disorder participants had fewer episodes of chronic depression (p=.012), but also had more treatments compared to unipolar disorder participants (p=0.005). Bipolar disorder participants also showed fewer episodes of depression (p=0.006).	"Bipolar TRD is a serious condition. In this hypothesis-generating analysis, VNS short- and long-term effects on bipolar and unipolar TRD were similar. Because these analyses were post hoc, these findings should not be interpreted as warranting clinical inference regarding effectiveness of VNS in patients with bipolar depression."	2-year follow-up of Rush 2005. Data suggest comparable results for both bipolar and unipolar treatment resistant depression.
Rush 2005 (score= N/A)	Vagus Nerve Stimulation	Secondary Analysis	Sponsored by Cyberonics, Inc. COI: One or more of the	N = 235 participants with primary diagnosis of	Mean age: 46.3±8.9 years; 74	Treatment Group: received vagus nerve	12 months	Reduction in $HRSD_{24}$ scores improved .45 points per month	"These 1-year open trial data found VNS to be well tolerated,	12-month follow-up of Rush 2005. Data suggest

		of Rush 2005.	authors have received or will receive benefits for personal or professional use.	major depressive disorder (MDD) or bipolar 1 or 2 disorder as criteria of DSM-IV	males, 131 females	stimulation at 20 Hz, 500 µs pulse width, and on/off cycle of 30 sec on and 5 min off for 2 week stimulation, output was 0.25 mA-3.5 mA increase in 0.25 mA increments (n=112) vs Control Group: (n=95)		(p<.001) with the most improvement in the first quarter (1.22 points, p<0.001). Improvement in 3rd quarter was (0.45 points, p=0.011). Treatment group improved more over time compared to the control group (-1.96 points, p=0.002).	suggesting a potential long-term, growing benefit in treatment-resistant depression, albeit in the context of changes in depression treatments. Comparative long-term data are needed to determine whether these benefits can be attributed to VNS."	VNS may benefit some patients with treatment resistant depression as there was reduction on depression rating scales.

Evidence for the Use of Electroconvulsive Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Geretsegger 2007 (score=8.0)	Electrocon vulsive Therapy	RCT	No sponsorship or COI.	N = 50 patients with chronic depression meeting DSM-III criteria for recurrent major depression or bipolar disorder	Mean age: 58.2 years; 7 males, 43 females	PROG-G Group: received propofol anesthetic (n=25) vs METH-G: received methohexital anesthetic (n=25) All patients received consecutive unilateral electroconvulsi	2, 8 weeks	Of the PRO-G group, 60% showed a reduction of 50% or more on the Hamilton depression rating scale compared to 76% of patients in the METH-G group. Patients in PRO-G group showed lower increase in blood pressure post-ECT (p<0.001).	"Propofol, as compared with methohexital, results in a more moderate increase in blood pressure and shorter seizure duration. The seizure quality did not differ significantly between the 2 groups. We detected a tendency toward	Data suggest that seizure duration is shorter in propofol vs methohexital but seizure quality is comparable in both. There was a trend towards improved cognition with propofol.

						ve therapy sessions 3 times per week			improved cognitive performance after anesthesia with propofol as compared with methohexital, but with statistical significance in only 2 cognition trials. Therefore, propofol is a safe and efficacious anesthetic for ECT treatment."	
Sackeim 2000 (score=7.0)	Electrocon vulsive Therapy	RCT	Sponsored by grants from the National Institute of Mental Health. No mention of sponsorship.	N = 80 patients with major depressive disorder based on the Hamilton rating scale for depression and the Research Diagnostic Criteria (RDC)	Mean age: 57.1 years; 29 males, 51 females	Group 1: received low dosage unilateral electroconvulsive therapy (ECT) (n=20) vs Group 2: received moderate dosage unilateral ECT (n=20) vs Group 3: received high-dosage unilateral ECT (n=20) vs Group 4: received high dosage bilateral ECT (n=20)	2 weeks, 2 months	HRSD scores yielded a between medication resistance classification and time point of $F_{3,216}$=2.83 (p=0.04). HRSD scores for treatment groups after 6 ECT's ($F_{3,71}$=2.99, p=0.04), 1-2 days after ECT ($F_{3,71}$=3.20, p=0.03), 1 week after ECT ($F_{3,71}$=2.84, p=0.04). After sixth ECT treatment, high dosage RUL and BL groups showed superior antidepressant response compared to low-	"Right unilateral ECT at high dosage is as effective as a robust form of BL ECT, but produces less severe and persistent cognitive effects."	Data suggest comparable efficacy between right unilateral ECT and BL ECT but there are less cognitive impairment (severity and persistence).

								and moderate-dosage RUL groups ($F_{1,77}$=9.38, p=0.003).		
Sackeim 2001 (score=7.0)	Electrocon vulsive Therapy	RCT	Sponsored by National Institute of Mental Health grants, Solvay Pharmaceuticals Inc., and MECTA Corporation. No mention of COI.	N = 84 patients with major depressive disorder meeting Research Diagnostic Criteria (RDC)	Mean age: 57.4 years; 28 males, 56 females	Nortriptyline: received 75-125 ng/mL of nortriptyline (n=27) vs Nortriptyline and Lithium: received a combination of nortriptyline and lithium 0.5-0.9 mEq/L (n=28) vs Placebo: (n=29)	4, 8, 12, 16, 20, 24 weeks	Relapse observed in 84% of placebo group, 60% of nortriptyline group, and 39% for nortriptyline-lithium group. Patients that relapsed showed higher HRSD scores compared to patients who did not relapse.	"Our study indicates that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT. Monotherapy wit nortriptyline has limited efficacy. The combination of nortriptyline and lithium is more effective, but the relapse rate is still high, particularly during the first month of continuation therapy."	Data suggest relapse at 6 months is highly probable without continuation pharmacothera py post ECT. In addition, monotherapy less effective than combination therapy but relapse rate is high in both groups during first month post ECT.
Bjølseth 2015 (score=7.0)	Electrocon vulsive Therapy	RCT	No sponsorship or COI.	N = 73 patients with major depression as defined by DSM-IV-TR criteria	Mean age: 74.8 years; 34 males, 39 females	BF Group: received electrodes placed 5 cm above outer angle of orbit on line parallel to sagittal plane (n=36) vs RUL Group: received electrode placed d'Elia (n=37). All	3 months	Efficacy achieved in both groups for decline in $HRSD_{17}$ scores. Mean change was 13.2±7.3 points for BF group compared to 14.7±7.1 points in the RUL group. Electrode placement showed decrease in symptom severity (p<0.001 for all	"In severe depression, high-dose ultra-brief right unilateral ECT appears to show matching acute antidepressant response to an equally high-dose brief pulse right unilateral ECT."	Data suggest comparable efficacy.

						patients received treatment 2 times a week via Thymatron System IV (0.5-1.0 ms pulse width) of current of 0.9 A with a frequency of 10-70 Hz.		groups). Remission $HRSD_{17}$ criteria was met by 38.9% of BF group compared to 51.4% of RUL group (p=0.285).		
Mayur 2013 (score=7.0)	Electrocon vulsive Therapy	RCT	No sponsorship or COI.	N = 45 patients with severe depression according to MINI international neuropsychi atric interview	Mean age: 43.2 years; 21 males, 14 females	BP-ECT: received 1 ms brief pulse unilateral ECT (n=18) vs UBP-ECT: received 0.3 ms ultra-brief pulse unilateral ECT (n=17) All patients received MADRS at baseline, and 24 hours after the eighth ECT session, and the end of the ECT course.	24 hours following the 8th ECT session	BP-ECT group showed m(SE) of 12.11±2.48 compared to UBP-ECT with 12.35±2.56. Depression severity declined in both groups (p=0.63).	"To conclude, 0.3 ms-ultrabrief pulse right unilateral ECT at six times threshold dose produced robust and matching acute anti-depressant effects to 1 ms-brief pulse 6 times threshold right unilateral ECT."	Data suggest comparable efficacy.
Stoppe 2006 (score=6.5)	Electrocon vulsive Therapy	RCT	No mention of sponsorship or COI.	N = 39 inpatients with major depression according to DSM-IV criteria	Mean age: 75.2 years; 17 males, 22 females	RUL ECT: received modified full-age dosing method (2.5 times above the threshold) (n=17) vs BL ECT: received initial dose of 50% of	1 month	Remission rates were 88.2% for RUL ECT group compared to 68.2% for BL ECT (p=0.25). Mean number of ECT sessions to achieve remission was 10.0±3.46 for RUL ECT group	"In elderly depressive subjects, high-dose RUL ECT is as effective as BL ECT yet produces less adverse effects and less cognitive impairment."	Data suggest comparable efficacy with BL-ECT being associated with less adverse effects and less cognitive impairment.

						maximal output (n=22)		compared to 10.0±2.81 for BL ECT group (p=0.37).		
Quante 2011 (score=6.5)	Electroconvulsive Therapy	RCT	No sponsorship. COI: Malek Bajbouj received unrestricted research grants from Cyberonics and Medtronic.	N = 41 patients with treatment resistant depression (major depressive disorder and bipolar depression according to DSM-IV)	Mean age: 56.5±13.9 years; 9 males, 32 females	Group 1: received electroconvulsive therapy 3 times per week for 3 weeks (9 sessions) at 4 times the seizure threshold (n=14) vs Group 2: received electroconvulsive therapy 3 times per week for 3 weeks (9 sessions) at 7 times the seizure threshold (n=15) vs Group 3: received electroconvulsive therapy 3 times per week for 3 weeks (9 sessions) at 10 times the seizure threshold (n=12)	3 weeks	All groups showed improved in HDRS-28 score (Group 1: p=0.003, Group 2: p<0.001, Group 3: p<0.001). After 1 week of ECT treatment, all groups showed reduction in HAMD scores (Group 1: p=0.012, Group 2: p<0.001, Group 3: p<0.014). Response rates observed were 55% in group 3 compared to 39% in group 1 and 35% in group 2 (p=0.582).	"A RULE CT with ultrabrief pulse stimulation and 4_ ST intensity is effective and from good tolerability. Higher intensity dosages seem to be associated with more cognitive side effects during a course of acute ECT treatment."	Data suggest adverse cognition effects are associated with higher ECT dosages.
Purtuloglu, T 2013 (score=6.5)	Electroconvulsive Therapy (ECT)	RCT	No sponsorship or COI.	N = 96 patients with Major Depressive Disorder	Mean age: 34.6 years; 96 males, 0 females.	Propofol group – patients received 1.5 mg/kg propofol	6 months.	Hamilton Depression Rating Scale (HDRS) mean (SD) score at baseline was	"In conclusion, propofol may improve major depressive disorder more	Data suggest Propofol is better than sodium thiopental for

				diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.		(n=48) vs. Sodium Thiopental group – patients received 2.5-3 mg/kg (n=48). All patients received 6 sessions of bilateral ECT 3 times per week with an ECT device.		37.3 (2.2) in the Propofol group and 36.7 (1.2) in the Sodium Thiopental group. At postintervention, the mean (SD) HDRS score was 10.7 (1.8) in the propofol group and 13.4 (3.3) in the sodium thiopental group.	than sodium thiopental in patients who are receiving ECT."	those receiving ECT for MDD as evidenced by improved HDRS-17 scores.
Brunoni 2017 (score=6.0)	Escitalopram/tDCS	RCT	Sponsored by a grant from Fundacão de Ampara à Pesquisa do Estado de São Paulo, NARSAD Young Investigator from the Brain and Behavior Research Foundation, FAPESP Young Researcher from the São Paulo State Foundation, and the National Council for Scientific and Technological Development Associacão Beneficente Alzira Denise Hertzog da	N = 245 patients with unipolar depression (DSM-5)	Mean age: 42.7 years; 79 males, 166 females	Escitalopram: received 10 mg escitalopram for 3 weeks and 20 mg thereafter (n=94) vs tDCS: received transcranial direct-current stimulation (tDCS) with 22 sessions each 30-min per day (2 mA of 15 sessions each day during the week then 7 sessions once a week until week 10) (n=94) vs Placebo: received same dosing as escitalopram group of a	10 weeks	Mean HRDS-17 scores decreased by 11.3±6.5 points in escitalopram group compared to 9.0±7.1 points in tDCS group, and 5.8±7.9 points in the placebo group. Escitalopram was superior to placebo ($p<0.001$) and tDCS was superior to placebo ($p=0.01$).	"In conclusion, tDCS did not show noninferiority to escitalopram in this placebo-controlled trial involving patients with unipolar major depressive disorder."	Data suggest escitalopram superior to tDCS which was better than placebo but tDCS was associated with increased new onset mania (escitalopram> tDCS> placebo).

			Silva, and scholarships from Brazillian Coordination, and FAPESP. No mention of COI.			placebo pill (n=60)				
Coleman 1996 (score=6.0)	Electrocon vulsive Therapy	RCT	Sponsored by a grant from the Charles A. Dana Foundation Consortium on Memory Loss and Aging. No mention of COI.	N = 96 patients, N = 70 patients with major depression by HRSD-24 scale and N = 18 controls	Mean age: 50.1 years; 41 males, 55 females	Depressed Patients: (n=70) Right Unilateral ECT: used the d'Elia placement vs Bilateral ECT: used the standard bifrontotempor al placement vs Low-Dosage ECT: received low stimulus intensity just above seizure threshold electroconvulsi ve therapy vs High-Dosage ECT: received high stimulus intensity 2.5 times the initial threshold vs Controls: (n=18) All patients except controls were assigned to double crossover	2 months	Depressed group showed improvement in SSMQ scores following ECT treatment and at 2-month follow-up. A main effect was observed for group (F (1.74) =13.74, p=0.0004), and an interaction between group and SSMQ subscale (F (1.74) =5.96, p<0.02). Tests indicate memory dysfunction prior to ECT and similar ratings to controls after ECT.	"In summary, we found marked improvement in SSMQ scores following ECT, strong relations between SSMQ scores and the severity of depressive symptoms, and a paucity of relations between SSMQ scores and objective cognitive measures."	Data suggest severity of depressive symptoms appears to be correlated with patients' reports of memory dysfunction. Shortly after ECT, both controls and study population reported similar memory function but 2 months post ECT, the study group trended towards reporting more "retrograde amnesia" in self-rated memory.

						treatments of ECT.				
McLoughlin 2007 (score=6.0)	Electroconvulsive Therapy (ECT)/rTMS	RCT	Sponsored by the NHS HTA Programme and in part by the Guy's and St Thomas' Charitable Foundation (R001126) and a 2003 Ritter Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD, USA). No COI.	N = 46 patients with major depressive disorder diagnosed with DSM-IV.	Mean age: 65.82 years; 14 males, 32 females.	rTMS group – participants received a 15 day course of rTMS of the left dorsolateral prefrontal cortex (n=24) vs. ECT group – participants received a 15 day course of ECT (n=22).	6 months.	The end-of-treatment HRSD scores were lower for ECT, with 13 (59%) achieving remission compared with four (17%) in the rTMS group.	"ECT is a more effective and potentially cost-effective antidepressant treatment than 3 weeks of rTMS as administered in this study."	Data suggest ECT was more cost effective than rTMS and at 6 months, more patients in the ECT group achieved remission compared to rTMS.
Eschweiler, GW 2006 (score=6.0)	Electroconvulsive Therapy (ECT)	RCT	Sponsored by the Tuebingen University Medical School for the generous grant AKF731. No mention of COI.	N = 92 participants with major depressive episode in monopolar or bipolar disorder according to the ICD-10 or DSM-IV.	Mean age: 54.6 years; 39 males, 53 females.	Bifrontal ECT – participants were administered six sessions of bifrontal ECT (n=46) vs. Right-unilateral ECT – participants were administered six sessions of right-unilateral ECT. (n=46).	No follow up. Treatment continued if psychiatrist felt necessary.	The mean Hamilton Depression score decreased from 27 to 17 points in both groups of 46 patients, resulting in 12 responders (primary endpoint defined as a decrease N50%) in each patient group (95% confidence interval for the odds ratio from 0.35 to 2.8).	"Both bifrontal and right unilateral electrode placements in ECT were reasonably safe and moderately efficacious in reducing symptoms of pharmaco-resistant major depression."	Data suggest no difference between placement of electrodes for ECT as there was comparable efficiency.

Bauer, J 2009 (score=6.0)	Electrocon vulsive Therapy (ECT)	RCT	No mention of sponsorship or COI.	N = 62 patients with major depression according to the ICD-10.	Mean age: 52 years; 18 males, 44 females.	Thiopental – patients received bilateral ECT. Anesthesia was introduced with thiopental (3mg/kg) followed by succinylcholin e (0.4 mg/kg) (n=31) vs. Propofol – patients received bilateral ECT. Anesthesia was introduced with propofol (1.5mg/kg) followed by succinylcholin e (0.4 mg/kg) (n=31).	No follow up.	The mean seizure duration of the patients in the thiopental group was 36.3 seconds versus 25.7 seconds in the propofol group (P = 0.001). The charge per treatment was 79.5 mC in the thiopental group versus 109.8 mC in the propofol group (P = 0.026). Sixteen patients in the propofol group (52%) reached the highest electrical dose versus 8 patients (26%) in the thiopental group (P = 0.014).	"Propofol significantly decreases seizure duration without significant difference in the clinical outcome. Using the employed treatment algorithm, patients anesthetized with propofol received higher electrical charge. Mini-Mental State Examination scores suggest that this results in more severe cognitive side effects. Results, however, might be confounded by the differences in age distribution in the groups."	Data suggest significant reduction in seizure duration with Propofol vs. Thiopental.
Freeman, CPL 1978 (score=6.0)	Electrocon vulsive Therapy (ECT)	RCT	No mention of sponsorship or COI.	N = 40 patients with major depressive disorder with minimum score of 15 on the HAMD and BDI	Mean age: 50.75 years; 11 males, 19 females	Stimulated ECT – received two treatments where the electrodes were applied to the head but no current passed. Received real ECT in third week. (n=40) vs. Real ECT –	No follow up.	Patients in the real ECT group were significantly less depressed ($p<0.005$ for Hamilton, Wakefield, VAS and Beck scales. Patients in the stimulated ECT group indicate significant improvement in	"The results show that E.C.T. is significantly superior to stimulated E.C.T. in the treatment of depressive illness.	Small sample. Data suggests ECT better than placebo.

						received bilateral ECT twice weekly from an 'Ectron' Mk IV machine. Received sham ECT in third week (n=40).		the VAS and Beck scales ($p<0.1$). Real ECT group was less depressed than the stimulated ECT group ($p<0.05$ Hamilton, Wakefield, and VAS scales).		
Dybedal, GS 2016 (score=5.5)	Electrocon vulsive Therapy (ECT)	RCT	No sponsorship or COI.	N = 65 patients with major depressive disorder diagnosed by the DSM-IV.	Mean age: 74.8 years; 29 males, 36 females.	RUL group – patients received right unilateral formula based ECT (n=34) vs. BF group – patients received bifrontal ECT (n=31).	3 months	There were no significant differences between the BF and RUL groups at any time. The retrograde memory score for public facts declined more for the RUL group ($P < 0.001$) than the BF group ($P=0.005$) from baseline to the first retest and remained stable for both groups from ECT treatment to follow up. .	"Our findings indicate that there were negligible differences in the cognitive effects of formula-based BF or RUL ECT. The overall cognitive effects of ECT were equally favorable for each of the groups."	Data suggest comparable efficacy.
Grunhaus, L 2002 (score=5.5)	Electrocon vulsive Therapy (ECT)/rTM S	RCT	Sponsored by an Established Investigator Award of the National Association for Research in Schizophrenia and Affective Disorders (NARSAD) and	N = 40 patients with major depression disorder diagnosed by the DSM-IV.	Mean age: 59.5 years; 11 males, 19 females.	ECT group – patients received at least 6 sessions of right unilateral or bilateral ECT (n=20) vs. TMS group – repetitive TMS was performed	No follow up.	The overall response rate was 58% (23 out of 40 patients responded to treatment). In the ECT group, 12 responded and eight did not; in the rTMS group, 11 responded and	"This study adds to the growing literature supporting an antidepressant effect for rTMS. This study is particularly relevant because it suggests that rTMS and ECT	Data suggest comparable efficacy but TMS less invasive than ECT.

			by a Stanley Foundation Research Grant to Leon Grunhaus. No mention of COI.			over the left dorsolateral prefrontal cortex at 90% motor threshold. Patients were treated with 20 sessions (five times per week for 4 weeks) of 10-Hz treatments (1200 pulses per treatment-day) at 90% motor threshold. (n=30).		nine did not (X^2 = .10, ns).	reach similar results in nonpsychotic major depressive disorder."	
Sackeim, HA 1993 (score=5.5)	Electrocon vulsive Therapy (ECT)	RCT	Sponsored by grants from the National Institute of Mental Health.	N = 96 patients with major depressive disorder with a pretreatment score of 18 or higher on the 24 item HRSD.	Mean age: 56.5 years; 37 males, 59 females.	Unilateral Therapy – patients received unilateral therapy with either a low dose (just above the seizure threshold) (n=23) or a high dose (2.5 times the threshold) (n=23). Vs. Bilateral Therapy – patients received bilateral ECT with either a low dose	1 year.	The response rate for low-dose unilateral ECT was 17%, as compared to 43% for high dose unilateral therapy (p=0.054), 65% for low-dose bilateral therapy (p=0.001), and 63% for high-dose bilateral therapy (p=0.001). Regardless of electrode placement, high dosage resulted in more rapid improvement (0<0.05).	"Increasing the electrical dosage increases the efficacy of right unilateral electroconvulsive therapy, although not to the level of bilateral therapy. High electrical dosage is associated with a more rapid response, and unilateral treatment is associated with less severe cognitive side effects after treatment."	Data suggest electrical dose increases will increase efficacy of right unilateral ECT but not as much in bilateral ECT. No difference observed in cognition between 2 groups.

						(n=23) or high dose (n=27).				
Pickering 1965 (score=5.0)	Imipramine / Phenelzine/ ECT	RCT	No mention of sponsorship or COI.	N = 269 patients with primary diagnosis of depression, diagnostic criteria not listed	Mean age: 55.3 years; 81 males, 169 females	ECT Group: received 4-8 treatments of electroconvulsive therapy for 3.5 weeks (n=65) vs Imipramine Group: received 50 mg of imipramine for 3.5 weeks (n=63) vs Phenelzine Group: received 15 mg of phenelzine for 3.5 weeks (n=61) vs Placebo: received placebo pill (n=61)	5, 8, 12, 24 weeks, 6 months	Imipramine was superior to both phenelzine and placebo. ECT group and imipramine were similar with 83% of patients and 85% of patients discharged from the hospital. Phenelzine showed 70% of patients discharged compared to 86% of placebo group.	"[I]t appears that that ECT and imipramine increased the frequency of recovery over and above the spontaneous rate shown by patients on the placebo."	Data suggest imipramine and ECT were better than phenelzine and placebo for improving depressive symptoms.
Bailine 2010 (score=5.0)	Electrocon vulsive Therapy	RCT	Sponsored by the National Institutes of Health. No mention of COI.	N = 220 patients diagnosed with bipolar or unipolar acute depression using Structured Clinical Interview for DSM-IV (SCID-1)	Mean age: 53.3 years; 0 males, 140 females	Group 1 was diagnosed unipolar depression (n=170) vs group 2 was diagnosed with bipolar depression (n=50). Within both groups, patients randomly assigned either right unilateral (RUL),	6 months	Group one had a 78.8% response rate compared to 80% for group 2. There was no difference between type of EP done and polarity.	"Both UP and BP depressions remit with ECT. Polarity is not a factor in the response rate. In this sample ECT did not precipitate mania in depressed patients."	Data suggest comparable efficiency but baseline comparability differences for age, age at onset of depression, numbers of episodes. Number of individual within groups randomized to each treatment

						bifrontal (BF) or bitemporal (BT) placement of pads for ECT. ECT was given at 1.5x seizure threshold for BF and BT and 6x seizure threshold for RUL. The treatment was given 3 times per weeks.				never specified. Baseline comparisons made between those with unipolar and bipolar depression.
Navarro 2008 (score=5.0)	Electroconvulsive Therapy	RCT	No mention of sponsorship or COI.	N = 33 remitter patients with severe major depressive disorder with psychotic episodes using the DSM-IV criteria.	Mean age: 70.5 years; 12 males, 21 females.	All patients underwent acute ECT until they did not show improvement or were remitters. Group 1 was given up to 2mg/day risperidone and nortriptyline for 6 weeks (n=17) vs group 2 was given electroconvulsive therapy with nortriptyline for 6-12 weeks.	Monthly up to 2 years or until relapse.	Group 1 relapsed in a shorter amount of time and more often than group 2 (p=0.009). The survival time was 16 months in group 1 vs 23 months in group 2. There was no difference between tolerability between the groups.	"This study supports the judicious use of combined continuation/maintenance ECT and antidepressant treatment in elderly patients with psychotic unipolar depression who are ECT remitters."	Small sample. Data suggest combination therapy of nortriptyline + ECT is best for continuation and maintenance of symptoms of psychotic depression vs nortriptyline alone.
Rosa 2006 (score=5.0)	TMS/Electroconvulsive Therapy	RCT	No mention of sponsorship. No COI.	N = 42 patients with unipolar depressive	Mean age: 43.6±10.5 years; 22	ECT Group: received right unilateral electric	2, 4 weeks	No group effect was observed (p=0.495) or group time	"Both treatments were associated with a degree of	Data suggest comparable efficacy

				disorder (DSM-IV)	males, 20 females	convulsive therapy, then 2 weeks later received bilateral ECT (n=15) vs rTMS Group: received repetitive transcranial magnetic stimulation (20 sessions 5x per week for 4 weeks) (n=20)		interaction (p=0.949). Between group VAS score did not differ (p=0.388) or time interaction (p=0.942). Response rates were 20% for ECT group and 10% for the rTMS group (p=0.631).	improvement in refractory depression and therefore add to the literature that rTMS can be an effective option to ECT as it is a less costly treatment and is not associated with anaesthetic and other ECT risks."	between rTMS and ECT.
Brunoni 2013 (score=4.5)	Sertraline/ tDCS	RCT	No COI. Sponsored by the São Paulo Research Foundation.	N = 120 participants who were antidepressant-free meeting DSM-IV criteria for unipolar, nonpsychotic major depressive disorder	No mention of age or sex distribution	Placebo medication and sham transcranial direct current stimulation (tDCS) (n=30) vs. Placebo medication and active tDCS (n=30) vs. Sertraline medication and sham tDCS (n=30) vs. Sertraline medication and active tDCS (n=30). All treatments given for six weeks. tDCS included 2-mA anodal left/cathodal right prefrontal tDCS (twelve	Follow-up at 2, 4, and 6 weeks	Significant difference in Montgomery-Asberg Depression Rating Scale scores between active tDCS and sertraline versus sertraline group (mean difference = 8.5; p = 0.002), versus tDCS group (5.9, p = 0.03), and versus placebo/sham tDCS (11.5, p < 0.001).	"In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety to tDCS and sertraline did not differ."	Data suggest combination sertraline and ECT is synergistic.

						30-minute sessions). Sertraline hydrochloride dosage was 50 mg/day.				
Errant, 2007 (score=4.5)	Electroconvulsive Therapy/TMS	RCT	Sponsored by National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment, Guy's and St. Thomas's Charitable Foundation and the National Alliance for Research on Schizophrenia and Depression. No COI.	N = 46 patients referred to ECT and diagnosed with major depressive disorder using Structured Clinical Interview for DSM-IV Axis 1 Disorders	Mean age: 65.8 years; 14 males, 32 females.	Group 1 – repetitive transcranial magnetic stimulation (rTMS) (magstim super rapid stimulator) to left of lateral prefrontal cortex at 110% motor threshold, 15 daily sessions with 20 trains in 55 sec intervals of 10 Hz for 5 seconds (n=24) vs Group 2 – ECT twice a week with 0.75-1.0 mg/kg methohexitone, 0.5–1.0 mg/kg suxamethonium. For bilateral frontotemporal ECT given at 1.5 times seizure threshold while right unilateral ECT given at 2.5 times	2-3 days after treatment and at 6 months	Hamilton Depression Rating Scale (HAM-D) scores were lower for group 2 at the end of treatment (p=0.002). No difference in HAM-D scores at 6 months (p=0.93). 13 patients in group 2 had a HAM-D score of 8 or lower vs 4 in group 1 after treatments (p=0.006). No difference between time and group on the Beck scale (p=0.25). No evidence that HAM-D score would change due to psychosis (p=0.06).	"rTMS was not as effective as ECT, and ECT was substantially more effective for the short-term treatment of depression."	Data suggest although ECT was initially better for depressive symptoms, at 6 months there was no difference between TMS and ECT.

						seizure threshold (n=22)				
Folkerts 1997 (score=4.5)	Electrocon vulsive Therapy/Pa roxetine	RCT	No mention of sponsorship or COI.	N = 39 patients who had a major depressive episode using ICD-10 guidelines	Mean age: 49.8 years; 18 males, 21 females.	Group 1 was given 0.5 atropine sulfate, 0.75-1.38 mg/kg methohexital, and 0.7-1.0 mg/kg succinylcholin e via IV with right unilateral ECT 3 times a week (n=21) vs group 2 was given 20 mg paroxetine daily and 40 mg within 7 days. Mean dose was 44 mg daily for 4 weeks (n=18)	4 weeks	There was a 59% decrease in HAMD score for group 1 vs 29% in group 2 ($p<0.001$). Prior treatment had a significant effect on the outcome ($p<0.05$). Group 2 had better results after the open study phase ($p<0.03$).	"The present study found ECT to be superior to paroxetine in medication-resistant major depression, in terms of both degree and speed of response"	Data suggest ECT better than paroxetine for treatment-resistant depression in terms of magnitude or response.
Mohagheghi , 2015 (score=4.5)	Electrocon vulsive Therapy	RCT	Sponsored by Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences. No COI.	N = 60 patients diagnosed with MDD using SCID-4.	Mean age: 34.25 years; 16 males, 44 females.	Group 1 was given a bilateral dose of ECT with 50-100% above seizure threshold. They were given 50 mcg of liothyronine orally every morning during treatment (n=30) vs group 2 was given lactose	2 months	Attention/concentr ations, visual memory and delayed recall all decreased after ECT was done ($p<0.05$). Group 1 had an increase in verbal memory and general memory ($p<0.01$).There is a difference in verbal memory ($p=0.001$), visual memory ($p=0.02$), general memory	"Liothyronine may prevent ECT-induced memory impairment in patients with MDD"	Data suggest liothyronine may prevent ECT- induced memory loss in MDD patients.

						tablets as placebos (n=30).		(p=0.001), and attention/concentration (p=0.05) between group 1 and 2.		
Arfwidsson 1973 (score=4.5)	Electroconvulsive Therapy	RCT	No mention of sponsorship or COI.	N = 57 patients who were referred to ECT with endogenous or mixed endogenous-psychogenic depression using the Cronholm & Ottosson depression Scale.	Mean age: 46.6 years; 26 males, 31 females.	Group 1 was given ECT with 50-150 mg of chlorpromazine daily for an average of 20 days (n=28) vs group 2 was given ECT with an identical placebo for an average of 21 days (n=29).	4-5 days, 1 and 3 months	There was no statistically significant difference between global effect 4-5 days after treatment, single symptoms, average number of treatments, days in hospital, or improvement. However, some comparisons showed that group 1 had a worse effect on the patients.	"There was a tendency to worse outcome with ECT plus chlorpromazine especially in the effect on inhibition. There is no reason to recommend the combination in the treatment of depressive disorders."	Data suggest a trend towards worse outcomes of ECT plus chlorpromazine.
Hansen, 2011 (score=4.5)	Electroconvulsive Therapy/TMS	RCT	Sponsored by Danish Council for Medical Research, Einar Geert-Jorgensen and Ellen Geert-Jorgensen Research Foundation, a Butcher Worzner and wife Inger Worzner grant, Aarhus University Foundation for Research in Mental Diseases, and	N = 60 patients diagnosed with moderate to severe depression using ICD-10 criteria and major depressive disorder using DSM-IV criteria.	Mean age: 49 years; 18 males, 42 females.	Group 1 – rTMS (magstim rapid stimulator) over right dorsolateral prefrontal cortex, received 2 60 sec 1 Hz trains at 110% intensity in a 180 sec intertrain interval for 15 consecutive week days (n=30) vs Group 2 –	4 weeks.	Both groups had HAM-D scores reduced (ACT and rTMS, p<0.001). There was a rate difference between the two methods at week 3 (p=0.035) and remission (p=0.003). The rate of success between the two groups was not significant at 4 weeks (p=0.2)	"Low-frequency rTMS was significantly less effective than ECT, but ECT had more adverse effects on cognitive function. However, the outcome does not point to right frontal low-frequency rTMS in the present stimulus design as a first-line substitute for ECT, but rather	Data suggest TMS less effective than ECT for depression treatment but has less adverse effects.

			the Foundation of Psychiatric Research. No COI.			given 2-6 mg/kg sodium thiopental, 0.5-1 mg/kg suxamethonium chloride, and 4-8 µg/kg Atropine, electrodes placed unilaterally over right hemisphere, intensity determined by age. Treatment given 3 times a week for 3 weeks (n=30).			as a treatment option for patients with depression who are intolerant to other types of treatment or not accepting ECT."	
Abdollahi, 2012 (score=4.5)	Electroconvulsive Therapy	RCT	No mention of sponsorship. O COI.	N = 60 patients diagnosed with major depressive disorder using DSM-IV criteria.	Mean age: 33.1 years; 25 males, 35 females.	Group 1 was given 2.5%, 3 mg/kg of sodium thiopental via IV (n=30) vs group 2 was given 0.2 mg/kg of etomidate via IV (n=30).	Not mentioned.	There was a difference in BDI scores between the groups after the treatment (p=0.004). There was a difference between the mean duration of seizures for the first, third, fourth, fifth, and sixth week (p=0.001, p=0.05, p=0.04, p=0.02, p=0.05 respectively).	"In conclusion, etomidate was associated with better antidepressant outcomes than sodium thiopental when used for induction of anesthesia in ECT."	Data suggest etomidate may be better than thiopental for MDD patients receiving ECT as etomidate was associated with a greater reduction in BDI score post treatment but results were not significant.
Gangadhar 1982 (score=4.0)	Imipramine /ECT	RCT	No mention of COI or sponsorship.	N = 32 patients with depression (ICD-9) and had primary affective disorder and	Mean age: 44.13 years; 14 males, 18 females	Modified bilateral ECT – six ECTs on alternate days for two weeks, then one ECT weekly for two	Follow-up at 3 and 6 months	ECT group had significantly lower Hamilton Scale for Depression (HRDS) score at end of week 2 ($p<0.05$).	"…it can be confidently claimed that from an overall point of view ECT is a superior form of treatment for	Data suggest ECT worked faster and was not associated with organic brain dysfunction at

				endogenous depression		weeks, followed by 'maintenance' ECTs once on the 6th, 8th, and 12th week, received placebo pills (n=16) vs. Imipramine – 25mg capsules, three daily during first week, six daily during 2nd-11th week. Received same ECT as above group (n=16)		However there were not statistical differences between treatment groups at any other time period afterwards (all p>0.05)	endogenous depression than imipramine."	the end of both three and six months.
Keshtkar, 2011 (score= 3.5)	Electroconvulsive Therapy/TMS									Data suggest both interventions improved symptoms of depression as well as improving the suicidal subscale score but the antidepressant effects of ECT were greater than TMS.[77]
Valiengo 2013 (score=3.5)	Sertraline, tDCS									Crossover trial. High dropout rate. Data suggest

[77] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

										sertraline was not a relapse predictor.

Evidence for the Use of Low-Field Magnetic Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Martiny 2010 (score=8.0)	Low Field Magnetic Stimulation	RCT	Sponsored by Lundbeck foundation and Re5 Aps. Dr. Martiny has received honorarium from Re5 and received funding from Re5.	N = 50 patients with a score of 3 or greater on Sackeim criteria, DSM-IV Major depression, 13+ on HAMD-D 17 score, no change in psychotropic drugs in previous 4 months	Mean age: 53.05±12.9 years; 15 males, 35 females.	Active (n = 25) participants had transcranially applied pulsed electromagnetic fields (T-PEMF) once daily for five weeks vs. Sham (n = 25) participants used same machines for T-PEMF but the machines were not creating pulsations	Follow-up each week for 5 weeks	Hamilton Depression Rating Scale ($HAMD_{17}$) scores at week 5: Active – 11.0, Sham – 16.0 ($p < 0.01$). Hamilton Depression Rating Scale ($HAMD_6$) scores at week 5: Active – 6.7, Sham – 9.8 ($p < 0.01$)	"The T-PEMF treatment was superior to sham treatment in patients with treatment-resistant depression. Few side effects were observed."	Relatively small sample. Data suggest T-PEMF significantly better than sham in treatment resistant depression patients.
Rohan 2014 (score=6.5)	Low Field Magnetic Stimulation	RCT	Sponsored by the Stanley Medical Research Institute 07TGS-1045. Authors of this publication have been awarded for LFMS, as well as inventors on the patents for TPEMF.	N = 63 participants who met DSM-IV criteria for either Bipolar Disorder or major Depression and were currently having a depressive episode with HAMD – 17	Mean age: 44.7±12.3 years; 15 males, 38 females.	Low field magnetic stimulation (LFMS) – received one 20 minute session (n = 34) vs. Sham LFMS one 20 minute session (n = 29)	No follow-up	Visual Analog Scale (VAS) scores: LFMS = -1.66, Sham = -0.06 (p=0.006). Hamilton Depression Rating Scale (HDRS-17): LFMS = -8.13, Sham = -5.01 (p=0.009)	"Low field magnetic stimulation may produce rapid changes in mood using a previously unexplored range of electromagnetic fields."	Single treatment study mixed population of bipolar and depression patients. Data suggest LFMS may benefit depressed patients by rapidly elevating mood.

				equal to 17 or greater						
Straasø 2014 (score=5.0)	Low Field Magnetic Stimulation	RCT	Sponsored by the Lundbeck Foundation. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 65 patients with TRD as manifested by a score of .3 on the Sackeim Scale (9), major depression according to DSM-IV, a score of 13 or more on the HAM-D17, and unchanged antidepressant medication during the previous 4 weeks.	Mean age: 48.07 years; 23 males, 42 females	Group 1: Received Transcranial Pulsating Electro Magnetic Fields (T-PEMF) once a day with treatment in the morning and a placebo in the evening for 8 weeks (n=34) vs Group 2: Received T-PEMF twice daily, in the morning and evening, for 8 weeks (n=31)	Follow-up at 8 weeks	Total remission rates (Hamilton Depression [HAM-D17] score <8) was 73.5% in group 1 and 67.7$ in group 2 (p=0.79) after 8 weeks of treatment. The mean HAM-D17 score for group 1 was 20.4 at baseline and 6.8 at 8 weeks, compared with 20.9 at baseline and 7.3 at 8 weeks for group 2 (p=0.92)	"The high remission rate obtained by the T-PEMF augmentation was not a dose effect (one versus two daily T-PEMF sessions) but was explained by the extension of the treatment period from 5 to 8 weeks."	Baseline comparability data missing. Compliance difficult to assess. Data suggest twice-daily T-PEMF not superior to single daily dose.

Evidence for the Use of Botulinum Toxin Injections

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Wollmer 2012 (score=7.0)	Botulinum toxin	Pilot study	Sponsored by the Gottfried & Julia Bangerter-Rhyner-Stiftung, Bern, Switzerland, a private	N = 30 subjects with MDD (SCID I; >15 points on the HDRS) with or without a history of	Mean age: 50.6 years; 7 males, 23 females.	Verum group: verum condition botulinum toxin A dissolved in solution of 0.9% NaCl	Follow up at 16 weeks	Verum group has a significant improvement in depression gradually than placebo, measured by the HAM-D17, score (ANOVA, n	"This study shows that a single treatment of the glabellar region with botulinum toxin may shortly accomplish a	Small sample of 30. Data suggest a single injection of botulinum toxin may alleviate some depression

			foundation that supports medical research. COI: one or more authors received honoraria for talks, compensation, and research grants.	dysthymic disorder (DSM-IV 300.4)		(100U/2.5 ml). Insulin syringes (30G) needles injected at five points in glabellar region. Males received two more units at each injection site (n=15) vs placebo group: Injected identical volumes in identical places with 0.9% NaCl. (n=15). All participants had 7 sessions (at baseline, 2, 4, 6, 8, 12, and 16 weeks)		¼ 30; F(6,168) ¼ 5.76, 3 ¼ 0.74, h2 ¼ 0.17, p < 0.001, two-sided), the Beck Depression Inventory, BDI, score (ANOVA, n ¼ 30; F(6,168) ¼ 3.79, 3 ¼ 0.51, h2 ¼ 0.12, p ¼ 0.01, two-sided) and the Clinical Global Impressions Scale, CGI, (ANOVA, n ¼ 30; F(6,168) ¼ 7.91, 3 ¼ 0.66, h2 ¼ 0.22, p < 0.001, two-sided).	strong and sustained alleviation of depression in patients, who did not improve sufficiently on previous medication."	symptoms compared to placebo
Wollmer 2014 (score=N/A)	Botulinum toxin	Secondary analysis	Sponsored by Gottfried and Julia Bangerter-Rhyner-Stiftung, Bern, Switzerland and the Brain and Behavior Research Foundation, New York, NY, USA. COI: one of more authors received honoraria for talks, research grants, compensation,	N = 30 subjects with MDD (SCID I; >15 points on the HDRS) with or without a history of dysthymic disorder (DSM-IV 300.4)	Mean age: 50 years; 0 males, 30 females.	Verum group: verum condition onabotulinumtoxin A dissolved in solution of 0.9% NaCl (100U/2.5 ml). Insulin syringes (30G) needles injected at five points in glabellar region. Males received two more units at	Follow up at 6 weeks	Subjects who received the verum and were responders had a significantly greater baseline score in the agitation item of the HAM-D scale than those who did not fulfill the criteria [n =6; 1.56 vs. 0.33, $t_{(13)}$ =3.04, d= 1.7, p =0.01]. The specificity was 56% (0.56, 95% CI=0.21–0.86) and	"These data provide a link between response to botulinum toxin treatment with a psychomotor manifestation of depression and thereby indirect support of the proposed facial feedback mechanism of action. Moreover, it suggests that patients with agitated	Data suggest facial feedback mechanisms may be linked to depression and agitation may be predictive of a positive response to botulinum toxin.

			and is a member on the advisory boards.			each injection site (n=15) vs placebo group: Injected identical volumes in identical places with 0.9% NaCl. (n=15). All participants had 7 sessions (at baseline, 2, 4, 6, 8, 12, and 16 weeks)		the sensitivity was 100% (1.0, 95% CI=0.54–1.0)	depression may particularly benefit from botulinum toxin treatment."	
Finzi 2013 (score=7.0)	Botulinum toxin	RCT	Sponsored by the Chevy Chase Cosmetic Center. COI: Finzi, E owns the Chevy Chase Cosmetic Center and has been awarded a patent for the treatment of depression with botulinum toxin.	N = 85 subjects with DSM-IV major depression with MADRS score of greater than or equal to 26 at screening, and a Clinical Global Impression e Severity score greater than or equal to 4 at screening.	Mean age: 48.4 years. 16 males, 69 females.	OBA group: 100 unit vial of OBA (Botox Cosmetic, Allergan) combined with 1.0 ml of 0.9% NaCl. (n=41) vs placebo group: 0.9% NaCl. (n=44) Insulin syringes (30G) needles used for injections. Males given more units due to their muscle mass.	Follow up at 3 and 6 weeks after injection.	At 6 weeks, response rates were 52% in the OBA group and 15% in placebo (Chi-Square (1) ¼ 11.2, p < 0.001, Fisher p < 0.001). At 6 weeks, remission rate (according to MADRS score) was also higher in the OBA group (27%) than placebo (7%).	"In conclusion, a single treatment with OBA to the corrugator and procerus muscles appears to induce a significant and sustained antidepressant effect in patients with major depression."	Dissimilar study drug given to males versus females. Baseline differences in depression duration (19.5 months vs 34.6 months) suggest randomization failure.
Magid 2014 (score=6.5)	Botulinum toxin	Crossove r design	Sponsored by a grant from the Brain & Behavior Research Foundation. COI: one of the	N = 30 subjects with a history of MDD (296.3x or 296.2x) for at least 6	Mean age: 49.5 years; 2 males, 28 females.	BTA first group: a concentration of 40 units (U)/1 mL dissolved in 0.9% NaCl	Follow up at 3, 6, 12, 15, 18, and 24 weeks.	On the HDRS scale, response rate for BTA-first was 55%, 25% in BTA-second and 0% in placebo at week 6 (p<.0001).	"Botulinum toxin A injection in the glabellar region was associated with significant improvement in depressive	Small sample. Data suggest botulinum toxin injected into the glabellar area was associated

			authors received a research grant that later became salary support.	months diagnosed by DSM-IV.		saline solution (n=11) vs placebo group: 0.9% NaCl saline solution (n=19) vs BTA second group: At week 12, placebo group received BTA (n=17). Insulin syringes (30G) needles used for injections		On the HDRS scale, remission rate for BTA-first was 18%, 18% in BTA-second and 0% in placebo at week 6 (p=0.057).There was a reduction in HDRS-21 scores in BTA-first (-46%), BTA-second (-35%), and placebo (-2%) (p<.001). Scores were similar on the BDI, PHQ-9, and CSS-GFL scales.	symptoms and may be a safe and sustainable intervention in the treatment of MDD."	with significant depressive symptom improvement.

Evidence for the Use of B Vitamins

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Hvas 2001 (score=8.5)	B Vitamins	RCT	Sponsored by the Danish Medical Research Council, the Health Found of "danmark's" Sygeforsiking, EU Biomed, The Institute of Experimental Clinical Research, Aarhus University,	N = 140 participants with mild to moderate increased plasma methylmalonic acid (P-MMA) (0.4-2.0 μmol/L)	No mention of mean age, median age for Vitamin B_{12} group: 75 years, median age for placebo group: 74 years; 42 males, 98 females	Intramuscular injections of 1 mg of cyanocobalamin (Betolvex), 1 injection per week for 4 weeks (n=70) vs. Intramuscular injections of 1 mL of isotonic sodium chloride (placebo), 1 injection per	Follow-up at 3 months	Decreased P-MMA and plasma total homocysteine in treatment group ($p < 0.001$, $p < 0.001$). No significant difference found in blood hemoglobin change ($p = 0.18$) or mean cell volume ($p = 0.71$). Symptoms of anemia ($p = 0.63$), neurologic	"Treatment with vitamin B_{12} reduces PMMA and plasma total homocysteine, but individuals with a mild to modest increase in P-MMA may have only limited clinical benefit from vitamin B_{12} treatment, at least in the short term."	Data suggest small benefit (if any) from vitamin B_{12} treatment on reducing plasma methylmalonic acid (P-MMA).

			the E. Danielsen and Wife Foundation, The Novo Nordisk Foundation, the Hans and Nora Buchard Foundation, the Mogens Svarre Mogensen Foundation, the Velux Foundation, and The Family Hede Nielsen Foundation. All authors worked for the Aarhus University Hospital.			week for 4 weeks (n=70)		symptoms (p = 0.21), gastroenterological symptoms (p = 0.32), or neurological disability score (p = 0.85) did not change between groups.		
Hvas 2004 (score= 8.5)	B Vitamins	Secondary Analysis of Hvas 2001	Sponsored by the Danish Medical Research Council, the Health Found of "danmark's" Sygeforsiking, EU Biomed, The Institute of Experimental Clinical Research, Aarhus University, the E. Danielsen and Wife Foundation, The Novo	N = 140 participants with mild to moderate increased plasma methylmalonic acid (P-MMA) (0.4-2.0 μmol/L) The MDI, a self-rating tool was used to measure depression based on DSM-IV and ICD-10.	No mention of mean age, median age for Vitamin B_{12} group: 75 years, median age for placebo group: 74 years; 42 males, 98 females	Intramuscular injections of 1 mg of cyanocobalamin (Betolvex), 1 injection per week for 4 weeks (n=70) vs. Intramuscular injections of 1 mL of isotonic sodium chloride (placebo), 1 injection per week for 4 weeks (n=70)	Follow-up at 3 months	78 individuals at baseline had cognitive impairment via Cambridge Cognitive Examination (CAMCOG), 40 based on Mini-Mental State Examination (MMSE), and 18 had symptoms of depression. Treatment did not improve cognitive function between groups via CAMCOG score (p = 0.43).	"A high proportion of individuals with an increased plasma methylmalonic acid had impaired cognitive function, and a rather high prevalence of depression was observed. However, vitamin B-12 treatment did not improve cognitive function or	Data suggest lack of efficacy for either cognitive function or depressive symptoms.

			Nordisk Foundation, the Hans and Nora Buchard Foundation, the Mogens Svarre Mogensen Foundation, the Velux Foundation, and The Family Hede Nielsen Foundation. All authors except Nexø worked for the Aarhus University Hospital.					Depression scores did not differ between groups either (p = 0.18)	symptoms of depression within the 3-months study period."	
Almeida 2014 (score=7.0)	B Vitamins	RCT	No COI. Sponsored by the National Health and Medical Council of Australia.	N = 153 participants with a major depressive episode in the context of a major depressive disorder (single episode or recurrent) per DSM-IV-TR.	No mention of mean age, all participants were aged ≥50 with a majority of participants being between 50 and 69 years; 67 males, 86 females	Citalopram plus 0.5mg of vitamin B12, 2mg of folic acid and 25mg of vitamin B6 (n=77) vs. Citalopram plus placebo (n=76). Citalopram daily dosages were 10 mg, and then 2 weeks later increased to 20 mg and could be maximized to 40 mg between 4 and 8 weeks. Vitamins and placebos were	Follow-up at 12, 26, and 52 weeks	At 12 weeks remission of depressive episode symptoms reached by 78.1% of those treated by placebo and 79.4% of those treated with vitamins (p = 0.84). At 26 weeks remission reached by 76.5% and 85.3%. At 52 weeks remission reached by 75.8% and 85.5% (effect of intervention over 52 weeks, odds ratio OR = 2.49).	"B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Replication of these findings would mandate that treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to manage major depression in middle-aged and older adults."	Data suggest 12 weeks of added B-vitamins did not enhance antidepressant response but maintained antidepressant response over one-year.

						in capsules and were taken daily.				
Ghaleiha 2016 (score=6.5)	B Vitamins	RCT	No COI or sponsorship.	N = 51 inpatients with major depressive disorder diagnosed via the Diagnostic and Statistical Manual of Mental Disorders 5 using Hamilton Depression Rating Scale (HDRS).	Mean age: 35.2 years; 24 males, 27 females	Thiamine (300 mg per day) (n = 25) vs. Placebo (300 mg per day) (n=24). After washout phase participants treated with fluoxetine (20 mg per day) for at least 12 consecutive weeks	Follow-up at 3, 6, and 12 weeks	Hamilton Depression Rating Scale (HDRS) scores for Thiamine and placebo groups, respectively: at baseline – 31.40, 32.77 (mean difference p = 0.25, d = 0.33), at 3 weeks – 21.52, 22.12 (p = 0.68, d = 0.12), at 6 weeks – 13.96, 18.50 (p = 0.0001, d = 1.29), at 12 weeks – 10.52, 12.64 (p = 0.04, d = 0.59)	"Among a sample of inpatients with MDD treated with a standard SSRI, compared to placebo, adjuvant thiamine produces improvements in symptoms of depression 6 weeks after medication intake. Adjuvant thiamine may have the potential to increase treatment adherence."	Data suggest at 6 weeks thiamine improved symptoms of depression.
Coppen 2000 (score=6.0)	B Vitamins	RCT	Sponsored by Scotia Pharmaceuticals . No mention of COI.	N = 127 with a new episode of depression and diagnosed with MDD via DSM-III-R	Mean age: 43.13 years; 45 males, 82 females	500 µm of folic acid daily (n=62) vs. 500 µm of placebo daily (n=65). All participants were also prescribed 20 mg of fluoxetine	Follow-up at 2, 4, 6, and 10 weeks	Patients receiving fluoxetine and folic acid had significantly better response to 10 weeks compared to placebo (Hamilton rating scale scores: 8.1 vs. 10.7, $p < 0.05$). Difference in scores greater in women (6.8 vs. 11.4, $p < 0.005$) at 10 weeks compared to men (10.9 vs. 9.7, $p > 0.05$)	"Folic acid is a simple method of greatly improving the antidepressant action of fluoxetine and probably other antidepressants. Folic acid should be given in doses sufficient to decrease plasma homocysteine. Men require a higher dose of folic acid to achieve this than	Data suggest folic acid augments the antidepressant effects of fluoxetine.

									women, but more work is required to ascertain the optimum dose of folic acid."	

Evidence for the Use of Acupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Ling, 2016 (score=7.0)	Acupuncture	RCT	Sponsored by the Youth Fund Project of Natural Science Foundation of China, the China Postdoctoral Science Foundation, and the Outstanding Young Innovation Foundation of Guangdong Provincial Department of Education. No mention of COI.	N = 143 patients with mild to moderate depression per Western diagnostic criteria of depression (20 points < HAMD 24-item version score < 35 points)	Mean age: 40.6 years; 61 males, 82 females.	Group 1: acupuncture dredging the liver and regulating the flow of theosophy, needle inserted at 4-5 mm depth, sessions lasted 30 minutes each, treatment given at least three times per week (with > 48 hours between sessions) for 12 weeks (n = 53) vs. Group 2: same as group 1 except needle inserted at 2-3 mm (n = 56) vs. Group 3: same as group 2 except needles were not	Follow-up at 1 and 3 months.	Comparing all three groups with the SF-36 scale, each time point increased in all 3 ($p<0.05$). Group 1 had more differences than group 2 and 3 ($p<0.0125$); group 2 and 3 had no significant differences ($p<0.0125$).	"Acupuncture can effectively improve the quality of life of patients with depression."	Data suggest non-significant improvement in quality of life from acupuncture.

						inserted in as many specific acupressure points (n = 54).				
Qu, 2013 (score=6.0)	Acupuncture	RCT	Sponsored by Key Project of the National Eleventh-Five Year Research Program of China, Key Project of Phase III of Guangdong and General Research Fund of Research Grant Council of HKSAR. No COI.	N = 160 patients with a diagnosis of MDD via the International Classification of Diseases (10th version) (ICD-10)	Mean age: 33.3 years; 75 males, 85 females.	Group 1: Paroxetine (PRX) alone – those not medicated had initial dose of 10 mg/day, escalated to 20 mg/day in one week, PRX taken for 6 weeks (n = 48) vs. Group 2: Manual manipulation acupuncture treatment (MA), 3 30-minute sessions per week for 6 weeks, along with PRX (n = 54) vs. Group 3: Manual manipulations with electrical stimulation (EA), 3 30-minutes sessions per week for 6 weeks, along with PRX (n = 58)	Follow-up at 1 month.	Group comparisons through HAMD-17 revealed significant differences between the 3 (PRX— r^2= 0.725; MA + PRX -- r2= 0.655; EA + PRX -- r^2 = 0.784). MA and EA treatments produced significantly higher reductions in scores compared to PRX alone (p=0.000), although no noteworthy differences were demonstrated through the two acupuncture groups. Higher response rates were seen through the MA and EA groups compared to PRX (69.8% and 69.6% vs 41.7%, p= 0.004).	"[A]s most antidepressant agents have broad side effects, acupuncture in manual and electrical stimulation modes provides a safe and effective treatment in augmenting the antidepressant efficacy and reducing the incidence of exacerbation of depression in the early phase of SSRI treatment."	Contact bias with acupuncture group. Data suggest electrical acupuncture better than manual acupuncture for sustained benefits and may be synergistic with antidepressant effects like those from Paroxetine.

Allen, 2006 (score=5.5)	Acupuncture	RCT	Sponsored by grants from the National Institutes of Health. No mention of COI.	N = 151 patients diagnosed with major depressive disorder via the DSM-IV MDD criteria	Mean age: 23.2 years; 55 males, 96 females	Group 1: Specific (SPEC) acupuncture treatment tailored to the individuals symptoms, based on Traditional Chinese Medicine (n = 49) vs. Group 2: Non-Specific (NONSPEC) acupuncture treatment that used legitimate acupuncture points but were not tailored to the individual (n = 50) vs. Group 3: Waitlist (WAIT) no treatment (n = 52)	No follow-up.	Symptom severity was assessed by the HAM-D17 or BDI throughout this study. HAM-D17 scales showed a significant drop in depression severity through all three groups ($z = -11.2$, $p<.001$). SPEC and NONSPEC had the greatest decreases at ($z = 3.5$, $p<.001$) and ($z = 4.3$, $p<.001$) when compared to the WAIT group. BDI scales showed a significant drop in depression severity across all individuals ($z = -13.6$, $p<.001$). When comparing groups, SPEC and NONSPEC both demonstrated declines in depression severity when compared to the waitlist group at ($z = 6.1$, $p<.001$) and ($z = 6.6$, $p<.001$), but they did not differ when compared to each other ($z = 1.3$, $p>.17$).	"Collectively, as most antidepressant agents have broad side effects, acupuncture in manual and electrical stimulation modes provides a safe and effective treatment in augmenting the antidepressant efficacy and reducing the incidence of exacerbation of depression in the early phase of SSRI treatment."	Waitlist control bias. Both specific and non-specific group improved compared to waitlist group.

Allen, 2000 (score=3.5)										Data suggest acupuncture may benefit depressed individuals.[78]

[78] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Aromatherapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Vitinius 2014 (Score=4.5)	Aromatherapy	RCT	Sponsored by German federal ministry if research and education grant (01KN1106). No mention of COI.	N = 27 female patients with diagnoses of mild to severe depression per BDI and BDI II.	Mean age: 31.8±7.1 years; 0 male, 27 females.	Verum group: patients received a 50 ml bulb verum intervention with a 0.2 ml phenylethyl alcohol cotton wool connected to nasal and silicon tubes for 3 nights (n=13) vs Placebo group: patients received no odorant intervention for 3 nights (n=14).	No mention of specific follow-up time length.	The primary outcome of this study was mood. The good mood or bad mood in the two groups (verum group=22.81±23.12 vs. placebo group=23.12±6.45) indicated no significant differences (95%CI=-2.23 to 1.62; p=0.747). During the 1st and 2nd period, ANCOVA (1.48; 95%CI=-3.09 to 6.05) and Hills-Armitage approach (-0.38; 95%CI=-2.18 TO 1.43) for good or bad mood outcome indicated no significant differences between the groups (p=0.508; p=0.67 respectively).	"Interval-triggered, nocturnal and subconscious application of rose odorant may be a psychotherapy enhancer in depressed inpatients. One of the important advantages of the here demonstrated, novel approach is the lack of side effects as well as avoiding olfactory adaptation, and the good tolerance of the odorant dispensing device by patients."	Crossover trial. Data suggest lack of efficacy for mood change but a trend towards improved sleep quality in rose group short intervention and short follow-up time.
Lemon 2004 (Score=2.0)										No blinding. Test group reported improvement in depression and anxiety significant dropouts in test

										group before end of intervention.[79]

Evidence for the Use of Light Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lam 2006 (score=9.0)	Light Therapy	RCT	One or more of the authors is a consultant or on the Speaker/Advisory Boards or has received research funds from: AstraZeneca, Canadian Institutes of Health Research, Eli Lilly, GlaxoSmithKline, Janssen, Lundbock, Merck, Roche, Servier, Vancouver Hospital Foundation, and Wyeth.	N = 96 patients with a DSM–IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.	Mean age: 43.5 years; 32 males, 64 females.	Light group: Exposure to white fluorescent light box (Model Daylight 10000, ultraviolet filter, rated at 10,000 lux at distance of 14 in from screen to cornea),with 20mg placebo pill 30 minutes after waking up (n=48) vs Fluoxetine group: Identical light box fitted with a neutral density gel filter to reduce light exposure to 100 lux, with 20mg of fluoxetine 30 minutes after waking up (n=48)	Follow up at weeks 1, 2, 4, and 8 or at unexpected termination.	No significant differences between light and fluoxetine group for clinical response rate ($\chi 2=0$, df=1, p=1.00) and CGI improvement since last visit (mean=1.90 [SD=1.15] versus 1.92 [SD=1.09], respectively) (t=0.09, df=94, p=0.93). Light group had greater improvement at only week 1. Fluoxetine group had greater treatment emergent adverse events.	"Light treatment showed earlier response onset and lower rate of some adverse events relative to fluoxetine, but there were no other significant differences in outcome between light therapy and antidepressant medication."	Data suggest light treatment resulted in an earlier response rate compared to fluoxetine but otherwise comparable efficacy
Michalak 2007 (score=N/A)	Light Therapy	CAN-SAD study/ seconda	Sponsored by the Canadian Institutes of Health Research. No COI.	N = 96 patients with a DSM–IV	Mean age: 66.7 years; 32	Light group: 10,000 lux light treatment (Uplift Technologies Inc., Model Daylight)	Follow up at 1, 2, 3, 4, 5, 6, 7, and 8 weeks	Q-LES-Q measures in the light group had average improvements (20.56; SD=13.11)	"Patients with SAD report markedly impaired QoL	Data suggest quality of life markedly improved with light therapy suggesting

[79] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

		ry analyses		criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton Depression Rating Scale.	males, 64 females	and a placebo (n=48) vs Fluoxetine group: 100 lux light and 20mg of fluoxetine. (n=48) Light treatment was done asap after waking up between 07:00 and 08:00 hours. Medication treatment was taken daily after light treatment. Treatments lasted for 8 weeks.		compared with fluoxetine group (21.77; SD=17.04) [F(1,79=0.13, N.S.]. SF-20 scores in the light group was 7.82 (SD=15.49) vs 9.38 (SD=14.39) in the fluoxetine group [F(1,79=0.22, N.S.]	during the winter months. Treatment with light therapy or antidepressant medication is associated with equivalent marked improvement in perceived QoL. Studies of treatment interventions for SAD should routinely include broader indices of patient outcome, such as the assessment of psychosocial functioning or life quality."	it has similar benefits as antidepressant therapy.
Enns 2006 (score=N/A)	Light Therapy	CAN-SAD post hoc analyses	Sponsored by the Canadian Institutes of Health Research. No mention of COI.	N = 95 patients with a DSM–IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥23 on the 24-item Hamilton	Mean age: 43.8 years; 32 males, 63 females	Light group: Received light therapy (10,000 lux) for 30 min in the morning and a placebo pill daily for 8 weeks. (n=48) vs Fluoxetine group: Received fluoxetine (20mg) and morning dim light exposure (200 lux) daily for 8 weeks. (n=48)	Follow up at 8 weeks and during summer (July or August)	Mean BDI-II score of SAD was 23.8 while non-SAD was 23.7. Sad group had lower neuroticism scores but higher openness scores than non-SAD group.	"The personality profile of SAD patients differs from both non-seasonal depressed patients and norms. Elevated openness scores appear to be a unique feature of patients with SAD. Since mood state has a significant impact on personality scores, assessment of personality in	Data suggest personality profile of SAD patients different from non-seasonal depressed patients as SAD patients tend to be more open

				Depression Rating Scale.					SAD patients should ideally be conducted when they are in remission."	
Lam 2016 (score=8.0)	Light Therapy	RCT	Sponsored by grant MCT-94832 from the Canadian Institutes of Health Research. One or more of the authors have received research funds, grants, honoraria, or have served on the advisory boards.	N = 122 adults with MDD (DSM-IV-TR) of at least moderate severity in outpatient psychiatry clinics in academic medical centers, MDD diagnosis confirmed with Mini International Neuropsychiatric Interview (MINI), also had Hamilton Depression Rating Scale	Mean age: 36.8 years; 46 males, 76 females.	10,000-lux fluorescent white light box for 30 min/d in morning plus 20mg placebo (n=32) vs Inactive negative ion generator for 30 min/d plus fluoxetine hydrochloride, 20mg/d) (n=31) vs Receiving light therapy and fluoxetine (n=29) vs Sham light therapy and placebo. (n=30). All patients took the pill every morning	Follow up at weeks 0, 1, 2, 4, 6, and 8 or at unexpected termination	Mean (SD) changes in MADRS score for the light was 13.4 (7.5), fluoxetine was 8.8 (9.9), combination was 16.9 (9.2), and placebo was 6.5 (9.6). Combination therapy was better than placebo in MADRS response (β = 1.70; *df* = 1; *P* = .005)	"Bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with non-seasonal MDD. The combination treatment had the most consistent effects."	Data suggest all treatment groups improved but that combination bright light and fluoxetine therapy was most efficacious

				score of 20 or above						
Martiny 2004 (score=7.5)	Light Therapy	RCT	No mention of sponsorship or COI	N = 102 out-patients with a diagnosis (DSM-IV) of non-seasonal major depression and A score of more than 13 on the 17-item Hamilton Depression Scale	Mean age: 44.6 years; 32 males, 70 females	White light, 10,000 lux, given 60 min daily over a period of 5 weeks (n=53) vs Dim red light, 50 lux, 30 min daily over a period of 5 weeks (n=54). Biolamp from SMIFA used for both groups. All participants also received 50mg of sertraline	Follow up at week 1,2,3,4, and 5	The bright light group compared with the dim red light group had a bigger reduction on the HAM-D17, HAM-D6, MES, and SIG-SAD score.	"The study results support the use of bright light as an adjunct treatment to antidepressants in non-seasonal depression."	Data suggest white light as adjunctive therapy to antidepressants for non-seasonal MD.
Martiny 2005 (score=N/A)	Light Therapy	Secondary Analyses Data of Lunde 2004	Sponsored by The Danish Medical Research Council, Eastern Region Research Foundation, Merchant L.F. Foght's Foundation, Johannes M. Klein and Wife's Memorial Foundation, The Tvergaard Foundation, The Danish Psychiatric Association, The Olga Bryde Nielsen	N = 102 subjects with major depression according to DSM-IV scale.	Mean age: 44.6 years; 22 males, 70 females	Bright light group: bright light (10,000 lux) for 1 hr daily (n=48) vs Dim light group: red dim light (50 lux) for 30 min daily (n=54). All subjects received 50 mg of sertraline daily and treatment for five weeks.	Follow up period of 4 weeks after treatment	Depression scores on all four depression scales (HAM-D17, HAM-D6, MES and SIGH-SAD) decreased more in the bright light group than the dim light group (P=0.001).	"The study results support the use of bright light as an adjunct treatment to antidepressants in non-seasonal depression."	Data supports use of white light as adjunctive therapy for non-seasonal MD.

			Foundation, The A.P. Møller and Chastine Mc-Kinney Møller Foundation, The Region 3 foundation and The Frederiksborg General Hospital Research Grant. No COI.							
Martiny 2005 (score=N/A)	Light Therapy	Secondary Analyses Data of Lunde 2004	Sponsored by The Danish Medical Research Council, Eastern Region Research Foundation; Merchant L.F. Foght's Foundation; Johannes M. Klein and Wife's Memorial Foundation; The Tvergaard Foundation; The Danish Psychiatric Association; The Olga Bryde Nielsen Foundation; The A.P. Møller and Chastine Mc-Kinney Møller Foundation; The Region 3 Foundation; Frederiksborg General Hospital (Research Grant). No COI.	N = 102 subjects with major depression according to DSM-IV scale.	Mean age: 44.6 years; 22 males, 70 females	Bright light group: bright light (10,000 lux) for 1 hr daily (n=48) vs Dim light group: red dim light (50 lux) for 30 min daily (n=54). All subjects received 50 mg of sertraline daily and treatment for five weeks.	No mention of follow up	MDI scores decreased more in the bright light group than the dim light group (P=0.55). PGWB scores increased at baseline and endpoint more than the dim light group (P=0.23). Endpoint score at the last visit in bright light group was 71.8, which is lower than the national norm score of 84.6 (P greater than or less than 0.05)	"The results advocate the use of bright light as an adjunct treatment of non-seasonal depression."	Data suggest bright white light may be adjunctive therapy for non-seasonal MD.

Martiny 2012 (score=7.5)	Light Therapy	RCT	One or more of the authors have received funding, served as a speaker, or have been on the advisory boards. Sponsored by Eli Lilly and Danish Agency for Science.	N = 75 adult patients with DSM-IV major depressive disorder	Mean age: 47.7 years; 31 males, 44 females	Wake therapy: Monday, Wednesday, and Friday, patients stayed awake through entire night, awake until 8pm the next day. Tuesday, Thursday, and Saturday nights, patients slept at 8pm and awoke at 8am. Light therapy done (Smifa Bio Lamp – color temperature of 5,500 k, 10,000 lux) with white light at 40 cm from screen for 30 minutes at 4am. (n=37) vs Tailored daily 30 minute minimum exercise with physiotherapist (n=38). All patients received 60mg of duloxetine	Follow up weekly.	Patients in the wake therapy group had better responses and remission than the exercise group.	"Patients treated with wake therapy in combination with bright light therapy and sleep time stabilization had an augmented and sustained antidepressant response and remission compared to patients treated with exercise, who also had a clinically relevant antidepressant response."	Data suggest 9 weeks of chronotherapeutic intervention resulted in a better sustained response for decreasing depressive symptoms compared to exercise.
Ruhrmann 1998 (score=7.5)	Light Therapy	RCT	Sponsored by a grant from Eli Lilly, Germany. No mention of COI.	N = 42 patients with a total score of at least 16 on the 21-items Hamilton Depression Rating Scale (HDRS) at entry and after the	Mean age: 41.1 years; 9 males, 33 females.	Fluoxetine group: Placebo during the 1st week then 5 weeks placebo light condition and 20mg of fluoxetine per day (n=20) vs Bright light group: placebo during the 1st week then 5 weeks of bright light (2 hr a day, 3,000 lux and a placebo pill)	Follow up weekly	Remission rate in bright light (50%) was better than fluoxetine (25%), P=0.10. HDRS scores improved faster in Light therapy than fluoxetine. However, atypical symptoms in fluoxetine had a quicker effect.	"Both treatments produced a good antidepressant effect and were well tolerated. An apparently better response to bright light requires confirmation in a larger sample."	Data suggest comparable efficacy between fluoxetine and bright light for the treatment of SAD

				placebo phase (1st week)						
Lieverse 2011 (score=7.0)	Light therapy	RCT	Sponsored by the Successful Aging Program of the Dutch Scientific Organization and the Chronicity Care Program of the Dutch Scientific Organization. No mention of COI.	N = 89 patients with major depressive disorder with a score of 5 or more on the Geriatric Depression Scale.	Mean age: 69.34 years; 31 males, 58 females	Bright light treatment: at home with a single layer of pale blue filter wrapped around florescent tubes, approximately 7500 lux for 60 minutes in the morning for three weeks daily. (n=42) vs Light treatment: at home with a single-layer of red filter wrapped around florescent tubes, approximately 50 lux for 60 minutes in the morning for three weeks daily. (n=47)	Follow-up at 3-weeks post treatment.	Scores improved on the HAM-D with the bright light therapy (BLT) more than placebo from T0 to T1 (7%; 95% CI, 4%-23%; *P*=.03) and (21%; 7%-31%; *P*=.001) from T0 to T2. When compared to T0, urinary free cortisol level was 37% lower (P=.003) compared to the placebo group. Evening salivary cortisol level decreased by 34% in the BLT group compared to a 7% increase (P=.02) in the placebo group. When compared to T0, by T1, sleep efficiency increased by 2% (P<.001) and rise in melatonin increased by 81% (P=.03) in the BLT group when compared to the placebo group. Get-up time was increased by 7% (P<.001) by T1 and 3% (P=.001) by T2 in the BLT group.	"In elderly patients with MDD, BLT improved mood, enhanced sleep efficiency, and increased the upslope melatonin level gradient. In addition, BLT produced continuing improvement in mood and an attenuation of cortisol Hyper excretion after discontinuation of treatment."	Data suggest BLT improved sleep efficiency, mood and melatonin level gradient in elderly MDD patients.
Rohan 2015 (score=6.5)	Light therapy/CBT	RCT	Sponsored by the National Institute	N = 177 volunteers with	Mean age: 45.6 years; 29	Light Therapy: 10,000 lux of cool-white fluorescent	Follow-up at 2 years.	Depression scores significantly improved with light therapy and	"In conclusion, these findings suggest that CBT-	Data suggest comparable efficiency.

			of Mental Health. No COI.	major recurrent depression with a seasonal pattern, passing the SIGH-SAD and DSM-IV-TR criteria for a Seasonal Affective Disorder (SAD) episode through the duration of the study.	males, 148 females.	light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive restructuring to improve coping with the change in weather, which in turn, alleviates depression. (n=88)		CBT-SAD when measured with SIGH-SAD and BDI-II. The SIGH-SAD score at each time-point differed from others ($p<0.01$), the difference between scores at weeks 4/5 fell low ($p=0.07$). Similar patterns were observed through the HAM-D ($F=119.80$, $df=6, 920$, $p<0.001$).	SAD and light therapy are comparably effective treatment modalities for targeting acute SAD. Accordingly, CBT-SAD should be disseminated into practice and considered as a viable alternative to light therapy in treatment decision making."	
Rohan 2016 (score= N/A)	Light therapy/CBT	2-year follow up of Rohan 2015	Supported by the National Institute of Mental Health. No COI.	N = 177 adults with major depression that were a part of a randomized trial of 6-weeks of CBT-SAD or light therapy.	Mean age: 45.6 years; 29 males, 148 females.	Light Therapy: 10,000 lux of cool-white fluorescent light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive	No follow up.	There was no difference in outcomes during the first year of follow-up. During the second winter of follow-up, CBT-SAD was associated with less SIGH-SAD recurrences ($p<0.013$) and remissions than light therapy recurrences ($p<0.032$). BDI-II remission rates were significantly lower in the CBT-SAD group ($p<0.022$) than the light therapy group ($p<0.082$).	"In conclusion, our prior report found that CBT-SAD and light therapy are comparably effective treatment modalities for acute SAD (8), but these follow-up data show better outcomes for CBT-SAD than light therapy two winters later. Accordingly, CBT-SAD should	During year one there were comparable findings but data suggest CBT superior to light therapy for treatment of SAD as CBT-SAD was associated with less severe symptoms and sustained fewer remissions.

						restructuring to improve coping with the change in weather, which in turn, alleviates depression. (n=88)			be considered as an efficacious SAD treatment and disseminated into practice, particularly if the focus is on recurrence prevention."	
Meyerhoff 2016 (score= N/A)	Light therapy for depression/ CBT	Secondary Analysis of Rohan 2015	Supported by the National Institute of Mental Health. No mention of COI.	N = 177 adults with major depression that were a part of a randomized trial of 6-weeks of CBT-SAD or light therapy.	Mean age: 45.6 years; 29 males, 148 females.	Light Therapy: 10,000 lux of cool-white fluorescent light through an ultraviolet filter with a 30-minute starting dose. Time was adjusted according to an algorithm to reduce negative side effects. (n=89) vs CBT-SAD: 12 (twice a week) group therapy sessions with 2 psychologists using SAD-protocol; behavioral activation and cognitive restructuring to improve coping with the change in weather, which in turn, alleviates depression. (n=88)	No follow-up.	BDI-II depression severity improved as treatment progressed with time ($p<0.001$). Higher treatment expectations from patients resulted in a lower depression severity ($p<0.001$) and a lower treatment expectation resulted in a higher treatment severity.	"Treatment expectations changed across treatment, affected outcome, and should be assessed and monitored repeatedly throughout treatment. Findings suggest that treatment expectations at mid-treatment are a mechanism by which CBT-SAD reduces depression, which should be replicated in SAD samples and examined for generalizability to non-seasonal depression. These findings underscore the importance of further research examining treatment expectations in	Data suggest treatment expectations change as a function of treatment and time and those with higher expectation had lower depression severity.

									mediating CBT's effects in depression and other types of psychopathology. "	
Rohan 2007 (score=6.5)	Light therapy for depression/ CBT	RCT	Supported by the National Institute of Mental Health and the Uniformed Services University of the Health Science (USUHS).No mention of COI.	N = 61 adults with major depressio n, meeting the SIGH-SAD criteria for a current SAD episode.	Mean age: 45 years; 6 males, 55 females.	Light Therapy (LT): 10,000 lux, 90-minute a day, one am and one pm for week one; dosing tailored to each individual response to treatment for weeks 2-6. (n=16) vs Cognitive Behavioral Therapy (CBT): group therapy, 1.5 hours twice-weekly (n=15) vs CBT + LT: received both treatments simultaneously for 6 weeks. (n=15) vs Minimal contact/delayed treatment control (MCDT): monitored weekly by in-person SIGH-SAD's for 6 weeks, then treated by LT. (n=15)	Follow-up at a session during the summer; following June or July.	CBT + LT had a larger proportion of patients with significant change throughout the duration of the treatment when compared to MCDT on SIGH-SAD, HAMD-D, and BDI-II scales ($p<.001$, $p<.001$, $p<.001$). CBT and CBT + LT is deemed effective for SAD treatment on all three scales.	"These findings suggest that CBT, alone or as an adjunct to LT, holds promise as an efficacious treatment for acute SAD that could be added to the clinician's therapeutic repertoire and warrants further study. However, the data are too preliminary to support widespread dissemination of CBT for SAD at present on the basis of this first controlled trial."	Data suggest combination CBT plus LT had a significantly greater number of clinically significant changes versus MCDT.
Chojnacka 2016 (score=6.0)	Light therapy for depression	RCT	No mention of sponsorship or COI.	N = 95 patients suffering from a current major depressiv e episode of 3 or more on	Mean age: 52.8 years; 20 males, 75 females.	Bright light treatment: 30 minutes of BLT at 10,000 lux between 8-9 A.M. (n=52) vs Placebo: "negative ion generator" for 30 minutes between 8-9 A.M. (n=43)	Follow-up weekly.	After 2 weeks of treatment, improvement was found in both groups on the HDRS scare ($p<0.001$). Response rates in the BLT group were 50% and 27.9% in the placebo group ($p=0.02$). Remission	"Although overall improvement in HDRS-21 scores were not superior in the BLT group, both response and remission rates were significantly higher among patients treated	Data suggest lack of efficacy for depression scores per HDRS-17 but remission and response rates in BLT treated groups and BLT was better than placebo in the

				the CGI-S scale for at least 6 weeks and taking antidepressants for 4 weeks prior to enrollment.				rates were 28.8% in the BLT group and 11.6% in the placebo group (p=0.04).	with BLT relative to those receiving the sham intervention. BLT was also more efficacious than placebo in the population of patients with drug-resistant depression. Further studies to define the subpopulation of patients with non-seasonal depression who may benefit the most from BLT are needed."	drug-resistant depression group.
Strong 2009 (score = 5.5, 4.0)	Light therapy for depression	RCT/Open Label Study	Sponsored by Apollo Light Systems. No COI.	N = 35 patients diagnosed with a score of 20 or less in the SIGH-Sad scale and a seasonal pattern of depression by the DSM-IV scale.	Mean age: 44.3 years; 9 males, 26 females.	Active treatment: blue-light, glance into light panel every 45 minutes for a few seconds daily between 6:00 AM and 8:00 AM (n=15) vs Placebo treatment: red-light, glance into light panel every 45 minutes for a few seconds daily between 6:00 AM and 8:00 AM (n=15)	Follow-up bi-weekly.	On HAMD-17, 32% point improvement was seen in the red-light group compared to 51% seen in the blue-light group (p=.043). On SIGH-SAD, 21% point improvement was seen in the red-light group, 40% in the blue-light group (p=.15).	"Narrow bandwidth blue-light therapy proved superior to red-light therapy. Blue-light therapy produced results similar to both previous 10,000 lux visible-spectrum light studies and many medication studies. The use of bright red panels supported claims that wavelengths of _470nm account for the documented	Data suggest blue light therapy better than red light (placebo) for SAD as reflected in HAM-D17 scores (double-blind phase) and by the end of the open label phase, subjects showed improvement on cell measures.

									effectiveness of light therapy."	
Martiny 2006 (score=5.5)	Light therapy/Sertraline	RCT	Supported by The Danish Medical Research Council, Eastern Region Research Foundation; Merchant L.D. Foght's Founds; Johannes M. Klein and Wife's Memorial Foundation; The Tvergaard Foundation; The Danish Psychiatric Association; Olga Bryde Nielsen's Foundation; and The Frederiksborg General Hospital Research Fund. No COI.	N = 92 patients diagnosed with non-seasonal major depression by the DSM-IV scale.	Mean age: 45.5 years; 29 males, 63 females.	Bright-light treatment: 10,000 lux white light for 1 hour in the morning with a dose of 50 mg daily sertraline, increased to a maximum of 150 mg if no observed improvement(n=48) vs Dim-light treatment: 100 lux dim red light for 30 minutes in the morning with a dose of 50 mg daily sertraline, increased to a maximum of 150 mg if no observed improvement (n=54)	Follow-up at 4 weeks.	Depression scores on the HAMD scale reduced from week 5 to 9. Treatment groups had similar scores at week 9 with high remission rates. Bright-light treatment group were statistically favored ($p<0.01$ and $p<0.05$) at week 5 but had no sustainable effect at week 9.	"Bright light did not have a sustained effect after discontinuation. The offset of effect was complete after 4 weeks."	Data suggest bright light does not sustain its effects after discontinuation. However, both the bright light group and the sertraline group improved depressive scores.
Jurvelin 2014 (score=5.5)	Light therapy for depression	RCT	Supported by Valkee LTD. and the Finnish Funding Agency for Technology Innovation (TEKES). COI: Jurvelin is an employee of Valkee Ltd, a sponsor for this study.	N = 89 patients suffering from Seasonal Affective Disorder with a score of 20 on the HAMD—SAD scale.	Mean age: 43.2 years; 22 males, 67 females.	Low dosage: 1 lumen of bright-light administered transcranially through the ear canals (n=28) vs Intermediate dosage: 4 lumens of bright-light administered transcranially through the ear canals (n=31) vs High dosage: 9 lumens of bright-light administered transcranially	Follow-up weekly.	HAMA, SIGH-SAD, and BDI scores of depression decreased in all three groups; 63% to 67% improvement measured, 74%-79% response rates, and 13%-29% remission rates were observed.	"These results suggests that transcranial bright light treatment may have antidepressant and anxiolytic effect in SAD patients, as both self- and psychiatrist-rated depressive and anxiety symptoms decreased in all treatment groups.	Data suggest transcranial bright light may act as an antidepressant and/or anxiolytic in SAD patients.

						through the ear canals (n=30)			These improvements are comparable to findings of earlier bright light studies that used conventional devices. The lack of dose response may be due to a saturation effect above a certain light intensity threshold. Further studies on the effects of transcranial bright light with an adequate placebo condition are needed."	
Rohan 2004 (score=5.0)	Light Therapy	RCT	Sponsored by the Uniformed Services University of the Health Sciences. No mention of COI.	N = 23 individuals who met the SIGH-SAD criteria for a current Seasonal Affective Disorder (SAD) episode	Mean age: 50.5 ± 12.6 years; 2 males, 21 females	Group LT: received standard light therapy treatment protocol (10,000 lux in 45-min doses twice daily) for 2 weeks (n=9) vs Group CBT: received SAD-tailored group CBT intervention (1.5-hour session twice a week for 6 weeks) (n=7) vs Group CBT+LT: received both standard light therapy and group CBT treatment (n=7)	Follow up at 1 year	Remission rates (per SIGH-SAD criteria) were 42.86% in CBT group, 55.55% in LT group, and 71.43% in CBT+LT group ($p<0.001$) at the end of the 6-week treatment period. Remission rates (per SIGH-SAD criteria) were 42.86% in CBT group, 37.50% in LT group, and 83.33% in CBT+LT group ($p=0.028$) at the 1 year follow-up.	"The nearly half of SAD patients who do not remit with light alone may benefit from CBT as an adjunct or alternative treatment, especially as a prophylaxis against episode recurrence."	Data suggest improvement observed in all 3 therapies but during the subsequent winter, combination CBT and LT appeared to improve long-term outcomes of symptom severity, remission, and relapse rates.
Martiny 2013 (score=5.0)	Light Therapy	RCT	Sponsored by Eli Lilly, The Danish Agency for Science,	N = 75 patients currently experien	Mean age: 47.5 years; 31	Group 1: received wake therapy, daily morning light therapy (10,000 lux daily for	No mention of follow-up past the duration of	Primary outcome was remission rates at day 5, based on Hamilton Depression Scores.	"The intervention induced an acute antidepressant response without	Data suggest wake therapy group better than exercise group for response rates

			Technology and Innovation, The Danish Medical Research Council, the Olga Bryde Nielsen Foundation, and the Frederiksborg General Hospital Research Grant. One or more of the authors have received or will receive benefits for personal or professional use.	cing a major depressive episode and with a HAM-D17 score of 13 or greater	males, 44 females	30 min), and duloxetine (medication) 60mg daily for 9 weeks (n=37) vs. Group 2: participated in an individual exercise program of at least 30 minutes daily and duloxetine 60mg daily for 9 weeks (n=38)	9-week study.	Mean HAM-D score for group 1 was 4.1, compared with 8.7 for group 2 after 5 days of treatment (p=0.004).	relapse between wake nights but with a diminishing effect after intervention. Development is still needed to secure maintenance of response."	although compliance is difficult to assess thoroughly. Response rates diminished at day 8.
Joffe 1992 (score=5.0)	Light Therapy	RCT	Sponsored by Bio-Brite. One or more of the authors have received or will receive benefits for personal or professional use.	N = 105 patients who fit the DSM-III-R criteria for seasonal affective disorder (SAD)	Mean age: 40.2 ± 9.9 years; 17 males, 88 females	Group 1: light therapy at 60 lux intensity, 30 minutes daily, in the morning, for 2 weeks (n=33) vs Group 2: light therapy at 600 lux intensity, 30 minutes daily, in the morning, for 2 weeks (n=38) vs Group 3: light therapy at 3500 lux intensity, 30 minutes daily, in the morning, for 2 weeks (n=34)	Follow-up for 1 week past duration of 2-week treatment phase.	For Group 1, the mean HRSD-SAD scores was 32.4 at baseline, 18.9 after week 1, and 16.4 after week 2. For Group 2, the mean HRSD-SAD scores was 32.2 at baseline, 15.7 after week 1, and 13.4 after week 2. For Group 3, the mean HRSD-SAD scores was 29.8 at baseline, 14.9 after week 1, and 13.1 after week 2. For effect of light therapy in treating SAD, $p<0.05$. For difference improvement results based between different intensities of light, $p>0.05$.	"[L]ight therapy has an antidepressant action by a nonspecific effect or that light is biologically active in the treatment of SAD across a wide range of intensities."	Data suggest light therapy acts as an antidepressant for individuals with SAD but the different intensities did not result in any significant effect differences.
Levitt 1994 (score=5.0)	Light Therapy	RCT	Sponsored by the Clarke Institute of Psychiatry	N = 43 patients with seasonal	Mean age: 37.6 years; 9	Group 1: received dim light (96 lux) therapy, using red light, 30 minutes in	1 week of follow up after 2-week	14 of 19 (74%) of Group 1 patients responded to treatment, compared	"This study did not find any difference in outcome in dim	Data suggest no difference in treatment response

			Research Fund. No COI.	affective disorder (SAD) according to the DSM-III-R criteria	males, 35 females	the morning, daily for 2 weeks (n=19) vs Group 2: received bright light (4106 lux) therapy, using red light, 30 minutes in the morning, daily for 2 weeks (n=24)	treatment phase.	with 16 of 24 (67%) of Group 2 patients. Response was considered as a >50% reduction in SIGH-SAD score. For difference in response rates between groups, p>0.05.	as compared with bright red light LED HMU therapy. Furthermore, patients in both treatments group tended to show a return of symptoms following withdrawal."	between bright versus dim lights.
Tsai 2004 (score=5.0)	Light Therapy	RCT	Sponsored by Nasional Science Council. No mention of COI.	N = 60 patients above the age of 65, with a score of 10 or higher on the Geriatric Depression Scale (GDS).	Mean age: 75 years; 33 males, 27 females	Group 1: sat in front of a light box (5000 lux) for 50 minutes in the morning, daily for 5 days (n=30) vs Group 2: Control group, received no treatment (n=30)	No mention of follow-up past duration of treatment	In the experimental group, average GDS score decreased from 18.0 to 13.2, compared with a decrease in average score of 16.9 to 16.6 in the experimental group (p<0.001).	"Based upon the results of this study, light therapy could be used to decrease depressive symptoms in the elderly."	Data suggest light therapy significantly reduced depressive symptoms in experimental group.
Lam 1992 (score=5.0)	Light Therapy	RCT	Sponsored by the Faculty of Medicine, University of British Columbia, and the Canadian Psychiatric Research Foundation. No mention of COI.	N = 33 patients meeting the DSM-III-R criteria for recurrent major depressive episodes, seasonal pattern	Mean age: 37 years; 13 males, 20 females	Group 1: received 2 hours light therapy (2500 lux) daily for 2 weeks, with UV-A rays of light (n=16) vs Group 2: received 2 hours light therapy (2500 lux) daily for 2 weeks with UV-blocked rays of light (n=17). Patients already taking medication instructed to continue treatment without modification	No mention of follow-up past duration of treatment	Mean SIGH-SAD scores were 33.7 at baseline and 16.4 at the end of week 2 for UV-A group (p<0.001). Mean SIGH-SAD scores were 31.4 at baseline and 14.3 at the end of week 2 for UV-blocked group (p<0.001). No significant difference in results based on UV-A or UV-blocked condition (p<0.7).	"We conclude that the UV-A spectrum does not increase the antidepressant response of light therapy."	Data suggest UV-A wavelengths do not increase the antidepressant response to bright light therapy.

Rosenthal 1993 (score=4.5)	Light Therapy	RCT	Sponsored by Bio-Brite. One or more of the authors have received or will receive benefits for personal or professional use.	N = 55 patients meeting the DSM-III-R criteria for winter seasonal affective disorder (SAD)	Mean age: 42 years; 9 males, 46 females	Group 1: received bright light (6000 lux) therapy for 60 minutes daily (n=10) vs Group 2: received bright light (6000 lux) therapy for 30 minutes daily (n=20) vs Group 3: received dim light (400 lux) therapy for 60 minutes daily (n=11) vs Group 4: received dim light (400 lux) therapy for 30 minutes daily (n=14)	No mention of follow up past duration of treatment	Mean SIGH-SAD scores for patients who received bright light was 31.0 baseline and 19.5 post-treatment. Mean SIGH-SAD scores for patients who received dim light therapy was 31.2 for baseline and 14.2 post-treatment (p-value not given).	"[T]he duration of treatment sessions did not affect outcome. There was no evidence that the brighter visor was superior in efficacy to the dimmer one. Significantly greater relapse occurred following withdrawal of the dimmer visor."	Data suggest comparable efficacy between the 2 intensities but significantly, greater relapse occurred after withdrawal from the dimmer visor.
Teicher 1995 (score=4.5)	Light Therapy	RCT	Sponsored by NIMH and Bio Brite. One or more of the authors have received or will receive benefits for personal or professional use.	N = 57 individuals who met the DSM-III-R criteria Seasonal Affective Disorder	Mean age: 41.5 years; 9 males, 48 females	Group 1: received 30 minutes of morning light therapy with a bright white light visor (600 lux) daily for 2 weeks (n=29) vs Group 2: received 30 minutes of morning light therapy with dim red light visor (30 lux) daily for 2 weeks (n=28)	Follow-up at 1-week post treatment phase.	For the entire cohort, mean Hamilton depression score decreased from 16.9 to 10.5 (37.9%) ($p<0.001$). Decrease in mean Hamilton depression score for Group 1 was 34.6% compared with 40.9% for Group 2 ($p>0.30$).	"There were no significant differences in therapeutic response between patients who were treated with red or white light. The results of this study suggest that the phototherapy light visor may function as an elaborate placebo."	Data suggest no difference between groups.
Kohno 2016 (score=4.5)	Light Therapy	RCT	No mention of COI or sponsorship.	N = 55 medical staff or students of Oita University Faculty of Medicine with no present	Mean age: 31 years; 37 males, 18 females	Intervention Group: 30 minutes morning bright light (10,000 lux) therapy daily for 5 consecutive days (n=27) vs Control Group: received no intervention (n=28)	No mention of follow-up past 5-day treatment phase.	[F]FDG uptake was increased in the right olfactory bulb for participants in Intervention group when compared with control group (p=0.015). [F]FDG uptake was increased in the left olfactory bulb for participants in	"The present findings suggest a possibility that 5-day bright light exposure may increase [F]FDG in the right olfactory bulb of the human brain, suggesting a	Data suggest 5 days of bright light exposure may increase [F]-fluoro dexyglucose uptake in the brain.

				or past psychiatric disorder as screened by Mini-International Neuropsychiatric Interview				Intervention group when compared with control group (p=0.037). [F]FDG uptake trended towards an increase in the right hippocampus in the intervention group in comparison with the control group (p=0.12)	possibility of neurogenesis."	
Rastad 2008 (score=4.5)	Light Therapy	RCT	Sponsored by Dalama County Council, the Center for Clinical Research Dalama and the Uppsala University. No COI.	N = 50 patients with Seasonal Affective Disorder (SAD) or Sub-clinical Seasonal Affective Disorder (S-SAD) as defined by the DSM-IV	Mean age: 45.8 years; 10 males, 40 females	Group 1: Received treatment in a light therapy room (white walls, light-colored furniture), weekdays for 1.5-2 hours for 3 weeks (n=25) vs Group 2: Participants were put on a 3 week wait list, and received light therapy after the trial (n=25)	One month follow-up	Participants from Group 1 showed a mean decrease in SIGH-SAD/SR score of 21.8 to 12.0, compared with 25.4 to 24.8 for the participants from Group 2 (p<0.001).	"Light room therapy was effective in reducing depressive symptoms in subjects with winter depressive mood. Results were maintained over a period of one month."	Data suggest light room therapy was effective for improving mild SAD as 54% treated with the light therapy improved vs placebo.
Eastman 1998 (score=4.5)	Light Therapy	RCT	Sponsored by the National Institutes of Mental Health. No mention of COI.	N = 96 patients with Seasonal Affective Disorder (SAD) diagnosed by the SIGH-SAD scale	Mean age: 36.7 years; 13 males, 83 females	Group 1: 1.5 hours of bright light (6000 lux) therapy in the morning, daily for 4 weeks (n=33) vs Group 2: 1.5 hours of bright light (6000 lux) therapy in the evening, daily for 4 weeks (n=31) vs Group 3: 1.5 hours of placebo light in the	No mention of follow-up past the duration of the 5-week study	After 4 weeks of treatment, 61% of patients responded to morning light (p<0.05), and 50% to evening light (p-value not given), compared with 32% to placebo.	"Bright light therapy had a specific antidepressant effect beyond its placebo effect, but it took at least 3 weeks for a significant effect to develop. The benefit of light over placebo was	Data suggest bright light therapy was effective for SAD but not significantly better than placebo until at least 3 weeks post intervention.

						morning, daily for 4 weeks (n=32)			in producing more of the full remissions."	
Terman 1998 (score=4.0)	Light Therapy	RCT	Sponsored by the National Institute of Mental Health, Bethesda. No mention of COI.	N = 124 subjects with Seasonal Affective Disorder (SAD) by DSM-III-R criteria.	Mean age: 39.4 years; 25 males, 99 females	Each subject received two consecutive treatments, lasting 10-14 days each. Group 1: morning light (10,000 lux) (n=19) vs Group 2: evening light (10,000 lux) (n=19) vs Group 3: morning light then evening light (10,000 lux) (n=27) vs Group 4: evening light then morning light (10,000 lux) (n=20) vs Group 5: high density negative air ionization for both treatments (n=20) vs Group 6: low density negative air ionization for both treatments (n=19)	No mention of follow up past the duration of the study.	68.1% of subjects responded to light at one or both times of the day. The odds ratio for improvement with morning light compared to evening light was 4.5:1 (p=0.002). Total remission rates were 47.4% in Group 1, 36.8% in Group 2, 25.9% in Group 3, 65.0% in Group 4, 40.0% in Group 5, and 5.3% in Group 6	"Bright light and high-density negative air ionization both appear to act as specific antidepressants in patients with seasonal affective disorder. Whether clinical improvement would be further enhanced by their use in combination, or as adjuvants to medication, awaits investigation."	Data suggest both bright light as well as negative air ionization act like antidepressants in SAD patients.
Kripke 1992 (score=4.0)	Light Therapy	RCT	Sponsored by the Department of Veterans Affairs. No mention of COI.	N = 51 hospitalized veterans with nonseasonal major depressive disorders as diagnosed by DSM-III criteria	Mean age: 48 years; 50 males, 1 female	Group 1: Treated with bright white light therapy (2000-3000 lux) for 3 hours in the morning and 3 hours in the evening for the duration of 1 week (n=25) vs Group 2: Treated with placebo dim red light (n=26)	2 days post-treatment	More patients showed improvement in bright white therapy group than dim red light group (p=0.023; specific statistics not given). Some relapse occurred within the 2 days following bright light therapy (no specific data given).	"1-week treatment results suggest that bright light might produce benefits for patients with nonseasonal depression. Bright light should not be recommended for routine clinical application before additional assessments with longer treatment	"Data suggest light color and brightness may influence non-seasonal MDD as the bright white light temporarily improved depression scores but partial relapse occurred within 2 days. Baseline depression scores were lower in placebo group.

									durations are done."	
Kragh 2017 (score=4.0)	Light Therapy	RCT	Sponsored by the Aase and Ejnar Danielsens Foundation, the Novo Nordisk Foundation, the Foundation for Research in Psychiatry, the Foundation for Advancement of Psychiatry, and the Health Research Fund of Central Denmark. No mention of COI.	N = 64 patients with moderate to severe depression according to ICD10 and a score of at least 18 on the HAM-D17 scale	Mean age: 39 years; 36 males, 28 females	Group 1: received "standard care" consisting of individual pharmacologic treatment, milieu therapy, exercise, psychoeducation and psychotherapy for 9 weeks (n=32) vs Group 2: received "standard care" with wake therapy (staying awake for 36 hours 2 days per week) and daily light treatment (30 min every day at 10,000 lux)) for 9 weeks (n=32)	Follow-up period of 4-20 days post-study	Patients in Group 2 had lower depression scores after 1 week of treatment, average HAM-D score of 17.39 compared with 20.19 in Group 1 (p=0.04). Average HAM-D scores were similar between the two groups during weeks 2-9 of treatment.	"The antidepressant effect initially achieved could not be maintained during the nine-week study period. However, sleep and general self-efficacy improved."	High dropout rate. Data suggest that although the initial antidepressant effect of wake therapy could not be sustained overall self-efficacy increased. Standard care bias.
Ozdemir 2015 (score=4.0)	Light Therapy	RCT	Sponsored by Yuzuncu Yil University Scientific Research Projects Office. No COI.	N = 50 patients diagnosed with Major Depressive Disorder for the first time diagnosed using the DSM-IV	Mean age: 35.5 years; 23 males, 27 females	Group 1: Venlafaxine starting at 75mg/day and increased to 150mg/day for 8 weeks (n=25) vs Group 2: Treated with Venlafaxine (same dosages as Group 1) and Bright Light Therapy (7000 lux) for 1 hour in the morning, daily for 8 weeks. (n=25)	Outcomes measured at week 1, 2, 4, and 8 of treatment duration. No mention of follow-up past duration of 8-week treatment	The mean HDRS depression score in decreased in both groups, the decrease in mean scores for Group 1 was 29.28 to 7.40, and the decrease in mean scores for Group 2 was 29.88 to 5.72 after 8 weeks of treatment ($p<0.01$).	"Both venlafaxine and venlafaxine + bright light therapy treatment strategies significantly reversed the depressive mood of patients with severe MDD; however, the latter induced significantly stronger and more rapid beneficial effects."	Data suggest either monotherapy of venlafaxine or combination therapy (venlafaxine and bright light therapy) significantly improved MDD symptoms but combo therapy resulted in stronger and more rapid results.

Avery 2001 (score=4.0)	Light Therapy	RCT	Sponsored by Royal Philips Electronics. No mention of COI.	N = 30 patients with Subsyndromal Seasonal Affective Disorder (SSAD) as assessed by SPAQ	Mean age: 40 years; 2 males, 28 females	Group 1: received bright light (2500 lux) therapy in the morning, 2 hours daily, for 2 weeks (n=16) vs Group 2: received bright light (2500 lux)therapy in afternoon, 2 hours daily, for 2 weeks (n=14)	No mention of follow-up past duration of 2-week treatment phase.	69% of patients who received morning light therapy experienced at least a 50% reduction of SIGH-SAD scores, compared with 43% of the afternoon light therapy group ($p<0.15$).	"Bright light given in the workplace improves subjective ratings of mood, energy, alertness and productivity in SSAD subjects. Morning and afternoon bright lights resulted in similar levels of improvement."	Data suggest bright light improved energy mood, alters and productivity in the workplace in those with SSAD but both morning and evening bright light exposure resulted in improvement.
Avery 2001 (score=4.0)	Light Therapy	RCT	Sponsored by the U.S. Public Health Service. No mention of COI.	N = 95 medication-free patients with Seasonal Affective Disorder as diagnosed by the DSM-IV criteria	Mean age: 40 years; 12 males, 83 females	Group 1: received bright light therapy for 30 minutes daily (10,000 lux) for 6 weeks (n=33) vs Group 2: received dawn simulation therapy, 1.5 hour dawn signal (250 lux) daily for six weeks (n=31) vs Group 3: Received a dim red light placebo treatment, 1.5 dawn signal (0.5 lux) daily for six weeks (n=31)	No mention of follow-up past duration of 6-week treatment phase.	Odds Ratios of Survival Model of Remissions were as follows: Dawn vs. placebo: 1.51 ($p=0.02$), bright light vs. placebo: 0.92 ($p=0.7$), dawn vs. bright light: 1.64 ($p=0.005$).	"Dawn simulation was associated with greater remission and response rates compared to the placebo and compared to bright light therapy. The hours of sunshine during the week before each assessment were associated with a positive clinical response."	Data suggest dawn simulation better than bright light or placebo for treatment of SAD.
Avery 2002 (score=3.5)										Sparse methods. Data suggest dawn simulation was effective in decreasing morning drowsiness compared to

										placebo in patients with SAD.[80]
Michalon 1997 (score=3.5)										Data suggest SAD affects cognition and neither white or red light improved cognitive function.

[80] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Evidence for the Use of Music Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Erkkilä 2011 (score=6.5)	Music therapy	RCT	Sponsored by new and emerging science and technology program of the European commission, and academy of Finland program for centers of excellence in research. The authors declared no COI.	N = 79 patients with diagnosis of unipolar depression per ICD-10.	Mean age: 35.6 years; 17 males, 62 females.	Music therapy group: patients received 20 music therapy included music listening, singing for free improvisation every bi-week with each session lasted 60 minutes (n=33) vs. Control group: patients received standard short-term care included depression and antidepressants training, and psychiatric counselling (n=46).	Follow-up at baseline, 3 and 6 months.	The primary outcome Montgomery Asberg depression rating scale (MADRS) in music therapy group (14.1±8.77 at 3 months follow-up; 14.89±9.6 at 6 months follow-up) and control group (16.43±9.33 at 3 months follow-up; 14.74±10.65 at 6 months follow-up) indicated significant difference at 3 months follow-up (p=0.03), but no significant difference at 6 months follow-up (p=0.13).	"Individual music therapy combined with standard care is effective for depression among working-age people with depression. The results of this study along with the previous research indicate that music therapy with its specific qualities is a valuable enhancement to established treatment practices."	Standard care bias. Data suggest music therapy in addition to standard care significantly improved depressive symptoms, but the duration was only 3 months with failure to improve at 6 months.
Fachner 2013 (score=N/A)	Music therapy	Secondary analysis of Erkkilä 2011	Sponsored by new and emerging science and technology program of the European commission, and academy of Finland program for centers of excellence in research. The	N = 79 patients with diagnosis of unipolar depression per ICD-10.	Mean age: 35.6 years; 17 males, 62 females.	Music therapy group: patients received 20 music therapy included music listening, singing for free improvisation every bi-week with each session lasted 60 minutes (n=33) vs. Control group: patients received standard short-term care included depression and	Follow-up at baseline, 3 months.	The hospital anxiety and depression scale anxiety subscale (HADS-A) in the study indicated significant correlation with fronto-lateral alpha asymmetry (r=0.33; p<0.01). The post Improvisational psychodynamic music therapy (MT) indicated increased asymmetry score for	"Alpha and theta changes in fronto-temporal and temporoparietal areas indicate MT action and treatment effects on cortical activity in depression, suggesting an impact of MT on anxiety reduction."	Data suggest music therapy may reduce anxiety in depressed individuals as measured by alpha and Theta changes in the fronto-temporal and temporoparietal areas of the brain.

			authors declared no COI.			antidepressants training, and psychiatric counselling (n=46).		theta ($p<0.018$) alpha ($p<0.04$).		
Chan 2009 (Score=4.0)	Music therapy	RCT	Sponsored by School of nursing at Hong Kong polytechnic university. No mention of COI.	N = 47 elder patients with depression per GDS depression scores.	Mean age: 74 years; 21 males, 26 females.	Experimental group: patients received 4 types of music intervention included western classical, western jazz, Chinese classical, and Asian classical music and each session lasted 30 minutes weekly for 1 month (n=23) vs. Control group: patients received no intervention but visited community center weekly for data record for 1 month (n=24).	No mention of follow-up.	The primary outcome of the study geriatric depression scale (GDS) score indicated significant decrease in experimental group (Baseline GDS=13.1; 3rd week GDS=9.8; 4th week GDS=7.9) and significant differences with control group (Baseline GDS=13.4; 3rd week GDS=14.4; 4th week GDS=15.8) (3rd and 4th weeks $p<0.001$).	"In the music group, there were statistically-significant decreases in depression scores ($P < 0.001$) and blood pressure ($P = 0.001$), HR ($P < 0.001$), and RR ($P < 0.001$) after 1 month. The implication is that nurses may utilize music as an effective nursing intervention for patients with depressive symptoms in the community setting."	Standard care bias. Data suggest significant improvement in BP, HR, RR and depression scores in music therapy group.
Castillo-Pérez 2010 (Score=3.5)										Data suggest music therapy may benefit those with mild or moderate depressive symptoms.[81]
Lai 1999 (Score=3.5)										Data suggest music may be beneficial for mind-body healing in depressive women.

[81] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow up:	Results:	Conclusion:	Comments:
Lemoine 2007 (score=6.5)	Insomnia Treatment	RCT	Sponsored by Servier. Authors received honoraria from Servier.	N = 332 participants who met DSM-IV criteria for major depressive disorder	Mean age: 40.15 years; 96 males, 236 females	Agomelatine 25-50 mg/day (n=165) vs. Venlafaxine 75-150 mg/day (n=167). Both medications given for 6 weeks	Follow-up at weeks 2, 4, and 6	At six weeks, Leeds Sleep Evaluation Questionnaire (LSEQ) "getting to sleep" score significantly higher in agomelatine than venlafaxine (70.5 vs. 64.1, p = 0.001). No significant difference between mean decrease in Hamilton Depression Rating Scale scores	"Agomelatine showed similar antidepressant efficacy with earlier and greater efficacy in improving subjective sleep than venlafaxine in MDD patients."	Data suggest equivalent antidepressant efficacy between agomelatine and venlafaxine but at 6 weeks, agomelatine exhibited better efficacy for patients getting to sleep.
Rush 1998 (score=6.5)	Insomnia Treatment	RCT	Sponsored by Bristol-Myers Squibb Pharmaceutical Research Institute, the Sarah and Charles Seay Center for Research in the Biological Basis of Psychiatric	N = 125 participants with nonpsychotic moderate to severe depression according to DSM-III-R criteria	Mean age: 36.49 years; 44 males, 81 females	Nefazodone 100 mg b.i.d. for 1 week, 200 mg b.i.d. from days 8 to 56 (n=64) vs. Fluoxetine 20 mg for 56 days (n=61)	Follow-up at weeks 1, 2, 3, 4, 6, and 8	Mean difference in Hamilton Depression Rating Scale scores at week 8: nefazodone = -11.4, fluoxetine = -12.2 (95% CI [-1.7, 2.8]). At week 8 percentage sleep efficiency: nefazodone = 88.3, fluoxetine = 81.2 ($p \leq 0.01$), percentage awake and movement time: nefazodone = 6.0, fluoxetine = 10.9 ($p \leq 0.01$, rapid eye movement latency: nefazodone = 88.9 minutes, fluoxetine = 87.0 minutes ($p \leq 0.01$)	"Nefazodone and fluoxetine were equally effective antidepressants. Nefazodone was associated with normal objective, and clinician- and patient-rated assessments of sleep when compared with fluoxetine. These differential sleep EEG effects are constant with the notion that nefazodone and fluoxetine may have somewhat different modes and spectra of action."	Data suggest comparable antidepressant therapeutic efficacy but nefazodone was associated with improved sleep measures compared to fluoxetine.

			Disorders, and the NIMH.							
Chung 2015 (score=6.5)	Insomnia Treatment	RCT	No COI. Sponsored by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong Special Administrative Region.	N = 150 participants having insomnia for more than 3 months and a history of major depressive disorder, with both insomnia and MDD meeting DMS-IV-TR criteria	Mean age: 49.3 years; 31 males, 119 females	Acupuncture – utilized TMC style, *Deqi* was achieved (n=60) vs. Minimal acupuncture – needled in areas with no therapeutic impact according to TCM style, *Deqi* not achieved (n=60) vs. Placebo acupuncture – needles placed 1 inch beside acupuncture points utilized in acupuncture group (n=30). Each treatment was given 3 times a week for 3 weeks	Follow-up at weeks 1 and 5	Sleep onset latency in minutes, wake after sleep onset in minutes, sleep efficiency percentage, and insomnia severity index scores were not significant different between groups at week 1 or at week 5 (group-by-time interaction, all $p > 0.05$).	"Acupuncture was well tolerated, but the efficacy was only mild and similar to that of minimal acupuncture and placebo acupuncture. A high proportion of patients remained clinically significantly affected by insomnia after treatment. The finding raises certain doubts about the value of acupuncture and underscores the difficulties in the treatment of residual insomnia in MDD."	Data suggest acupuncture comparable to minimal acupuncture and placebo, thus showing lack of efficacy for insomnia.
Quera-Salva 2011 (score=6.0)	Insomnia Treatment	RCT	Sponsored by Servier. COI, one or more of the authors have received	N = 138 participants with moderate to severe major depressive disorder meeting	Mean age: 41.4 years; 49 males, 89 females	Agomelatine 25-50 mg/day (n=71) vs. Escitalopram 10-20 mg/day (n=67). Both medications were given for 24 weeks	Follow-up at week 2, 6, and 24	Sleep latency in minutes was significantly better in agomelatine group compared to escitalopram at weeks 2 ($p < 0.001$), 6 ($p = 0.013$), and 24 ($p < 0.0001$). Number of sleep	"This study showed that the clinical effects of agomelatine on sleep and wake parameters are different from that of escitalopram."	Data suggest agomelatine improved sleep latency and overall clear thinking compared to escitalopram.

			or will receive benefits for personal or professional use.	DSM-IV criteria				cycles were also statistically higher in agomelatine group at weeks 2, 6, and 24 (all $p < 0.0001$)		
Fava 2002 (score=5.5)	Insomnia Treatment	RCT	No mention of COI. Sponsored by Lilly Research Laboratories, Eli Lilly and Company.	N = 284 participants meeting DSM-IV major depressive disorder criteria	Mean age: 42.88 years; 115 males, 169 females	Fluoxetine 20 mg/day (n=92) vs. Sertraline 50 mg/day (n=96) vs. Paroxetine 20 mg/day (n=96). All treatments given for 4 weeks	Follow-up at 4 weeks	No difference in mean Hamilton Depression Rating Scale (HAMD) scores between medications at 4 weeks ($p = 0.365$). No difference in HAMD sleep disturbance questions ($p = 0.868$) or HAMD cognition factor questions ($p = 0.841$)	"In summary, this study showed no statistically significant differences in the efficacy or tolerability of fluoxetine, sertraline, and paroxetine during acute treatment of major depressive disorder."	Data suggest similar efficacy between all 3 SSRIs (fluoxetine, sertraline, or paroxetine) and response was independent of significant baseline insomnia. No difference in treatment efficacy between any of these SSRIs.
Fava 2011 (score=5.5)	Insomnia Treatment	RCT	Sponsored by Sepracor, Marlborough. COI, one or more of the authors have received or will receive benefits for personal or	N = 545 participants who met DSM-IV criteria for major depressive disorder and insomnia related to MDD	Mean age: 40.99 years; 182 males, 363 females	Morning fluoxetine 20 mg/day plus nightly eszopiclone 3 mg/day (n=270) vs. Morning fluoxetine 20 mg/day plus nightly placebo (n=275). Treatments given for 8 weeks	Follow-up at weeks 1, 4, and 8	At week 8 the fluoxetine and eszopiclone group showed improved sleep latency in minutes ($F = 15.2$, $p = 0.0001$), wake time after sleep in minutes ($F = 22.15$, $p < 0.0001$), and total sleep time in minutes ($F = 12.77$, $p = 0.0004$)	"In this study, eszopiclone/fluoxetine co-therapy was relatively well tolerated and associated with rapid, substantial, and sustained sleep improvement, a faster onset of antidepressant response on the basis of CGI, and a greater magnitude of the antidepressant effect."	Severe depression or suicidal ideation patients excluded. Although zolpidem ER given in addition to escitalopram improved sleep quality for up to 24 weeks, it did not increase the antidepressant effects of the escitalopram. This combination was better than placebo.

			professional use.							
Fava 2006 (score=5.5)	Insomnia Treatment	RCT	Sponsored by Sanofi-aventis US. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 385 participants meeting DSM-IV-TR criteria for major depressive disorder	Age and gender information only given for 380 participants. Mean age: 42.95 years; 139 males, 241 females	Escitalopram 10 mg/day plus zolpidem extended-release 12.5 mg/day (n=193) vs. Escitalopram 10 mg/day plus placebo daily (n=192). All medications given for 7 weeks. Those with Hamilton Depression Rating Scale scores ≥ 50% decrease compared to baseline were kept for an additional 16 weeks	Follow-up at weeks 2, 4, 6, and 8 and then at weeks 12, 16, 20 and 24	Mean total sleep time significantly greater for zolpidem group at each assessment time period ($p < 0.05$)	"Zolpidem extended-release administered concomitantly with escitalopram for up to 24 weeks was well tolerated and improved insomnia and some sleep-related next-day symptoms and next-day functioning in patients with MDD but did not significantly augment the antidepressant response of escitalopram."	Data suggest eszopiclone administered with fluoxetine in patients with MDD experienced significant improved sleep and daytime functioning versus placebo group and depressions scores decreased in the most severely depressed.
Krystal 2007 (score=5.5)	Insomnia Treatment	RCT	Sponsored by Sepracor. COI, one or more of the authors have received or will receive benefits for personal or	N = 545 participants meeting DSM-IV criteria for insomnia and comorbid major depressive disorder	Mean age: 41.9 years; 176 males, 369 females	Fluoxetine 20 mg/day and eszopiclone 3 mg/day (n=270) vs. Fluoxetine 20 mg/day and placebo (n=275). Treatments were given for 8 weeks	Follow-up at weeks 2, 4, 8 and 10	Mean Hamilton Depression Rating Scale scores at week 8 were statistically greater in eszopiclone group compared to placebo ($p = 0.0004$) and maintained at week 10 ($p < 0.0001$). This same group had maintained improvements in sleep latency in minutes, wake after sleep onset in	"In this study, eszopiclone discontinuation did not result in significant CNS or benzodiazepine withdrawal AEs, rebound insomnia, or rebound depression; and improvements in sleep and depressive	Placebo controlled. Data suggest discontinuation (withdrawal) of eszopiclone after cotherapy with fluoxetine did not lead to significant loss in the gains made improving sleep and symptoms of depression.

			professional use.					minutes, and total sleep time in minutes between weeks 8 and 10 (all $p < 0.05$)	symptoms were maintained."	
Yeung 2011 (score=5.5)	Insomnia Treatment	RCT	No COI or sponsorship.	N = 78 participants meeting DSM-IV criteria for major depressive disorder and insomnia complaints	Mean age: 48.1 years; 16 males, 62 females	Electroacupuncture – needles placed on acupoints based on traditional Chinese medicine (TCM) (n=26) vs. Minimal acupuncture – needles placed on areas where no therapeutic effect will take place according to TCM (n=26) vs. Placebo acupuncture – needles placed one inch away from areas used in electroacupuncture (n=26). Treatments given three times per week for 3 weeks	Follow-up at weeks 1 and 4	Significant group by time interaction in Insomnia Severity Index (ISI) ($p = 0.04$), Pittsburgh Sleep Quality Index (PSQI) ($p = 0.03$), and sleep diary-derived sleep efficiency ($p = 0.01$), with no difference between electroacupuncture and minimal acupuncture.	"Compared with placebo acupuncture, electroacupuncture and minimal acupuncture resulted in greater improvement in subjective sleep measures at 1 week and 4 week post-treatment. No significant difference was found between electroacupuncture and minimal acupuncture, suggesting that the observed differences could be due to nonspecific effects of needling, regardless of whether it is done according to traditional Chinese medicine theory."	Data suggest both minimal acupuncture and electroacupuncture better than placebo in improvement of subjective sleep measures.
McCall 2010 (score=5.5)	Insomnia Treatment	RCT	Sponsored by the NIH, Sepracor, and Mini Mitter.	N = 60 participants meeting DSM-IV criteria for major	Mean age: 41.5 years; 20 males, 40 females	Fluoxetine 20 mg/day combined with eszopiclone 3 mg/day (n=) vs. Fluoxetine 20 mg/day	Follow-up at 8 weeks	No significant interaction terms in any insomnia poor health related quality of life (HRQOL) models. Primary measure of HRQOL,	"ESZ treatment of insomnia in depressed patients is associated with multiple favorable	Placebo controlled. Data suggest eszopiclone improved both sleep and symptoms of depression compared to placebo.

			COI, one or more of the authors have received or will receive benefits for personal or professional use.	depressive episode and reporting sleeping complications		combined with placebo (n=). All treatments administered for 8 weeks		the daily living and role functioning subscale (DLRF), scores were lower in eszopiclone group compared to placebo (0.81 vs. 0.85)	outcomes, including superior improvement in HRQOL, depression severity, and sleep."	
Manber 2016 (score=5.5)	Insomnia Treatment	RCT	Sponsored by the US national Institutes of Health. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 150 participants meeting DSM-IV-TR criteria for insomnia and major depressive disorder	Mean age: 46.6 years; 40 males, 110 females	Both groups received 16 weeks of medication management every 2 weeks. Seven 45-minute sessions of cognitive behavioral therapy of insomnia (CBT-I) (n=75) vs. Seven 45-minute sessions of control therapy for insomnia (CTRL) (n=75)	Follow-up at 1, 2, 3, 4, 6, 8 and 12 weeks	CBT-I had significant decreased insomnia severity (p = 0.028). Depression remission percentage between groups was not significantly different (44% versus 36%)	"CBT-I is an efficacious treatment for insomnia comorbid with MDD among patients treated with antidepressant medications. Improvement in insomnia may be related to the change in depression."	Data suggest CBT superior to control for improving insomnia in MDD patients on antidepressant therapy of escitalopram, sertraline, or desvenlafaxine.
Carney 2017 (score=5.5)	Insomnia Treatment	RCT	No mention of COI. Sponsored by	N = 107 participants with insomnia meeting	Mean age: 42.0 years; 34 males,	Cognitive Behavioral Therapy for Insomnia (CBT-I) and	Follow-up at 2, 4, 6, and 8 weeks	No statistical difference in subjective sleep (via daily sleep diaries) between groups.	"Although all group self-reported sleeping better after treatment, only	Placebo controlled. Data suggest all groups reported improved sleep but only CBT group on objective sleep measures

			the National Institute of Mental Health	Research Diagnostic Criteria and major depressive episode via SCID	73 females	Escitalopram – 10 mg/day (n=36) vs. Cognitive Behavioral Therapy for Insomnia (CBT-I) and Daily placebo (n=36) vs. Escitalopram 10 mg/day and 4 sessions of sleep hygiene control (n=35). Medication given for 8 weeks and sessions delivered every two weeks		Both CBT groups improved in total wake time in minutes ($p = 0.03$). Polysomnographic objective sleep had no significant difference ($p = 0.07$)	the CBT-I groups improved on objective sleep, and AD + SH's sleep worsened. This suggests that we should be treating sleep in those with depression with an effective insomnia treatment and relying on self-report obscures sleep worsening effects.	and SH group showed sleep measures worsened.
Bélanger 2016 (score=5.5)	Insomnia Treatment	RCT	Sponsored by the National Institute of Mental Health. Morin received research grant form Novartis.	N = 188 participants with chronic insomnia meeting DSM-IV criteria, with 45 having comorbid depression or anxiety	Mean age: 47.4 years; 71 males, 117 females	Behavioral therapy (BT) – weekly 45-60 minute sessions (n=63) vs. Cognitive Therapy (CT) – weekly 45-60 minute sessions (n=65) vs. Cognitive Behavioral Therapy (CBT) – up to 75 minute sessions (n=60). All treatments	Follow-up at weeks 2, 4, 6, and 8	Proportion of responders was smaller in those with comorbidity in BT (34.4% versus 81.6%, $p = 0.007$) and CT (23.6% versus 57.6%, $p = 0.02$) groups. There was no statistical difference in this proportion in CBT group	"The presence of a comorbid anxiety or mild to moderate depressive disorder did not reduce the efficacy of CBT for insomnia, but it did for its single BT and CT components when used alone."	Data suggest presence of anxiety in mild to moderate depression did not decrease CBT efficacy on insomnia.

						were given for 8 weeks				
Manber 2008 (score=5.0)	Insomnia Treatment	RCT	Sponsored by the National Institute of Mental Health. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 30 participants meeting DSM-IV-TR for major depressive disorder and insomnia	Mean age: 35 years; 12 males, 18 females	7 sessions of cognitive behavioral therapy for insomnia (CBTI) plus Escitalopram 5-20 mg/day (n=15) vs. 7 sessions of CTRL (quasi-desensitization) plus Escitalopram 5-20 mg/day (n=15). Therapy sessions given weekly for 5 weeks and then biweekly for 2 weeks	Follow-up at 2, 4, 6, 8 and 12 weeks	CBTI group had higher rate of remission in depression compared to CTRL group (61.5% versus 33.3%, p = 0.13). CBTI group also had higher remission rate in insomnia (50.0% versus 7.7%, p = 0.05)	"This pilot study provides evidence that augmenting an antidepressant medication with a brief, symptom focused, cognitive-behavioral therapy for insomnia is promising for individuals with MDD and comorbid insomnia in terms of alleviating both depression and insomnia."	Pilot study. Data suggest addition of focused CBT to antidepressant therapy may improve both depression and insomnia.
Watanabe 2011 (score=4.5)	Insomnia Treatment	RCT	Sponsored by the Ministry of Health, Labour and Welfare, Japan. COI, one or more of the authors have received	N = 37 participants meeting DSM-IV major depressive disorder	Mean age: 50.5 years; 14 males, 23 females	Treatment as usual (n=17) vs. Treatment as usual with brief behavioral therapy for insomnia, 4 weekly 60 minute sessions (n=20)	Follow-up at 4 and 8 weeks	Brief behavioral therapy group had significantly lower mean Insomnia Severity Index (ISI) scores at 8 weeks (p < 0.0005). This group also had higher rates of remission in insomnia (50% versus 0%) and depression (50% versus 0%) compared to treatment as usual.	"In patients with residual depression and treatment refractory insomnia, adding brief behavioral therapy for insomnia to usual clinical care produce statistically significant and clinically substantive added benefits."	Treatment as usual bias. Data suggest at 8 weeks the brief behavioral therapy group improved in sleep measures related to refractory insomnia.

			or will receive benefits for personal or professional use.							
Asnis 1999 (score=4.5)	Insomnia Treatment	RCT	Sponsored by Lorex Pharmaceuticals, Skokie. No mention of COI.	N = 190 participants meeting DSM-IV major depressive disorder and also persistent insomnia	Mean age: 41.6 years; 40 males, 150 females	Placebo daily (n=96) vs. Zolpidem 10 mg/day (n=94). Medications given for 4 weeks	Follow-up at weeks 1, 2, 3, and 4	Zolpidem group had longer sleep times ($p < 0.05$), greater sleep quality ($p < 0.05$), and reduced number of awakenings ($p < 0.05$) compared to placebo	"In this defined patient population, zolpidem, 10 mg, was effectively and safely co-administered with an SSRI, resulting in improved self-rated sleep, daytime functioning, and well-being."	Placebo controlled. Data suggest zolpidem administration in persistent insomnia depression patients who have been treated with an SSRI improved sleep, daytime function and overall well-being.
Thase 2002 (score=4.5)	Insomnia Treatment	RCT	COI, one or more of the authors have received or will receive benefits for personal or professional use. Sponsored by Bristol-Myers Squibb	N = 597 chronically depressed participants meeting DSM-III-R/DSM-IV criteria for chronic depression	Mean age: 43.6 years; 203 males, 394 females	Cognitive Behavioral Analysis System of Psychotherapy (CBASP) – 16-20 individual 45-60 minute sessions given over 12 weeks (n=192) vs. Nefazodone – mean final dosage: 466 mg/day for 12 weeks (n=201) vs. Combination of both	Follow-up at weeks 4 and 12	Mean change in Hamilton Depression Rating Scale scores (HAMD) insomnia ratings for CBASP, nefazodone, and combination groups, respectively: from weeks 0-4 = 0.6, 1.2, 1.3 (CBASP < nefazodone [$p = 0.003$], CBASP < combination [$p < 0.001$), nefazodone = combination [$p = 0.54$], from weeks 4-12: 0.7, 0.8, 1.1 (CBASP = nefazodone [$p = 0.22$], CBASP <	"Despite comparable antidepressant efficacy, monotherapy with nefazodone or CBASP resulted in markedly different effects on the magnitude of temporal course of insomnia symptoms associated with chronic forms of major depression."	Data suggest either nefazodone + CBT or nefazodone alone were better than CBT alone for improving insomnia associated with chronic major depression.

			Company and Mental Health Intervention Research Center.			treatments (n=204).		combination [p = 0.02], nefazodone = combination [p = 0.26])		
Ashworth 2015 (score=4.0)	Insomnia Treatment	RCT	No mention of sponsorship. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 41 participants meeting DSM-IV-TR criteria for insomnia and a Beck Depression Inventory score of at least 17	Mean age: 36.76 years; 16 males, 25 females	1 session of Cognitive Behavioral Therapy for Insomnia (CBT-I) every 2 weeks (n=21) vs. 1 session of self-help CBT-I with written materials every 2 weeks (n=21). Treatments administered over 8 weeks	Follow-up at weeks 2, 4, 6, 8, and 20	Beck Depression Inventory II scores in CBT-I group decreased by on average 11.93 compared to self-help group ($p < 0.001$). Insomnia Severity Index scores in CBT-I group decreased by on average 6.59 compared to self-help group ($p = 0.001$).	"CBT-I administered by a therapist produced significant reductions in both insomnia and depression severity posttreatment and at follow-up, compared with a control condition in which participants received only written CBT-I."	Data suggest 8 weeks of therapist delivered CBT is significantly superior to self-help CBT for both decreasing insomnia but improvement of other depression related symptoms.
Combs 2014 (score=4.0)	Insomnia Treatment	RCT	No COI. No mention of sponsorship.	N = 202 participants meeting DSM-IV criteria for major depressive disorder	Mean age: 52 years; 49 males, 153 females	Supervised aerobic exercise – three 45-minute exercise sessions (n=51) vs. Home-based aerobic exercise – met with exercise physiologist	Follow-up at weeks 2, 4, 8, 12, and 16	All groups showed improvement in sleep disturbance ($p = 0.004$). Active treatments did not show greater improvement compared to placebo ($p = 0.867$). Improvements in sleep were comparable in	"In summary, we found that although exercise treatment did not significantly improve sleep symptoms among depressed adults, improvements in sleep symptoms were strongly	Data suggest lack of efficacy for improved sleep as neither exercise nor sertraline were better than placebo. However, exercise was all questionnaire-based and without compliance data or objective measures.

						for instruction, then completed exercises at home, recorded with exercise log (n=53) vs. Sertraline – 50-200 mg/day, given up to 4 dosages of zolpidem if experiencing insomnia (n=49) vs. Placebo – dosing equal to sertraline group (n=49). All treatments administered for 4 months		exercise and sertraline (p = 0.841)	associated with improvements in depressive symptoms across all treatment groups and also predictive of subsequent depression relapse."	
Norell-Clarke 2015 (score=4.0)	Insomnia Treatment	RCT	Sponsored by Stiftelsen Professor Bror Gadelius Minnesfond, Psykiatrifonden, and the Research Committee of Örebro County Council, Sweden. No	N = 64 with insomnia disorder diagnosed via the Duke Structured Clinical Interview for Sleep Disorders and depressive symptoms of MDD via SCID-I	Mean age: 51.5 years; 15 males, 49 females	Group Cognitive Behavioral Therapy for Insomnia, 4 two hour biweekly sessions(CBT-I) (n=32) vs. Group Relaxation Training, 4 two hour biweekly sessions (RT) (n=32)	Follow-up at post-treatment and 6 months	Insomnia Severity Index scores at baseline, post-treatment, and 6 months, respectively: CBT-I = 18.3, 9.7, 7.9, RT = 20.1, 14.1, 14.4(F = 26.5, p < 0.001). Beck Depression Inventory II scores at baseline, post-treatment, and 6 months, respectively: CBT-I = 23.0, 14.7, 12.0, RT = 21.2, 18.5, 16.4 (F = 2.73, p = 0.104)	"Group CBT-I is an efficient form of insomnia-treatment for people with insomnia comorbid with depressive symptomatology. The mixed results regarding depression outcomes warrants replication and further studies into treatment mechanisms."	Data suggest CBT-I superior to relaxation therapy for improving sleep quality, sleep time, and awakenings.

			mention of COI.							
Cohn 1983 (score=4.0)	Insomnia Treatment	RCT	No mention of COI or sponsorship.	N = 53 participants receiving TCA therapy for depressive disorder for at least 6 weeks prior to study and had symptoms of sleep disturbance, diagnostic criteria given for depressive disorder	Mean age: 41.5 years; 15 males, 38 females	Crossover design – each group would receive one treatment for 4 days, then 1 washout day, then 4 days on other treatment. First received triazolam – instructed to take three 0.25 mg tablets if they did not receive a good night's rest the night before (n=27) vs. First received placebo – some instructions and dosage as triazolam group (n=26)	Follow-up at days 5 and 10	All efficacy questions on Physician's Sleep Questionnaire showed triazolam better than placebo	"No worsening in depression or anxiety was seen with either triazolam or placebo; some measures indicated improvement in anxiety and depression symptoms on triazolam."	Trial of only 4 days duration, precluding more than ultra-short term efficacy. Placebo controlled, double blind crossover study. Depression severity not assessed at start of study. Data suggest addition of triazolam (a hypnotic) to TCAs is more effective than placebo plus TCA for improved sleep measures and increasing an overall "rested" feeling upon awakening.
Wagley 2012 (score=3.5)										Small sample, waitlist control bias. Data suggest brief CBT is beneficial in sleep and depression outcomes in depressed outpatients.
Dominguez 1984 (score=3.5)										Placebo controlled. Data suggest triazolam added to imipramine was better than placebo for improved sleep but had no effect on

										imipramine efficacy for depressive symptoms.[82]
Blom 2015 (score=3.5)										Data suggest internet delivered CBT for insomnia was somewhat effective but not for depression.
Blom 2017 (score=NA)		3 year follow-up of Blom 2015								Data suggest patients who have depression and insomnia should be offered CBT for insomnia in addition to antidepressants for depressive symptoms.
Shimodera 2014 (score=3.0)										Treatment as usual bias, baseline dissimilarities in treatment durations. Data suggest addition of brief CBT can benefit insomniac depressed patients with quality of life.

[82] Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.