NEW YORK STATE OF OPPORTUNITY. Workers' Compensation Board

Medical Treatment Guidelines

Traumatic Brain Injury

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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 months,
- 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 information regarding 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.

B. Traumatic Brain Injury

Effective: 05/02/2022

B.1 Overview

This clinical practice guideline presents recommendations for assessing and treating adults with traumatic brain injury (TBI).

Traumatic brain injury (TBI) is defined as a form of acquired brain injury. It occurs when a sudden trauma causes damage to the brain.

Trauma may include any of the following: the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other forces.

There are three broad acuity categories of TBI. TBI is classified as mild, moderate or severe depending on the extent of the damage to the brain. Mild TBI is also known as a concussion.

These categories incoprporate the Glasgow Coma Scale which is a neurological scale that provides an objective measure of the conscious state of a person for initial as well as subsequent assessment.

Mild TBI- Concussion, includes at least one of:

- The person was not unconscious or was unconscious for less than 30 minutes.
- Memory loss lasted less than 24 hours.
- The GCS was 13 to 15

Moderate TBI, which includes:

- The person was unconscious for more than 30 minutes and up to 24 hours.
- Memory loss lasted anywhere from 24 hours to seven days.
- The GCS was nine to 12.

Severe TBI, which includes:

- The person was unconscious for more than 24 hours.
- Memory loss lasted more than seven days.
- The GCS was eight or lower.

Table 1: Classification of TBI Severity

If a patient meets criteria in more than one category of severity, the higher severity level is assigned			
Criteria	**Mild**	**Moderate**	**Severe**
Structural Imaging	Normal	Normal or Abnormal	Normal or Abnormal
Loss of Consciousness (LOC)	0-30 min	>30 min and < 24 hrs	> 24 hrs
Alteration of Consciousness / Mental State (AOC)*	Up to 24 hrs	>24 hrs; Severity Based on Other Criteria	
Posttraumatic Amnesia (PTA)	0-1 day	>1 day and <7 days	>7 days
Glasgow Coma Scale (GCS) (Best Available Score in First 24 Hours	13-15	9-12	<9

The Glasgow Coma Scale is a neurological scale that provides an objective measure of the conscious state of a person for initial as well as subsequent assessment it is a method for bedside assessment of impairment of conscious level, the clinical hallmark of acute brain injury.

Glasgow Coma Scale

Response	Scale	Score
Eye Opening	Eyes open spontaneously	4 Points
	Eyes open verbal command, speech or shout	3 Points
	Eyes open to pain (not applied to face	2 Points
	No eye opening	1 Point
Verbal Response	Oriented	5 Points
	Confused conversation but able to answer questions	4 Points
	Inappropriate responses but words discernable	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
Motor Response	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticte posture	3 Points
	Extensor (rigid) response, decebrate posture	2 Points
	No motor responses	1 Point

Adapted from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974, 81-84.

Alteration of mental status must be immediately related to the head trauma. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, and difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

TBI may lead to a wide range of short or long-term issues including but not limited to:

- **Cognitive Function** (attention and memory)
- **Motor function** (extremity weakness)
- **Sensation** (hearing, vision, impaired perception and touch)

- **Neurologic** (headaches, impaired coordination, balance and seizure)
- **Behavior** (emotional regulation, depression, anxiety, aggression, impairments in behavioral control, personality changes)

Mild TBI/Concussion is generally relatively benign and self-limited; however, in a small percentage of cases the symptoms persist. While most patients have resolution of symptoms over a period of a few days to a month, some patients may have persistence of symptoms beyond one year post-injury. Persistent symptoms refer to a variety of physical, cognitive, emotional, behavioral and sleep symptoms that may endure for weeks or months following a concussion.

Post-concussion syndrome is a term that is used by many practioners to describe the persistence of a constellation of symptoms beyond the usual recovery period after a concussion. Although initial complaints of impaired memory, attention and executive function are common immediately following ~~m~~TBI, the vast majority of individuals recover within a few hours to days. However, some patients report new, persistent or worsening cognitive symptoms weeks, months or sometimes years postinjury. Those who have persistent post-concussion symptoms, may have pre-morbid or comorbid conditions that may play a role in the persistence of the PCS symptoms and this should be considered in the evaluation and management of post concussive syndrome.,

TBI may result in lifetime deficits. As a result, long-term medical management may be indicated. Management and treatment should be based on the clinical evaluation and revaluation of the medical diagnosis(es) and associated impairment, cognitive ability, anticipated functional gains, and progress demonstrated by documented functional outcomes. Management and treatment may include a continum of services ranging from inpatient to outpatient rehabilitation, to supportive living programs, based upon the severity of the TBI and associated impairments.

While these guidelines are typically written for care of patients in the ambulatory/outpatient setting, it is recognized that TBI carries with it an increased probability of patients requiring therapeutic interventions, typically delivered in the inpatient hospital setting, to be continued in other settings, such as long term care, community or outpatient rehabilitation, or even home care. These guidelines do not capture those interventions, and clinical decision-making regarding such interventions should be made on a case-by-case basis, based on the severity of the ongoing symptoms and the resultant type and magnitude of clinical needs, the complexity of which may require a multi-disciplinary approach.

Possible TBI Related Symptoms (list is not all inclusive of TBI related symptoms)

Physical Symptoms	Cognitive Symptoms	Behavioral/Emotional Symptoms
Headache, dizziness, balance disorders, nausea, fatigue, sleep disturbance, blurred vision, sensitivity to light, hearing difficulties/loss, tinnitus, sensitivity to noise, seizure, transient neurological abnormalities, numbness, tingling	Problems wih attention, concentration, memory, speed of processing, judgement, executive control	Depression, anxiety, agitation, irritability, impulsivity, aggression

B.2 Initial Assessment

A thorough history and a focused physical examination guide the initial assessment of a patient complaining of potentially work-related TBI.

B.2.a Red Flags

The assessment (history and physical exam) should include evaluation for "Red Flags" which may raise suspicion of serious underlying medical, neurological (brain, spinal cord, peripheral nerves) and/or orthopedic conditions (see Table 2.)

Table 2. Red Flags

Disorder	Medical History	Physical Examination/Diagnostic Testing
Increased Intracranial Pressure	Altered consciousness, coma Headache History of hypertension Organ-system relevant history features if history of focal intracranial damage or bleeding	Altered mental status Altered consciousness Concurrent elevated blood pressure Organ-system relevant physical examination features if history of focal intracranial damage or bleeding
Intracerebral hemorrhages	Headache Nausea & vomiting Organ-system relevant history features if history of focal intracranial damage or bleeding	Altered consciousness Organ-system relevant physical examination features if history of focal intracranial damage or bleeding
Central nervous system Impairments	Abnormal balance Loss of consciousness Nausea Visual difficulties Organ-system relevant history features if history of focal intracranial damage or bleeding	Vertigo lasting for more than seconds Vestibular dysfunction Hearing loss (unilateral) Visual dysfunction Organ-system relevant physical examination features if history of focal intracranial damage or bleeding
Fracture	Major trauma, such as vehicular accident or fall from height Minor trauma or strenuous lifting in older or potentially osteoporotic patients Metabolic risks for osteopenia (including renal failure, hyperthyroidism, rheumatic disorders, debility and inheritance)	Percussion tenderness over specific spinous processes,examination of the skull, facial bones, cervical spine for focal findings. Careful neurological examination for signs of neurological compromise
Substance Abuse with Risk of Withdrawal	Substance(s) abuse Prior substance(s) withdrawal	Dilated Pupils Tachycardia Sweating
Progressive Neurologic Deficit	Progressive limb numbness or weakness, bowel or bladder control impairment, gait ataxia Progressive loss in any sensory function (e.g., vision, hearing, balance, sensation) Severe spine pain	Progressive loss in any sensory function (e.g., visual acuity/Snellen, visual fields, audiometry, Romberg, balance, sensation) Significant and progressive myotomal motor weakness Significant and increased sensory loss – in anatomical distribution

		Radicular signs Corticospinal tract involvement (gait ataxia, Babinski sign, hyperreflexia, and limb spasticity, etc.) Other neurological impairment(s)
Myelopathy	Ataxic gait, impaired upper limb coordination, poor or reduced finger movements, bladder and/or bowel control impairment (incontinence)	Hyperreflexia, ataxia, clonus, pathologic reflexes (Babinski, Hoffman) Other neurological impairment(s)

Adapted from van den Hoogen 95; Jarvik 02; Bigos 94.[160-162] , Silbert 95 (1517-22), Hurwitz 96 (1746-61), Grad 1989 (281-4), Szmirnai 2001 (68-71), Bruce 2001(688-93), Berger 99 (175-81), Snyder 93 (253-8), Zaki 93 (110-12), Forsyth 93 (1678-83), Hiroki 2003 (34-100), Hong 2003 (210-14)

B.3 Diagnosis

B.3.a Medical History and Physical Exam

As TBI clinical presentations are so varied, comprehensive medical histories and physical examinations are necessary to assess the patient's TBI. The diagnostic approach needs tailoring to the specific patient, particularly to factors such as the patient's exact mechanism of injury(ies), age, past medical history, underlying medical conditions and prior injury history.

A) A medical history encompassing a review of: • Current symptoms and health concerns • Setting and mechanism of injury • Severity/duration of altered consciousness and immediate symptoms • Presence of co-occurring injuries • Pre-existing medical and mental health conditions • Potentially contributing psychosocial factors
B) An examination including an assessment of: • Mental status and cognition • Physical status • Cranial nerves • Extremity tone, strength and reflexes • Gait and balance
C) An assessment of the patient's clinical status, including whether there has been improvement of deterioration since the time of injury. This may require additional information from others, including eyewitnesses to the injury.
D) Determination of the need for urgent neuroimaging to exclude a more severe brain injury, such as a structural abnormality or hemorrhage.

Adapted from the NSW Minstry of Health, Closed Head Injury in Adults – Initial Management (PD2012_013).

B.4 Imaging Studies

Imaging studies may support a diagnosis and are not indicated in all patients. Specific studies include:

B.4.a Skull X-Rays

Recommended – for the evaluation of TBI patients

Indications - Head trauma thought to be sufficiently forceful to potentially fracture the skull. Indicated as well for further evaluation of bony step-offs and other clinical signs of fracture.

Frequency/Dose/Duration - Generally only obtained at presentation. Occasionally re-xrayed at followup.

B.4.b Magnetic Resonance Imaging (MRI)

Recommended – for the evaluation of TBI patients.

Indications - Head trauma thought to be sufficiently forceful to potentially cause intracranial hemorrhage, epidural hemorrhage, subdural hemorrhage and/or other traumatic brain injury(ies). Subsequent or follow-up MRI studies may be indicated for evaluation of ongoing symptoms, or to assess a missed diagnosis, and/or resolution of prior defects.

Frequency/Dose/Duration - Generally only obtained at presentation. Sometimes obtained to evaluate ongoing symptoms to assess a missed or secondary diagnosis.

Rationale - MRI is superior to CT for assessing intracranial injuries, especially those without hemorrhage . MRIs are helpful in diagnosing surgical emergencies and evaluation of the extent of TBI injury(ies) and are thus recommended for evaluating TBI patients.

B.4.c Computed Tomography (CT)

Recommended – for the evaluation of TBI patients, generally in the emergency room setting to rule out significant anatomical defects

Indications - Head trauma thought to be sufficiently forceful to potentially cause cranial fracture, intracranial hemorrhage, epidural hemorrhage, subdural hemorrhage and/or other traumatic brain injury(ies).

Frequency/Dose/Duration - Generally only obtained at presentation or at the initial, comprehensive evaluation. MRI is generally preferred for subacute to chronic brain parenchymal evaluation, sometimes obtained to evaluate ongoing symptoms to assess a missed or secondary diagnosis.

Rationale - CT is particularly useful for unstable patients with potential need of surgical intervention. CT is not recommended for diagnosis and treatment planning of TBI.

B.4.d Vascular Imaging Tests

Recommended – for the evaluation of patients with TBI.

Indications - Symptoms and/or signs consistent with vascular injury.

Frequency/Dose/Duration - Usually only one assessment is needed.
Rationale - Vascular Imaging are selectively recommended for diagnosis of vascular injury associated with TBI.

B.5 Other Diagnostic Testing

B.5.a Electroencephalography (EEG)

Recommended – for the evaluation of seizure risk or seizure syndromes in patients with TBI

Indications - Evaluation of seizure-like activity in patients with TBI.

Frequency/Dose/Duration - Generally only one assessment. However, repeat EEG may be indicated in the context of continued seizure like activity, or after a postivie initial EEG, but in the absence of continued seizure activity.

Rationale – for diagnosis and management of seizures related to TBI.

B.6 Screening / Outcome Measures

B.6.a King-Devick (K-D)

Recommended - For those employees who might may have a reasonable possibility that they may sustain a head injury (for example, professional contact sports) this tool may provide a useful baseline, and point of reference for subsequent testing.

Indications –King-Devick (K-D) is performed as a sideline assessment, and has been used most often in contact sport athletes to enhance the detection of concussion in those with a known baseline measurement.

Frequency/Dose/Duration- Pre injury baseline evaluation Then measured after subsequent potential TBI event(s).

B.6.b Sport Concussion Assessment Tool (SCAT)

Recommended - For those employees who might may have a reasonable possibility that they may sustain a head injury (for example, professional contact sports) this tool may provide a useful baseline, and point of reference for subsequent testing.

Indications –SCAT is performed as a sideline assessmentat, and has been used most often in contact sport athletes to enhance the detection of concussion in those with a known baseline measurement.

Frequency/Dose/Duration - Pre injury baseline evaluation Then measured after subsequent potential TBI event(s).

B.7 Neuropsychological Assessment

Neuropsychology is a specialized branch of psychology that evaluates neurocognitive dysfunction. Neurocognitive dysfunction may be reflected in personality, intelligence, attention, executive function, reasoning, problem solving, information processing, and memory. Cognitive testing generally consists of a comprehensive evaluation of the patient's cognitive status by specific neurologic domains.

Neuropsychology occupies a prominent role in the evaluation and treatment of TBI patients, especially moderate and severe patients. In most cases, mild TBI resolves within a few days and thus there is little role for professional evaluation(s) and treatment(s) other than natural recovery. However, neuropsychology is also highly helpful in the evaluation of mild TBI patients with persistent symptoms beyond one month. Neuropsychology employs assessments that frequently consist of a thorough clinical and neuropsychological assessment of TBI and various types of tests and test batteries to identify abnormalities related to TBI. These tests typically undergo frequent revisions and the most up-to-date version of the tests should be administered. Normally, patients are given a battery of tests in numerous different domains including but not limited to intelligence, memory, executive function, speech, language, visual spatial to assess impacts of, and plan treatment of, TBI patients. It should also be noted that this review is not intended to be all inclusive. Additional tests may be performed as clinically indicated. Selection of specific testing domains is based upon clinical judgement on a case by case basis.

B.7.a Neuropsychological and Neurocognitive Assessment

Recommended - for the evaluation and treatment of TBI patients.

Indications - Moderate or Severe TBI patients experiencing cognitive difficulties. Mild TBI patients with ongoing symptoms are also candidates for neuropsychological assessments. May be performed to help guide treatment, oversee psychological and cognitive-related treatments and may later be performed as part of an evaluation for end-of-healing, clinical plateau and return to work.

Benefits - Identify and measure psychological, neuropsychological, social, behavioral and cognitive capabilities, potentially allowing better tailoring of therapy(ies) to address the specific deficit(s).

Frequency/Dose/Duration - Generally, a comprehensive assessment with a battery of tests is performed once or twice assessing numerous different domains including but not limited to , intelligence, memory, executive function, speech, language, visual spatial, processing speed, mood and personality. Ongoing focused assessments and treatments are then provided targeting deficits or functional issues identified in the assessment. May be used to target specific rehabilitation strategies and then later help determine the extent of residual deficits, if any.

B.8 Vision

Overview
TBI may create a constellation of vision, oculomotor, and related problems. Oculomotor problems are prominent with oculomotor-based reading difficulties as the most common symptom in patients with TBI. Additional visual symptoms in a TBI include, but are not limited to: eye-focusing problems; difficulty judging distances; diplopia; dizziness, vertigo, vision-derived nausea, increased sensitivity to visual motion, photosensitivity, visual inattention and distractibility and difficulty judging distances (relative and absolute).

A MD/DO or OD with appropriate training and experience in TBI related visual disturbances should provide a comprehensive vision evaluation, utilizing standard examination techniques and ancillary tests to establish a diagnosis of visual disorders associated with TBI and develop a treatment plan including rehabilitative interventions. Rehabilitative interventions may include vision therapy, reading spectacles, prism spectacles and/or tinted spectacles.

B.8.a Visual Acuity Testing

Recommended – in select patients.

Indications - Generally only an issue with severe TBI or concerns of TBI-related impact on vision.

Benefits - Identification of deficits in visual acuity.

Frequency/Dose/Duration - Generally one assessment. May be used a second time to detect improvement or resolution or upon referral to a specialist as clinically indicated.

Rationale - Visual Acuity Testing is the primary means to evaluate impairments in visual acuity and thus is recommended for the evaluation of TBI patients.

B.8.b Visual Evoked Potentials (VEP)

Recommended – in select patients to assess the visual sytem when other more common methods are not possible.

Indications - Severe TBI with inability to test visual system with more common methods, such as bedside testing, or Snellen testing.

Benefits - Ability to assess the visual system.

Frequency/Dose/Duration - May be used at baseline. If there are abnormalities and the injury continues to preclude other testing, then followup testing with visual evoked potentials is reasonable.

B.8.c Visual Field Testing

Recommended – in select patients.

Indications - Generally indicated with severe TBI or concerns of TBI-relatedimpact on visual fields, or reported viual field deficits.

Benefits - Identification of deficits in fields.

Frequency/Dose/Duration - Generally one assessment. May be used a second time to detect improvement or resolution.

B.8.d Visual PerceptionTesting

Recommended – selectively for severe TBI, or patients with TBI and visual symptoms.

Indications - Generally only indicated with severe TBI or concerns of significant impact on vision.

Benefits - Identification of deficits in the interpretation of visual inputs.

Frequency/Dose/Duration - Generally one assessment. May be used a second time to detect improvement or resolution.

B.8.e Fluorescein Angiography

Recommended – in select patients.

Indications – for the evaluation of of visual impairment associated with TBI where visualization of the retinal blood vessels is indicated

Frequency/Dose/Duration - Generally a one-time assessment.

B.9 Neuro-Otology: Vestibular and Audiological Evaluation

Vestibular and audiological dysfunction with symptoms that include hearing loss, dizziness, and balance problems are common in patients with TBI. Based upon the clinical evaluation, neurotologic evaluation and diagnostic testing for significant pathology may include audiometry, tympanometry, and vestibular function (ENG/VNG, rotary chair testing,) as clinically indicated. Some tests may need to be repeated to clarify the diagnosis and treatment plan.

B.9.a Audiometry

Recommended – for select patients with reported hearing loss, tinnitus or balance disturbance.

Indications - TBI with reduced hearing or tinnitus, especially but not solely if the mechanism of injury was a blast. There is a low threshold for

screening all TBI patients with audiometry. Identification and quantification of hearing deficits and to determine the presence and type (nonorganic, conductive, sensorineural, presbycusis, or mixed) of hearing loss based on the audiogram and other tests reasonably deemed necessary.

Potential to identify candidate for TBI-related hearing loss amenable to correction with hearing aids.

Frequency/Dose/Duration - Baseline measure. May need second assessment at end of healing.

B.9.b Tympanometry

Recommended - for select patients with hearing loss, tinnitus or balance disturbance.

Indications - Procedure that measures middle ear pressures and used to help identify the presence of tympanic membrane perforations, ossicular abnormalities or disruptions, and the presence of fluid in the middle ear as a result of head trauma.

B.9.c Brainstem Auditory Evoked Response

Recommended – in select patients.

Indications - Severe TBI with inability to test auditory system with more common methods, such as bedside testing, or audiometry.

Frequency/Dose/Duration - May be used at baseline. If there are abnormalities and the injury continues to preclude other testing, then followup testing with auditory evoked potentials is reasonable.

B.9.d Vestibular Function Testing

Vestibular function testing has been used to help define the severity, possible underlying causes, and possible outcomes of an individual's dizziness and/or balance disturbace.

B.9.d.i Rotary Chair Testing

Recommended – for select patients for the asssessment of vestibular impacts of TBI.

Indications - Rotary chair testing examines vestibular and oculomotor functioning (dizziness, balance issues) associated with TBI.

Frequency/Dose/Duration - Generally only assessed once.

B.9.d.ii Electro- or Video-Nystagmography (ENG/VNG)

Recommended – in select patients for the assessment of dysequilibrium and dizziness associated with TBI.

Indications –ENG/VNG measures inner ear/central balance function in patients needing further diagnostic evaluation of vestibular function. The test measures eye movement responses to inner ear balance stimulation making use of the vestibulo-ocular reflex and may be helpful in the assessment of balance problems (disequilibrium) and dizziness.

Frequency/Dose/Duration - Generally only assessed once.

Other testing

B.9.g Swallow Studies

Recommended – for select patients experiencing swallowing difficulities or other swallowing related symptoms.

Rationale - Swallowing impairment (dysphagia) is common in some severe TBI patients due to prolonged intubation or tracheostomy, the traumatic injury itself, medications or weakened swallowing muscles due to lack of use. These patients may require testing to determine swallow function, extent of dysfunction, and adequacy of airway protection. Although there are many different tests they all evaluate the ability of the patient to swallow. The threshold for evaluating swallow studies is low among those with prolonged intubation, tracheostomy, difficulty swallowing or signs of gagging or aspiration.

B.10 Surgical/Operative Procedures

Procedures are at the discretion of the physician based on clinical assessment/evaluation and clniical judgement.

B.11 Rehabilitation

B.11.a Occupational Therapy

Recommended – in select patients with TBI and associated functional deficits.

Indications - For patients with TBI and functional physical deficits.

Frequency/Dose/Duration – May be prescribed on a daily basis in the inpatient setting or two to three times per week in the outpatient setting.

Duration of supervised exercise is dependent on the severity of the deficits. Further therapy should be based on ongoing functional improvement with transition to a home based program.

B.11.b Physical Therapy

Recommended – in select patients with TBI and associated functional deficits.

Indications - For patients with TBI and functional physical deficits.

Frequency/Dose/Duration – May be prescribed on a daily basis in the inpatient setting or two to three times per week in the outpatient setting.

Duration - of supervised exercise is dependent on the severity of the deficits. Further therapy should be based on ongoing functional improvement with transition to a home based program.

B.11.c Strengthening Exercises

Recommended – for patients with TBI and associated functional deficits.

Indications - For patients with TBI and functional physical deficits.

Frequency/Dose/Duration – May be prescribed on a daily basis in the inpatient setting or two to three times per week in the outpatient setting.

Duration of supervised exercise is dependent on the severity of the deficits. Further therapy should be based on ongoing functional improvement with transition to a home based program.

B.11.d Stretching and Flexibility Exercises

Recommended - for use in the treatment of patients with TBI and associated functional defecits.

Indications - For patients with TBI and functional physical deficits.

Frequency/Dose/Duration – May be prescribed on a daily basis in the inpatient setting or two to three times per week in the outpatient setting.

Duration of supervised exercise is dependent on the severity of the deficits. Further therapy should be based on ongoing functional improvement with transition to a home based program.

B.11.e Aerobic Exercise

Recommended – in the treatment of select subacute, chronic and postoperative TBI patients

Indications - For patients whose TBI has resulted in a documented detioration in their physical conditioning due to TBI. and functional physical deficits

Frequency/Dose/Duration – May be prescribed on a daily basis in the inpatient setting or two to three times per week in the outpatient setting.

Gradual increase in exercise intensity will be based on patient tolerance. Duration of supervised exercise is dependent on the severity of the documented deconditioning. Further therapy should be based on ongoing improvement in exercise tolerance and functional improvement, with transition to a home based progam

B.11.f Manipulation for Chronic Cervicogenic Headache Pain

Recommended – for treatment of chonic cervicogenic headache pain associated with TBI.

Frequency/Dose/Duration - Once or twice a week for four to five up to eight total sessions.

B.11.g Aquatic Therapy

Recommended – as a trial for the treatment of subacute or chronic TBI in select patients.

Indications - When TBI impairments are sufficiently severe that removing effects of gravity improves ability to perform therapeutic activities, e.g., range of motion exercises. Land-based exercise is generally preferable for mild TBI or for patients largely recovered, as it tends to be more sustainable for most patients.

Frequency/Dose/Duration - Program should generally begin with three to four visits per week. Patient should have demonstrated evidence of functional improvement within the first two weeks to justify additional visits. Program should include up to four weeks of clinically supervised aquatic therapy with progression towards a land-based, self-directed physical activity or self-directed aquatic therapy program by six weeks. Durations beyond 6 weeks should be limited to severe TBI patient injuries who are still demonstrating objective improvements at six weeks that cannot be achieved with land-based activities.

B.11.h Biofeedback

Recommended – in the setting of post traumatic headache.

Not Recommended – in the treatment of TBI patients.

B.11.i Vestibular Rehabilitation

Recommended – selectively for patients with mild, moderate or severe TBI with vestibular dysfunction associated with dizziness, vertigo, visual blurring, oscillopsia (a jumping of the visual field associated with movement of the head), and feeling off balance.

Indications - Post TBI with vestibular symptoms to decrease sympotms and improve dynamic and static balance.

Frequency/Dose/Duration: Initially one to two times per week dependent on severity of symptoms, and progress with revaluation and documentation of continued improvement.

B.11.j Visual / Oculo Training

Recommended – for use in the treatment of TBI patients visual and visual-cognitive disorders.

Indications - TBI with any of the following: accommodation, blurred vision, ocular motility abnormalities, difficulty with gaze, tracking difficulties, diplopia, disequilibrium in visually stimulating environments, impaired visual memory, light sensitivity, visual-spatial processing and problems with visual field integrity.

Frequency/Dose/Duration - Dependent on severity of symptoms, and progress with revaluation and documentation of continued improvement.

B.11.k Oculomotor Training

Recommended – for the treatment of select TBI patients.

Indications - TBI with accommodative dysfunction of at least two to four weeks duration. Identification and treatment of accommodative dysfunction related to TBI.

Frequency/Dose/Duration - Two 60-minute sessions/week for nine sessions total; dependent on the continuation of symptoms.

B.11.l Neurocognitive Behavioral Therapies

Recommended – for use in the treatment of TBI patients with cognitive deficits.

Indications – Used to rehabilitate patients with moderate to severe TBI with cognitive deficits such as, difficulty with concentration, memory, and/or psychological and psychosocial functioning Rare mild TBI patients with ongoing and significant symptoms may be candidates.

Frequency/Dose/Duration - Frequency is generally tailored based on individual factors of severity and need. Ten to 16 treatments with

documentation of progress toward achievement of measurable goals every two weeks. Maximum Duration: 16 treatments. Therapy may need to be more frequent and of longer duration for patients with moderate to severe dysfunction.

B.11.m Memory Rehabilitation

Recommended – for use in the treatment of select TBI patients with memory retrieval deficits post TBI.

Indications - Memory problems post TBI. May be selectively indicated for mild TBI patients with significant memory deficits, with the goal to improve memory retrieval.

Frequency/Dose/Duration- Frequency is generally tailored based on individual factors of severity and need ten to 16 treatments with documentation of progress toward achievement of measurable goals every two weeks. Maximum Duration: 16 treatments. Therapy may need to be more frequent and of longer duration for patients with moderate to severe dysfunction.

B.11.n Acupuncture

Acupuncture has been used to treat some patients with TBI . It has be used to treat headache related symptoms, muscle spasticity, insomnia and cervical disorders. Cervical spine disorders are likely the most common indication for acupuncture among TBI patients.

Recommended – for select use in patients with chronic TBI for treatment of headache, muscle spasticity, insomnia and cervical disorders related to TBI.

Indications - As an adjunct treatment option for a limited course during which time there are clear objective and functional goals that are to be achieved.

Frequency/Dose/Duration: Usual program is ten sessions over three to four weeks. An initial trial of five to six appointments is recommended Additional treatment should be based upon improvement in objective functional measures to justify an additional six sessions, for a total of 12 sessions.

B.11.o Adaptive Devices

B.11.o.i Adaptive Devices, Casting and Orthotics

Recommended – selectively for treatment of TBI patients.

Indications - Impairment significant enough to require a device to position the extremity for function, e.g., sufficient foot drop that a device may foster better walking and avoid stumbling;

sufficient wrist drop that a device positions the extremity for better grasp. Manufactured devices typically suffice, but in some cases, custom-made orthotics and casts are required to accommodate specific circumstances or injury/patient-specific characteristics. Adaptive devices include but are not limited to ankle-foot orthotics, adaptive footware, upper and lower extremity braces, walkers, canes and rollators.

Note - Evaluation for orthotics should include evaluation of the footwear that is to be worn by the patient, including the nature of the fore-soles. Fronts of shoes and boots can catch on carpets and low-lying irregular surfaces, and modifications of shoes and boots may mitigate slip, trip, and fall risks posed by footwear.

B.11.p Body Weight Support Treadmill Training

Recommended – for use in the treatment of TBI patients who have an inability to walk safely.

Indications - Inability to walk, or inability to walk safely while having sufficient ability to move the lower extremities.

Frequency/Dose/Duration - The optimum regimen needs to be tailored to the patient's abilities and stage of recovery.

Indications for Discontinuation - Ability to walk with a walker, or to walk unassisted.

B.11.q Vocational Rehabilitation Programs

Recommended – for treatment of select patients with TBI.

Indications - Vocational rehabilitation programs may be helpful for those with mismatch between current abilities and job cognitive and physical demands, with a potential for greater impact in those with greater mismatch.

B.12 Behavioral Programs

B.12.a Behavioral Programs

Recommended – for use in the treatment of select patients with TBI.

Indications - TBI with behavioral issues, especially if not trending towards resolution.

Benefits - Improved awareness and function. Resolution of functional and impairing difficulties, especially those that may inhibit return to quality life and work.

Frequency/Dose/Duration - Social skills training program of 12 weekly three-hour group sessions with therapist plus one weekly individual session with clinical psychologist.

B.12.b Anger Management Therapy

Recommended – for treatment of select patients with TBI.

Indications -TBI patients with anger management needs, either as an underlying cause of the TBI or as a consequence of it.

Frequency/Dose/Duration – five to eight weekly individual therapy sessions.

Rationale - Recommended for treatment of select patients with TBI with anger issues as there is little else to manage these problems.

B.12.c Suicide Prevention

Recommended – for treatment of patients with TBI.

Indications - Patients with TBI and depression or depressive symptoms, with or without suicidal ideation.

Frequency/Dose/Duration - ten weekly two-hour sessions. Longer duration of treatment, or greater intensity/acuity of treatment, as may be clinically indicated.

Rationale - Recommended for treatment of selective patients with TBI and depression or depressive symptoms, with potential suicide risk, with or without suicidal ideation.

B.12.d Substance Abuse Counseling

Recommended – for use in the treatment of select patients with TBI.

Indications - Illicit substance(s) use, substance(s) abuse, substance(s) involved in TBI event, and/or problematic substance(s) use or overuse.

Evidence for the Use of Substance Abuse Counseling

B.13 Medications

Treatment of chronic post-traumatic deficits often involves the use of medication. Drug treatment requires clinical assessment, close monitoring of the patient's response to therapy, and ongoing revaluation of treatment. This includes lowering and/or discontinuing medications when symptoms improve and periodic trials of lowering medications when symptoms are stable.

Medications alone are unlikely to provide complete symptom relief. Non-pharmacologic interventions should be used in combination with pharmacologic treatments to minimize the amount of medication necessary in patients with TBI. A primary goal of pharmacologic therapies treatment is to improve the patient's function. Post-traumatic deficits require continuing participation in rehabilitative programs appropriate to and consistent with the level of recovery and techniques such as cognitive rehabilitation, cognitive behavioral therapy, and other individualized physical and psychological practices, as described elsewhere in this guideline.

If clinically indicated, prescription medications should be given an appropriate trial in order to test for therapeutic effect and tolerance of the medication. The length of an appropriate trial varies widely depending on the drug, as well as the individual and his/her response to the drug. Certain medications (e.g. antidepressants) may take several weeks to months to determine efficacy, while others (e.g. psychostimulants) may require only a few doses

Many of the drugs discussed in the medication section are FDA-approved for other indications but may appropriately be used for various aspects of TBI treatment and associated conditions. When prescribing off-label FDA use of a medication, indications, as well as clinical and functional goals should be clearly stated as part of a comprehensive, functionally-based treatment plan.

Patients who sustain a TBI are especially sensitive to central nervous system side effects, such as sedation, dizziness, cognitive impairment, and motor impairment. Usually, initial doses of medications may need to be lower than normal, and medication doses should be slowly titrated upward as cinically appropriate.

A detailed medication history is essential. Numerous medications have potential side effects that may aggravate TBI-related symptoms (or cause TBI-like symptoms) such as headaches, dizziness, vision orhearing changes, fatigue and other symptoms. For example, benzodiazepines, tricyclics and anticonvulsants can cause or aggravate dizziness. The temporal relationship to the onset of symptoms and the initiation/dosing of these medications should be evaluated.

B.13.a Headaches

Headaches are a common physical symptom occurring in individuals following TBI (mild, moderate, or severe). The most common patterns of posttraumatic headaches are: (i) tension-type headaches, including a cervicogenic component, and (ii) migraine headaches.

The normal recovery from posttraumatic headaches following mild TBI or concussion is usually rapid (hours to days) with most headaches resolving within three months. However, in some cases, headaches may last longer and are referred to as persistent posttraumatic headaches. Long-term maintenance plans are necessary in chronic headache management. Medications may be indicated for an indefinite period.

Characterization of the predominant clinical phenotype in posttraumatic headaches is critical to establishing appropriate pharmacologic and non-pharmacologic management strategies. Regardless of the treatment modality, pain treatment is more likely to be successful if the intervention starts at the onset of a headache rather than waiting for the headache pain to escalate.

Pharmacologic interventions may be appropriate for treatment of and/or prevention (prophylaxis) of headaches. In the acute phase of management of posttraumatic headaches, narcotic analgesics should be avoided, if possible. Also, special consideration is recommended for the assessment of medication-overuse headaches.

Non-pharmacologic management may include education on lifestyle modifications, PT, cervical manipulation, acupuncture and cognitive behavioral therapy (CBT).

Prophylactic Treatment
Patients who experience more than three tension headaches per week may benefit from prophylactic therapy designed to prevent tension headaches.

Interventions to reduce headache frequency should be considered when migraine headaches occur more than once a week, or are disabling despite aggressive acute interventions and compromise work attendance or daily life.

B.13.a.i Non-Steroidal Anti-Inflammatory Medications

Recommended - for treatment of headache, associated with TBI.

Administration of PPIs, H2 blockers and sucralfate along with these NSAIDS may reduce the risk of duodenal and gastric ulceration associated with NSAID use but do not impact possible cardiovascular complications.

NOTE: Headache may be made worse by chronic overuse of analgesics such as NSAIDs or acetaminophen (particularly daily) and may cause chronic daily headache, otherwise known as medication overuse or rebound headache or rebound. In most cases, headaches improve after an analgesic washout period

B.13.a.ii Acetaminophen

Recommended - for treatment of headache, associated with TBI, particularly in patients with contraindications for NSAIDs.

Dose/Frequency: Per manufacturer's recommendations; may be utilized on an as-needed basis. There is evidence of hepatic toxicity when exceeding four gm/day.

NOTE: Headache may be made worse by chronic overuse of analgesics such as NSAIDs or acetaminophen (particularly daily) and may cause chronic daily headache, otherwise known as medication overuse or rebound headache or rebound. In most cases, headaches improve after an analgesic washout period.

B.13.a.iii Topical Drug Delivery

Recommended - Topical drug delivery (e.g., capsaicin, topical NSAIDs (topical diclofenac) and topical salicylates (e.g., methyl salicylate)) for post TBI headache may be an acceptable form of treatment in select patients.

Indications: These agents may be used in those patients who may not tolerate oral medications or prefer topical treatments over oral medications.

B.13.a.iv Triptans and Ergot Alkaloids

Recommended – for post-TBI migraine headaches.

Indications - Post-TBI migraine headaches.

Frequency/Dose/Duration - Per manufacturer's recommendations.

B.13.a.v Anticonvulsant Medications

Recommended - Anticonvulsants for post-traumatic headaches.

Indications- Anticonvulsants including gabapentin, topiramate or divalproex for prophylactic treatment of posttraumatic tension and migraine headaches.

B.13.a.vi Antidepressants

Recommended – for prophylactic treatment of patients with post-traumatic headaches.

Indications - Antidepressants including tricyclic antidepressants for prophylactic treatment of post traumatic tension and migraine headaches.

B.13.a.vii Beta Blockers

Recommended - Propanolol for prophylactic treatment of post-TBI tension and migraine headaches.

Indication- Prophylactic treatment of post TBI tension and migraine headaches.

Frequency/Dose/Duration - Per manufacturer's recommendations.

B.13.a.viii Anti-Emetics

Recommended- For treatment of nausea/vomiting associated with post traumatic headaches.

B.13.a.ix Botulinum Toxin Injections: Chronic Migraine Headaches

Recommended - for selective use among individuals with chronic migraine headaches associated with TBI.

Indications - For treatment of chronic migraines associated with TBI. Generally not first line treatment. Botox treatment can significantly reduce migraine frequency, migraine severity and acute medication usage.

Frequency/Dose/Duration - Generally, injections will need to be repeated every three months. Target muscles, doses, and efficacy should be reevaluated on a regular basis.

AbobotulinumtoxinA, onabotulinumtoxinA, and incobotulinumtoxinA are among the more common formulations that may be considered.

B.13.b Medications (Conditions other than Headache)

B.13.b.i Non-Steroidal Anti-Inflammatory Medications

Recommended - for treatment of musculosketal pain and fever control associated with TBI.

Administration of PPIs, H2 blockers and sucralfate along with these NSAIDS may reduce the risk of duodenal and gastric ulceration associated with NSAID use but do ot impact possible cardiovascular complications.

B.13.b.ii Proton Pump Inhibitors (PPIs)

Recommended – for use with NSAIDs for select TBI patients.

Indications - NSAID use with risk factors for GI bleeding (e.g., elderly, diabetes mellitus, rheumatoid arthritis).

Benefits – May decrease risk of GI bleeding from NSAIDs.

B.13.b.iii H2 Blockers

Recommended - selectively for treatment of TBI patients.

Indications - NSAID use with risk factors for GI bleeding (e.g., elderly, diabetes mellitus, rheumatoid arthritis).

Benefits – May *decrease* risk of GI bleeding from NSAIDs. May reduce risk of stress ulcers.

Frequency/Dose/Duration - Dose and frequency for proton pump inhibitors, sucralfate, and H2 blockers are as recommended by manufacturer.

B.13.b.iv Sucralfate

Recommended – for treatment of TBI patients

Indications - NSAID use with risk factors for GI bleeding (e.g., past history of GI bleeding, elderly, diabetes mellitus, rheumatoid arthritis.

Benefits – May *decrease* risk of GI bleeding from NSAIDs.

Frequency/Dose/Duration - Dose and frequency for proton pump inhibitors, sucralfate, and H2 blockers are as recommended by manufacturer.

Evidence for the Use of Sucralfate

B.13.b.v Acetaminophen

Recommended - for treatment of musculosketal pain and fever control associated with TBI, particularly in patients with contraindications for NSAIDs.

Dose/Frequency: Per manufacturer's recommendations; may be utilized on an as-needed basis. There is evidence of hepatic toxicity when exceeding four gm/day.

B.13.b.vi Topical Drug Delivery

Recommended: Topical drug delivery (e.g., capsaicin, topical NSAIDs (topical diclofenac) and topical salicylates (e.g., methyl salicylate)) for post TBI musculosketal pain may be an acceptable form of treatment in select patients.

Indications: These agents may be used in those patients who may not tolerate oral medications or prefer topical treatments over oral medications.

B.13.b.vii Neurostimulants

Recommended – for select TBI patients with cognitive problems including arousal, initiation, memory, and attention problems associated with TBI.

Frequency/Dose/Duration - Medications typically used for this purpose include dopaminergic agents (amantadine, methylphenidate, bromocriptine, and carbidopa/levodopa), wake-promoting stimulants (modafinil), and acetylcholinesterase inhibitors (donepezil). Six weeks duration may initially be appropriate to start. Longer duration may be indicated for ongoing deficits, provided there are also ongoing cognitive improvements.

Evidence for the Use of Neurostimulants

B.13.b.viii Anti-Spasticity Agents

Recommended – for treatment of TBI patients with muscle spasticity and hypertonia associated with TBI.

Frequency/Dose/Duration – Oral medications typically used for this purpose include tizanidine, dantrium, baclofen. Per manufacturer's recommendations.

B.13.b.viii.a Inthrathecal Baclofen (ITB) Pump

Recommended – for highly selective use among TBI patients.

Indications - For treatment of severe, chronic muscle spasticity and dystonia associated with TBI that is unable to be sufficiently controlled through non-invasive means that included other pharmaceutical, including baclofen at 80-160mg/day. Also should have considered and tried at least one of: diazepam, clonidine and/or dantrolene. Should have severe hypertonia sufficient to interfere with activities of daily living.

Frequency/Dose/Duration - Generally at least two trials of saline and intrathecal dose of baclofen to confirm efficacy before

consideration of implantation of an intrathecal pump.

B.13.b.viii.b Botulinum Toxin Injections

Recommended – for selective use among individuals with chronic muscle spasticity or dystonia in patients with moderate-to-severe TBI.

Indications - For treatment of chronic muscle spasticity, dystonia, associated with TBI. Botulinum toxin injections may be indicated if the patient cannot tolerate oral pharmaceutical agents, if poor arousal precludes the use of oral agents, or if the spasticity or dystonia is focal in nature and would benefit from a targeted treatment protocol.

Frequency/Dose/Duration - Generally, injections will need to be repeated every three months. Target muscles, doses, and efficacy should be reevaluated on a regular basis. AbobotulinumtoxinA, onabotulinumtoxinA, and incobotulinumtoxinA are among the more common formulations that may be considered.

B.13.b.ix Antiseizure/Anticonvulsant

Posttraumatic seizures are a frequent complication accompanying traumatic brain injuries.

Antiseizure prophylactic medications have been administered following TBI.

Recommended - Prophylactic antiseizure medications are generally recommended during the seven days after a moderate to severe TBI associated with cerebral contusion or intracranial bleeding to prevent early seizures.

Recommended – in the treatment of post TBI seizures to both treat and prevent the progression of the initial seizure, as well as to reduce the risk of subsequent seizures after an initial post TBI seizure has occurred

B.13.b.x Antidepressants

Recommended – for treatment of TBI patients with depressive symptoms or depression.

Indications - For the treatment of depression in TBI patients.

Evidence for the Use of Antidepressants

B.13.b.xi Atypical Antipsychotics

Recommended – for adjunctive treatment of acute major depression (aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine, risperidone, or ziprasidone). These may be effective for maintenance treatment.

Recommended- for treatment post TBI mood and or behavioral disturbance.

Recommended for augmentation of antidepressants in treating MDD associated with TBI.

Recommended - in select patients with psychosis associated with TBI.

Indications - Treatment of depressive disorders with psychotic characteristics including:

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 affect of a bizarre or odd quality
8. Severe symptoms

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

B.13.b.xii Benzodiazepines

Recommended – for treatment of TBI patients with indications for anxiety disorders including panic attacks secondary to TBI.

Recommended- for treatment of TBI patients with post-traumatic movement disorders.

Recommended- for treatment of TBI patients with post traumatic epilepsy.

Indications - Uses include discrete issues with anxiety, panic attacks, agitation and insomnia.

Note - As benzodiazepines impair memory and cognitive recovery, those TBI patients requiring a course of benzodiazepines after TBI should be tapered as soon as practical.

Evidence for the Use of Benzodiazepines

B.13.b.xiii Corticosteroids

Not Recommended – for treatment of TBI.

B.13.b.xiv Excitatory Amino Acid Inhibitors

Not Recommended – for treatment of TBI.

B.13.b.xv Sedatives, Sedative Hypnotics

Not Recommended – for treatment of TBI patients.

Evidence for the Use of Sedatives, Sedative Hypnotics, Analgesics and Narcotics

B.13.b.xvi Beta Blockers

Recommended – for treatment of TBI patients.

Recommended - for management of tachycardia in TBI patients.

Recommended – may be used as an option for hypertensive management.

Recommended - may also be used to treat paroxysmal sympathetic hyperactivity or agitation.

Frequency/Dose/Duration - Per manufacturer's recommendations.

Evidence for the Use of Beta Blockers

B.13.b.xvii Aminosteroids

Not Recommended – for treatment of TBI patients.

Evidence for the Use of Aminosteroids

Neuroendocrine Complications

Neuroendocrine abnormalities following TBI are common. Hypopituitarism is a common complication. Approximately one-third of patients with TBI have persistent anterior pituitary disorders. These potential TBI pituitary endrocrine complications may include but are not limited to abnormalities of thyroid function, antidiuretic hormone, ACTH-cortisol levels and glucose metabolism which may require specialized medical evaluation and treatment.

B.13.b.xviii Deamino Arginine Vasopressin (Desmopressin)

Recommended – for diabetes insipidus associated with TBI.

Indications - Desmopressin is recommended for treatment of diabetes insipidus.

Frequency/Dose/Duration - Per manufacturer's recommendation.

B.13.b.xix Levothyroxine

Recommended - for hypothyroidism associated with TBI

Indications - for treatment of hypothyroidism with referral to an endocrinologist, or clinician with appropriate training and experience as clinically indicated.

Frequency/Dose/Duration **-** *determined based on patient clinical factors.*

B.13.b.xx Growth Hormone (subcutaneous injection)

Recommended - for growth hormone deficiency associated with TBI.

Indications - for treatment of growth hormone deficiency with referral to an endocrinologist, or clinician with appropriate training and experience as clinically indicated.

Frequency/Dose/Duration **-** determined based on patient clinical factors.

B.13.b.xxi Hydrocortisone

Recommended - for adrenal insufficiency associated with TBI.

Indications - for treatment of adrenal insufficiency with referral to an endocrinologist, or clinician with appropriate training and experience as clinically indicated.

Frequency/Dose/Duration **-** *determined based on patient clinical factors.*

B.13.b.xxii Testosterone Supplementation

Recommended - for testosterone deficiency associated with TBI.

Indications - for treatment of testosterone deficiency with referral to an endocrinologist, or clinician with appropriate training and experience as clinically indicated.

Frequency/Dose/Duration **-** determined based on patient clinical factors.

B.14 Injection Therapy

B.14.a Radiofrequency Neurotomy for Cervicogenic Headache

Recommended – select patients exhibiting temporary benefit following three occipital nerve blocks with fluoroscopic guidance.

Recommended – for select patients with a positive diagnostic block. To be considered positive the patient should report a reduction of pain of 50% or greater from baseline for the length of time appropriate for the local anesthetic used, correlated with functional improvement.

The patient should also identify activities of daily living that are impeded by their pain. The physician should observe and document functional improvement in the identified activities in the clinical setting.

Frequency: Twice a year as indicated by improvement in pain and function. Successful neurotomy (rhizotomy) usually provides from six to nine months of relief.

B.14.b Occipital Nerve Blocks

Recommended – in select patients for cervicogenic and migraine headache secondary to TBI.

Indications -Unilateral cervicogenic headaches, with headache precipitated by neck movement or pressure over the greater occipital nerve, reduced neck range of motion. Post-traumatic migraine headaches are another potential indication. Headaches should be resistant to other forms of treatment (e.g. NSAID, acetaminophen, stress reduction, exercise etc.).

Benefits - Potential for reduced headache intensity, frequency and duration. Potential for reductions in use of other medications.

Frequency/Dose/Duration - Optimal duration of one to three sessions.

Time to Produce Effect - Approximately 30 minutes for local anesthetic; 48 to 72 hours for corticosteroid.

Patients should be reassessed after each injection for a documented 50% improvement in pain.

Evidence for the Use of Occipital Nerve Blocks

Appendix A: Evidence Tables

Evidence for the Use of Skull X-Rays

Author Year Score:	*Category:*	*Study type:*	*Conflict of Interest:*	*Number:*	*Age/Sex*	*Area of Head:*	*Diagnoses:*	*Type of X-rays:*	*CT Used:*	*MRI used:*	*More than an one rater:*	*Blinding of rater:*	*Myelography:*	*Surgery Performed:*	*Clinical Outcomes Asessed:*	*Long-term Follow-up (mean when noted):*	*Results:*	*Conclusion:*	*Comments:*
McGlinchey, 1998 (5.0)	Skull X-Ray	Diagnostic	No mention of COI.	N=50	No mention of age or gender.	Skull	Traumatic Brain Injury	Radiography	-	-	+	-	-	-	-	-	Two film and three film series were utilized and a 94.4% confidence level for 2 films and 94.6% for 3 series. Of the 150 skull fracture series viewed as 2 films, 87 wer correctly diagnosed with a	"A two-view skull series has no statistically deleterious effect on either diagnostic accuracy or confidence of interpretation when compared with a three-view series given an accurate clinical history. A two-view skull series can safely be adopted in the routine assessment of head injury given dependency on site of trauma. It should be stress	Data suggest comparable results with no benefit of using a three-view skull series over two-view series.

																	confidence level of 92.7%. When viewed as 3 films, 92 were correctly diagnosed with a confidence level of 93%. No statistical difference was observed with 2 or 3 film series.	that such a policy does not preclude a more extensive skull series given an unreliable history, severe trauma or suspicious findings on the initial films."	

Evidence for the Use of Computed Tomography (CT)

Author or Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Area of Body:*	*Diagnoses:*	*Type of CT used:*	*Surgery Performed:*	*Clinical Outcomes Assessed:*	*Results:*	*Conclusion:*	*Comments:*
Orrison 1994 (6.5)	CT	Diagnostic	No mention of COI.	N= 107	No gender or age distribution mentioned	Brain	emergency room-referred head trauma patients, between May 15, 1988 and June 30, 1989	high-resolution CT system (9800 Quick, General Electric, Milwaukee, Wis) Vs 0.064-T permanent magnet (MTP Access, Toshiba America MRI, South San Francisco, Calif) All participants underwent both imaging	None	CT - conventional gantry angulation, section thickness (3 to 10 mm), radiographic techniques, and contrast enhancement (when clinically indicated) MR - T1-weighted spin-echo sequence (400-600/20-40/2-4 [repetition time/echo time/excitations]) or a gradient-echo sequence (68/24/3) with a flip angle of 60°, and more T2-weighted spin-echo images (1500-2500/30-105 /2)	MR sensitivity was significantly higher than CT for detecting contusions ($p < 0.001$), subdural and epidural hematoma ($p < 0.001$), shearing white matter injury ($p < 0.001$), and sinus involvement ($p < 0.001$). CT sensitivity was signficiantly higher than MR in detecting fracture ($p < 0.001$). Both scans did not differ significantly for detecting superficial	"CT and MR are complementary studies in the evaluation of acute head trauma. MR is necessary to define or exclude contusions, deep shearing injury, and extraaxial fluid collections in acute head trauma."	Data suggest CT and MRI are good imaging tools for assessing acute head injuries. MRI is able to exclude contusions, shearing injuries and detect extra-axial fluid collection.

								processes			soft tissue injury. MR sensitivity overall for detecting abnormalities was 96.4%. CT sensitivity was 63.4%.		
Raj 2014 (5.0)	CT	Diagnostic	No COI. Supported by Finska Läkaresällskapet, the Maire Taponen Foundation, and a Helsinki University Hospital	N= 869	No gender distribution was described Mean age overall 57 years (ranges from 43 – 68)	Brain	Moderate to severe TBI (GCS score 3-13) and complicated mild TBI (GCS scoare 13-15)	Marshall CT classification, Rotterdam CT score, Helsinki CT score	None	mass lesion type, size, presence, location, thickness of traumatic subarachnoid hemorrhage (tSAH), presence of intraventricular hemorrhage (IVH), status of suprasellar cisterns, status of ambiens cisterns, status of fourth ventricle, midline shift, and cortical sulcus effacement	The Helsinki CT score was better than the Marshall and Rotterdam CT scores (AUC, 0.74-0.75 vs 0.63-0.70; P<.001). Using the Helsinki score increased the prognostic result of the clinical model (AUC neurological outcome + 0.02, p=0.002, AUC mortality +0.01, p=0.21). The Marshall and Rotterdam scores did	"The use of the Helsinki CT score significantly improved outcome prediction accuracy, and the Helsinki CT score is a feasible alternative to previous CT scoring systems. The Rotterdam and Marshall CT systems were of modest value in predicting long-term outcome in this large sample of patients with mild complicated, moderate, and severe TBI. External validation of the Helsinki CT score in independent data sets is advocated to	Data suggest Helsinki CT score helped improve the accuracy of the outcome of the outcome predictions at 6 months post TBI.

											not provide an improved predictive value to the model (p > 0.05).	show generalizability."	
Williams MW 2013 (5.0)	CT	Observational Study	Supported by Wayne State University Graduate School, National Institute of General Medicine - Initiative for Maximizing Student Development, and the National Institute on Disability & Rehabilitation Research – Traumatic Brain Injury Model Systems Project (H133A080044).	N= 288	60 females, 228 males Mean age 38.1 years (ranging from 16 – 86)	Brain	mild complicated, moderate or severe traumatic brain injury	CT scan including the Marshall classification	None	Glasgow Coma Scale, midline shift > 5 mm, presence or absence of additional indices (intracranial hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, punctate/petechial hemorrhage, and intraparenchymal fragments), Neuropsychological Battery scale, Disability Rating Scale, Satisfaction with Life Scale	The use of CT characteristics and neuropsychological tests did not improve prediction of life satisfaction. These variables did help improve prediction of return to work at 2 years post injury. Neuropsychological tests added to outcome predictions of functional disability. CT characteristics did not improve prediction of long-term functional disability.	"This study adds to the body of literature supporting the unique value of inpatient neuropsychological evaluations in making long-term functional outcome predictions for individuals with traumatic brain injury."	Data suggest the addition of neuropsychological tests to CT results provides additional information for long term outcome prediction.
Bosco	CT	Diagnostic	No COI.	N= 81	22 female	Brain	Those admitte	CT scans of six	None	Glasgow Coma Scale,	The final model	"A spatial mapping of all	Data suggest that

2014 (4.5)					s, 59 males Mean age 26 ± 14 years		d to intensive care unit after severe head injury, with GCS score ≤ 8	regions of interest: frontobasal (f), central (c), parietal (p), temporal (t), occipital (o), subcortical (sc), and mesencephalic (mc)		encephalography within first six days after injury, intracranial mass lesions, neurophysiological investigation using electric stimulation of median nerve (at the wrist for 0.2 ms)	created for predicting the outcome of a TBI patient included the somatosensory-evoked potentials (SEPs) primary complex (pN20/fP20/cP22), SEPs middle latency (N30/P45/N60), and CT scan hypodensity values. These variables combined showed a significantly improved predictive power of the Glasgow Outcome Scale ratings when compared to just using pN20 alone ($p<0.0001$).	early SEPs components on frontocentral-parietal areas of both major-lesion and minor-lesion hemispheres allows a detailed analysis of outcome prediction and a better prognostic evaluation than using the N20-P25 cortical component alone.	the addition of early cortical somatosensory- evoked potentials (SEPs) components provide statistically enhanced outcome prediction in acute TBI.
Wardlaw JM 2002 (4.0)	CT	Prospective Observational Study	Supported by the UK Medical Research Council	N= 1,131	No gender distribution describ	Brain	Those with THI, all grades of THI,	Evaluate which features on the admissio	None	Size of lesions (extradural haematoma, subdural	Age, Glasgow coma score (GCS), pupil reaction,	"Age, GCS, and pupil reaction were all previously shown to be significant	Data suggest multiple variables may be

			and the Clinical Research Initiative in Clinical Neurosciences		ed other than a 3:1 ratio Mean age for all 37 years		admitted to neurosurgical center from January 1, 1989 to July 16, 1996	n CT scan might add significantly to other baseline clinical information for predicting survival in patients with head injury.		haematoma, subarachnoid haemorrhage, parenchymal contusions, white matter lesions, basal ganglia; presence of depressed fracture or intracranial air, of amount of any midline shift, of compressed, dilated, or normal ventricles and basal cisterns	presence of subarachnoid blood, and the simple grading of the overall appearance of the scan (all p<0.001).	predictors of patient survival after head injury. A further two, easy to identify, CT scan variables are independent prognostic variables, and might help to identify patients at high risk of death at the time of admission."	significant for predicting post head injury survival.
Marshall LF 1991 (4.0)	CT	Prospective Observational Study	Supported by National Institute of Neurological Disorders and Stroke Contracts (Pilot Traumatic Coma Data Bank)	N= 746	No gender or age distribution described	Brain	Severe traumatic brain injury	Not specified	None	the status of the mesencephalic cisterns, the degree of midline shift in millimeters, and the presence or absence of one or more surgical masses	CT diagnosis was a highly significant independent predictor of mortality (p = 0.0001) when age and motor score were included in the model; when CT diagnosis was not included, the fit was poor (p = 0.041).	This more accurate categorization of diffuse head injury, based primarily on the result of the initial CT scan, permits specific subsets of patients to be targeted for specific types of therapy. Patients who would appear to be at low risk based on a clinical examination, but who are known from the CT scan	Data suggest this is a more accurate classification system for categorizing head injury and helps guide therapy.

												diagnosis to be at high risk, can now be identified.	
Petroni G 2010 (NA)	CT	Prognostic Study	No COI. Supported by U.S. Department of Education, National Institute on Disability and Rehabilitation Research, Fogarty International Center of the National Institutes of Health, and National Institute of Neurological Disorders and Stroke and Fogarty International Center of the NIH	N= 148	28 females, 120 males Mean age 34 years (ranging from 14 – 77 years)	Brain	create an accurate and reliable instrument for predicting outcome from TBI that physicians in Argentina, and perhaps other middle- and low-income countries, can use to make treatment decisions, guide prognosis discussions with patients and families, and conduct	Within 24 hours, type not specified	None	Globally: presence or absence of abnormalities, specifically: presence or absence of compression of basal cisterns, midline shift (> 5 mm), extradural hematoma, subdural hematoma, contusion, and traumatic subarachnoid hemorrhage (TSAH)	More than 58% of the patients died, 33.8% within the first 24 hours and 19.6% during acute care.	This study provides rigorous, prospective data that [170] validates the generalizability of the five World Health Organization/Organization Mondiale de la Sante´ TBI prognostic predictors outside of the developed world, and (2) provides outcome benchmarks for mortality and morbidity from severe TBI in developing countries.	Prognostic Study validating benchmarks for morbidity and mortality outcome predictors in developing countries.

							research.						
Thomas BW 2009 (NA)	CT	Prognostic Study	No COI.	N= 887	266 females, 621 males Mean age 42 ± 20.8 years	Brain	mild (GCS 13-15), moderate (GCS 9-12), or severe (GCS 3-8) TBI	Scheduled repeat brain CT (SRBCT)	None	Injury Severity Score (ISS), history of vascular disease and anticoagulant/antiplatelet use, prothrombin and international normalized ratio at admission, hours from IBCT to SRBCT, admitting Glasgow Coma Scale (GCS), total number of CT scans during hospitalization, type of brain injury (subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, or mixed bleed)	692 (78%) patients had no worse SRBCT and neurological changes later developed in 11 (1.6%) patients	"A worse SRBCT is more likely to result in neurologic intervention. SRBCT remains useful in assessing patients with TBI."	Prognostic Study suggesting that a worse SRBCT is associated with longer hospitalization, higher mortality and probably will result in extended medical and surgical interventions.

Evidence for the Use of Magnetic Resonance Imaging (MRI)

Author Year (Score):	Category:	Study type:	Sample size:	Age/Sex:	Sponsorship/ COI:	Area of Body:	Diagnoses:	Type of MRI used:	Type of CT used:	T1 Weighted	T2 weighted	X-ray:	Myelography:	More than	Surgery	Clinical	Long term follow-up:	Results:	Conclusion:	Comments:
Yuh 2013 (7.0)	MRI	Prospective Study	N=135	97 males, 38 females; Mean age 40 ± 17.	Supported by the National Institutes of Health grants. No COI.	No specific planes/regions mentioned.	Patients with mild traumatic brain injury.	Yes	No specification	No	No	No	No	No	No	Yes	12 ± 3.9 days	MRI identified many more acute traumatic intracranial lesions than CT. 64/135 vs 37/135 abnormalities.	"We show for the first time that traumatic intracranial findings on conventional CT and MRI account for a significant portion of the variability in outcome in MTBI. Routine performance of brain MRI on MTBI patients may not currently be cost-effective."	Data suggest MRI identified more traumatic intracranial findings than did CT to predict 3 month outcomes post mild TBI.
Lagares 2009 (6.5)	MRI	Prospective	N=100	83 males, 17 females;	Study was supported by a grant	Frontal unilateral, bifrontal, temporal, bitemporal	Traumatic brain injury		No	Yes	Yes	No	No	No	No	Yes	6 months	MRI findings located frontal unilateral	"The anatomical substrate of TBI	Data suggest MRI added benefit

				Mean age of 33 (15-71)	from the Fundacion Mutua Madrilena.													in 23%, bifrontal 41%, temporal 14%, bitemporal 8%.	depicted by MR could be a useful prognostic tool in patients suffering moderate and severe head injury."	to aid in prognosis of moderate to severe TBI patients with a GCS of 4 or less.
Gentry 1988 (6.5)	MRI	Prospective	N = 40	32 males, 8 femals; Mean age of 26.6 years.	No mention of sponsorship or COI.	Axial Coronal	Acute closed-head trauma	0.5 Tesla cryogenic system	Picker 600/1200 scanner	Yes	Yes	No	No	No	No	Yes	No	For diffuse axonal injury, CT only detected 19% of lesions. T1-weighted MR was also more sensitive (72.3%), but less sensitive than T2-weighted MR (92.4%).For cortical contusion CT detected 15.4%, T1-weighted MR 58.3%, and T2-weighted MR 95%.	"In summary, MR has significant advantages over CT in evaluating patients with closed head trauma."	Data suggest MRI and CT are comparable for the detection of hemorrhagic lesions but MRI better for detecting non hemorrhagic lesions but CT is best for assessment of unstable TBI patients possibly requiring surgery.

																		For hemorrhagic sensitivity was similar across all imaging methods.		
Kara 2008 (6.0)	MRI	Prospective	N = 124	76 males, 48 females; male mean age 61 (15-40), female age 63 (41-70).	No mention of sponsorship or COI.	Coronal, axial, sagittal planes	Severe head trauma with neurological deficits despite normal CT scans.	1.5 Tesla	Yes	No	No	No	Yes	No	No	Yes	6 months	Detection of contusional lesions on both T1 (92.6%) and T2 (96.3%) weighted slices. Most corpus callosum were in the temporal region (50.3%), frontal (29%), and parietooccipital (14.5%).	"This study supports the importance of MRI in detecting acute and subacute hemorrhagic and nonhemorrhagic lesions, infarcts and brainstem injuries in severe CCI."	Data suggest MRI can detect subtle lesions which go undetected in CT but correlate with neuropsychological condition which may have prognostic benefit.
Moen 2012 (5.5)	MRI	Longitudinal	N = 58	43 males, 15 females; Mean age 33.4 (11.4-63.4)	KGM and TS have, during the study period, received a research grant from the liaison	Hemispheres, corpus callosum, brainstem, thalamus/BG/cerebellum	Moderate to severe traumatic brain injury	1.5 Tesla	No	Yes	Yes	No	No	No	No	Yes	1 year	Only 60% of patients with traumatic axonal injury (TAI) stage 3 in early MRI had brainste	"The most important finding was that non-haemorrhagic TAI lesions depicted in FLAIR sequence	Data suggest early MRI predict clinical outcome as later MRI shows less lesions such that

					committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU). No COI.													m lesions at 3-months post injury. Diffusion sequences had fewer lesions than the T2*GRE and T2 fluid attenuated inversion recovery (FLAIR) sequences.	s, including brainstem lesions, often disappeared during the first 3 months."	prognosis is likely related to early MRI results.
Lui 2014 (5.5)	MRI	Prospective Study	N=23	17 males, 6 females; Mean age of 33.65 ± 11.21.	Supported in part by grants from the National Institute of Health. No COI.	Thalamus, Frontal lobe.	Mild Traumatic Brain Injury.	3.0 Trio MRI	None	No	No	No	No	No	No	No	Yes	23 days	Best classifiers for MTBI diagnosis included the mean kurtosis of the Thalamus which had a 74% accuracy. All features which had an 80% accuracy. And minimal-redundancy maximal-relevance	"This work serves as a pilot study showing that a combination of features including MRI metrics can classify patients with mTBI and controls with 86% accuracy, up from 74% for the best single feature	Pilot study. Data suggest a combination of tools including MRI and classification metrics can accurately classify mild TBI patients. 86% accuracy which is better than any single tool.

																		(mRMR) of 86%.	alone. Furthermore, mRMR feature selection optimizes this process by selecting relevant and no redundant features. ”	
Huisman 2003 (5.5)	MRI	Retrospective	N = 25	19 males, 6 females; Mean age 31 ± 10.	No mention of sponsorship or COI.	Corticomedullary junction, central white matter, corpus callosum, brainstem, interior/exterior capsula.	Acute closed head injury	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	No follow up reported.	MRI within 48 hours with 427 shear injury lesions were seen in 25 patients. Diffusion-weighted imaging (DWI) missed 117 or 427 lesions that were seen on T2/fluid-attenuated inversion recovery (FLAIR) or gradient echo (GRE).	“DWI yields additional information in closed head injury and could represent a valuable tool in the depiction of DAI.”	Data suggest DWI is beneficial in visualizing shearing injuries not seen with T2/FLAIR or T2* sequences but DWI is less sensitive than T2* for imaging hemorrhagic lesions.

Geurts 2012 (5.5)	MRI	Retrospective	N=56	33 males, 23 females; Median age & range 31 (12-78).	No sponsorship or COI.	Frontal, temporal, parietal or occipital lobar grey and/or white matter, corpus callosum, subcortical, cerebellum, brain stem.	Traumatic Brain Injury	3 T MRI	None	No	Yes	No	No	No	No	Yes	7 weeks	Post-hoc Wilcoxon signed rank tests with Bonferroni correction (p<0.008) revealed that with SWI (Susceptibility Weighted images) more lesions were detected compared to T2*-GRE (T2-gradient recalled echo) (p<0.001), FLAIR (Fluid Attenuated Inversion Recovery) (p<0.001) and T2WI (T2-Weighted Imaging) (p<0.001). In turn, T2*-GRE showed more	"Susceptibility Weighted Imaging is the most sensitive sequence in the detection of small haemorrhagic lesions."	Data suggest significant inter-rater reliability disagreement in the interpretation of TBI lesions. T2-GRE and SWI show better sensitivity than T2WI and FLAIR in the detection of hemorrhagic lesions from trauma.

																		lesions than T2WI (p<0.001) and FLAIR (p<0.001).		
Snow 1986 (5.0)	MRI	Prospective, case studies	N = 35	No mention of mean age or all genders.	No mention of sponsorship or COI.	None specified.	Head trauma	0.5 Tesla	8800	Yes	Yes	No	No	No	No	Yes	No	21 cases had intracerebral lesions. 7 patients with head trauma had normal findings on CT and MRI scans. After 72 hours MRI was found to be superior to CT in the detection of intra- and extracerebral traumatic lesions.	"[I]f CT is negative or the abnormalities identified on CT are insufficient to explain the clinical condition of the patient, MRI should be performe."	Data suggest MRI superior to CT for visualization of non-hemorrhages continuous CT superior in diagnosing SAH or acute parenchymal bleeds.
Wilson 1988 (4.5)	MRI	Retrospective/Prospective	N = 25	Distributions of age: 16-30 (N=10) 31-45 (N=4)	Research was supports by the Medical Research Council.	Head	Closed head injury	0.15 Tesla, 6.38 MHz	EMI 1010	Yes	Yes	No	No	No	No	Yes	11 months	Neuropsychological tests were associated with neuroimaging abnormal	"[C]ontrasts should be sought between primary shearing injuries	Data suggest classifications of early and late MRI were strongly correlate

				46-60 (N=5) 61-73 (N=6)/ 18 Males 7 Females														ities than others. The depth of lesion detected by MRI was correlated with psychological impairment. Late MRI was significantly associated with outcomes on neuropsychological tests (p<0.001).	and secondary ischemic damage, and we consider that serial MRI investigations of Head injured patients are a priority for future research. ”	d. Neurological outcomes were strongly correlated with late MRI and had minor correlation or no correlation with early MRI or early CT suggesting outcomes relate to lesions seen on late MRI.
Hughes 2004 (4.5)	MRI	Longitudinal study	N = 80	59 males, 21 females; Mean age of 31.	No mention of sponsorship or COI.	Head	Mild traumatic brain injury	1.0 Tesla		Yes	Yes	No	No	No	No	Yes	2 years	Initial MRI showed abnormalities in 26/80 patients. 2/26 had findings definitely related to traumatic injury. MRI showed non-specific abnormalities in patients	“We have demonstrated using routine MRI techniques that non-specific abnormalities are common in a group of patients with MTBI.”	Data suggest non-specific abnormalities are common in mild TBI patients as seen on MRI. Abnormal MRI did not predict a poor outcome.

																		with mild traumatic brain injury. However, abnormal MRI did not predict poor long-term outcome.		
Wilberger 1987 (4.5)	MRI	Diagnostic/case study	N=24	No mention of Gender; Mean age of 28.	No mention of sponsorship or COI.	All different planes without patient movement.	Severely head injured patients	0.35 & 0.5 T super conducting magnet	Siemens DR3 scanner	Yes	Yes	No	No	No	No	Yes	3 days	MRI demonstrated lesions that were not seen on CT. There were a total of 10 contusions, 5 brain stem injuries, 5 diffused white matter injuries, and 4 subdural hematomas. White matter injuries were seen on either T2 or T1 images. Brain stem injuries	"MRI is anatomically sensitive and pathologically specific in patients with severe head injuries. Suspected white matter shear injuries or contusions, brain stem injuries, diffuse white matter injuries, and subdural hematomas can all be demonst	Data suggest MRI is more sensitive in imaging severe head injury in lieu of a normal CT and normal ICP.

																		were best seen using T2 weighted images.	rated by MRI."	
Ingebrigtsen 1999 (4.5)	MRI	Prospective	N = 50	29 males, 21 females; Mean age of 33 (10-72).	The study was supported by The Lærdal Foundation for Acute Medicine, the Norwegian Research Council, and the Skane County Council's Research and Development Foundation.	Transverse plane of whole brain.	Traumatic Brain Injury	0.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	3 months	CT scans within 12 hours, MRI within 48 hours. 14 (28%) had detectable serum levels S-100 protein. Detectable limits were associated with MRI finding of brain contusion and related to cranial fracture. 8/14 had normal MRI despite detectable serum levels.	"Detectable serum levels are related to a brain contusion revealed by MRI and impaired neuropsychological functioning on measures of attention, memory, and information processing speed."	Data suggests that the presence of serum S-100 protein correlated to diminished attention memory and the speed of information processing.
Giugni 2005 (4.5)	MRI	Prospective	N = 21	19 males, 2 females; Mean age 26.8	No mention of sponsorship or COI.	Whole brain, frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal	Severe traumatic injury and suspected diffus	1.5 Tesla	No	Yes	Yes	No	Yes	No	No	Yes	No	Turbo proton echo-planar spectroscopic imaging (t-PEPSI) and	"Substantial benefits may be gained from rapid T2*-	Relatively small sample. Data suggest comparable efficacy for

				(18-40).		ganglia, corpus callosum, periventricular, infratentorial	e axonal injury (DAI).											gradient-recalled echo (GRE) were used to increase sensitivity. GRE was superior to t-PEPSI in depicting DAI lesions in the temporal lobe (74 vs. 37; p<0.004). In the other regions the sequences had similar sensitivities.	weighted MR imaging in patients with severe TBI."	detection of diffuse axonal damage in severe TBI patients between GRE and t-PEPSI.
Huang 2015 (4.5)	MRI	Prospective Controlled Trial	N=222 (111 w/ TBI)	TBI Group: 43 males, 68 females; Mean age 37.14 ± 12.76. Control Group:46 males,	No sponsorship or COI.	Transverse plane of whole brain.	Mild Traumatic Brain injury	3 T MR Scanner	Yes, unknown.	Yes	Yes	No	No	No	No	Yes	24.76 days	36/11 in TBI group showed micro bleeds using Susceptibility Weighted Angiography (SWAN) and 12/111 in control group. K value of	"We recommend addition of SWMRI technique as a complementary sequence to the MRI protocol for	Data suggest the presence of TBI-related microbleeds are correlated to short term memory function which could possibly

				65 females; Mean age 39.67 ± 9.38														interobserver agreement for detection of micro bleeds by SWAN was 0.908. Digit spans scores were lower in the micro bleed group (p=0.017). No difference in continuous performance test results between micro bleed group and control.	patients with mTBI."	be a biomarker for TBI severity.
Jenkins A 1986 (4.0)	MRI	Prospective	N = 50	No mention of gender or age.	No mention of sponsorship or COI.	Transverse plane. Looking at cortical/subcortical lesions.	Mild and severe head injury	1.5 Tesla	EMI 1010	Yes	Yes	No	No	No	No	Yes	No	25/50 had abnormal CT scans, significantly less than detected by MRI (p<0.001). 46/50 had abnormalities with	"MRI can provide a striking picture of the immediate effects on the brain of a head injury."	Data suggest detects post TBI brain damage better than CT. Also, lesions in the cerebral hemisphere of 15

																		the T2 weighted studies were more sensitive. MRI detected cortex lesions in 44/50 and Ct scan showed 23/50.		comatose patients may be a key factor for unconsciousness.
Wedekind 1999 (4.0)	MRI	Prospective	N = 57	44 males, 13 females; Mean age for female 28 (14-49) and males 36 (13-68).	This study was supported by the Bundesministerium fur Bildung und Forschung.	Transverse, sagittal, coronal planes	Mild, moderate, and severe head injury based on the Glasgow Coma Scale (GCS).	1.0 or 1.5 Tesla	None	Yes	Yes	No	No	No	No	Yes	No	MRI was superior to electrophysiologic (EP) due to its higher density prognostic information obtained.	"MRI in head injury provides several features relevant to prognosis.."	Data suggest MRI visualized lesions in the corticosubcortical region and midbrain were linked to poorer outcomes.
Laalo 2014 (4.0)	MRI	Diagnostic	N= 89	No mention of Gender of age.	No sponsorship or COI.	The locations used were frontal lobe, temporal lobe, parietal lobe, occipital lobe, corpus callosum, basal ganglia, brain stem and	Traumatic Brain Injury	1.5 T MRI	No	Yes	Yes	No	No	No	No	Yes	66 months	First neurologist with more experience [170] found 370 findings vs less experienced neurologist (R2) who	"The interpretation of TBI findings in late-stage MRI is difficult, yielding significant variability even between	Data suggest late stage chronic TBI as imaged by MRI shows significant interpretative variability which

						Cerebellum.												found 264, and original findings totaled 173. Most common findings were white matter hypersensitivities (172/370). No statistically relevant correlations were found between the misinterpretation of findings and clinical parameters.	specialists in neuroradiology."	affects diagnosis.
Himanen 2005 (4.0)	MRI	Prospective	N = 61	41 males, 20 females; Mean age 29.4 ± 10.8.	This work was supported by grants from Turku University Central Hospital and the Turku University	Left /right hippocampus, lateral ventricle.	Traumatic brain injury	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	1 month to 20.1 years.	The volume of the left hippocampus from MR scans was significantly associated with lower Wechsler	"In conclusion, the long-term memory impairments after TBI are associated with MRI volumetric	Data suggest TBI severity is not as prognostically important as the degree of diffuse injury developing into atrophic

					Foundation.													Memory Scale (WMS) score.	measures ."	changes which may cause long term memory deficits.

Evidence for the Use of Magnetic Resonance (MR) Spectroscopy (MRS)

Author/Year Study Type	*Category*	*Study type*	*Conflict of Interest*	*Sample Size*	*Age /Sex*	*Area of Head*	*Diagnoses*	*Type of MRS used*	*Types of imaging used*	*CT*	*T1 weighted images*	*T2 weighted images*	*X-ray*	*Myelography*	*More than one rater*	*Surgery Performed*	*Clinical outcomes assessed*	*Long term follow-up (mean when noted)*	*Results*	*Conclusion*	*Comments*
Tollard 2009 (5.0)	MR Spectroscopy	Diagnostic	Sponsored by Assistance Publique-Hoˆpitaux de Paris and French Health Ministry (AOM 05 101 to LP). No COI.	N = 58 TBI group 1 (n= 19) TBI group 2 (n= 24) Healthy control	Mean age was 35 40 males and 3 females.	Whole brain	Closed-TBI	H-MRS	MRI	+	+	+	-	-	+	+	+	1 year	At the 1 year follow-up 19 patients had unfavorable outcomes (44%) and 24 had favorable outcomes (56%). MRS had 75% sensitivity and 75%	"FA and NAA/Cr may potentially be quantitative outcome prediction tools at the subacute phase of TBI. H-MRS and DTI show higher levels of	Data suggest FA and Naa/Cr may be of use for predicting TBI outcomes in the subacute phase.

				s (n= 15)														specificity. Combined MRS and FA data predicted unfavorable outcomes with up to 86% sensitivity and 97% specificity.	accuracy when compared to MRI alone."	
Friedman 1999 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by the European Community project TMR/Networks ERBFMRXCT970160. No mention of COI.	N = 28	Mean age was 33.926 males and 2 females	Whole brain	mTBI and/orsTBI TBI group (n=14) Healthy control (n=14)	H-MRS - STEAM	MRI-1.5 Tesla	-	+	+	-	-	+	-	+	6 months	H-MRS diagnostic testing shows early NAA concentrations in gray matter predict overall neuropsychological performance (r = 0.74, p = 0.01). Neuropsychological function improved in patients with TBI (t=-4.36, p=0.002). Proton MRS shows neurochemical	"H-MRS provides a rapid, noninvasive imagine tool to assess the extent of neuronal damage after sustaining a TBI. Proton MRS can be paired with conventional MR examinations with minimal additional time."	Data suggest H-MRS, while non-invasive may assist in determining injury severity post TBI when combined with MR and help predict outcomes.

																			changes in normal WM and GM after TBI.		
Signoretti 2008 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by by National Institutes of Health Grant NS12587 to Drs. Bullock and Marmarou, and by National Institutes of Health Grant NS19235 to Dr. Marmarou. No mention of COI.	N = 30	Mean age was 33.2 sTBI group: 18 males and 7 females Control group: No gender data available	L/R hemisphere	Severe TBI sTBI group (n=25) Healthy control (n=5)	H-MRS	CT	+	+	+	-	-	-	-	+	-	The NAA/Choline and NAA/Crratios were significantly correlated with GOS scores at 6 months ($p<0.01$). High metabolite ratios were associated with good outcomes.	"When conventional neuroimaging techniques reveal no abnormalities, it is possible H-MRS can detect posttraumatic neurochemical damage. "	Data suggest the use of HMR can detect neurochemical damage in the post TBI injured brain when conventional imaging cannot and mitochondrial integrity appear correlated to NAA levels.

Yeo 2011 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by by the National Institutes of Health (grants R24-HD050836, R21-NS064464-01A1, and 3 R21 NS064464-01S1 to A.M.). No COI.	N = 60	Age range: 18-50 26 males and 34 females	L/R temporal, occipital, parietal, and frontal lobes.	mTBI mTBI group (n=30) Healthy controls (n=30)	H-MRS	CT	+	+	+	-	-	-	-	+	3-5 months	No differences between the healthy controls and mTBI patients in attention, working memory, memory, processing speed, and executive functioning during neuropsychological performance (p>0.10). There as a positive relationship between mTBI and white matter creatine (WM Cr) and glutamate-glutamine signal (Glx) (p=0.002). Metabolite levels were elevated	"Results indicate that neurometabolite concentrations are systematically altered by mTBI. H-MRS can detect changes in neurometabolites with fewer errors than conventional neuroimaging."	Data suggests that an estimate of pre-morbid intelligence was positively associated with the magnitude of the metabolite normalization seen during follow-up suggesting those factors which underly intelligence may be related to faster recovery..

																		for white matter Cr (p=0.026) and Glx (p=0.028) compared to healthy controls. T1 and T2 images found no trauma-related pathology.		
Dhandapani 2013 (4.5)	MR Spectroscopy	Diagnostic	No sponsorship or COI.	N = 53	Mean age was 33 44 males and 9 females	Whole brain	Closed-TBI TBI group (n=41) Healthy controls (n=unknown)	Single voxel (SV) MRS	1.5 Tesla	+	-	-	-	-	-	-	+	3 months	41 patients underwent MRS (36/41 show abnormalities) and 56 patients underwent SPECT (41/56 show hypoperfusion). CT scans revealed 50% had MRS abnormalities and 64% had SPECT hypoperfusion.	"ECD-SPECT examinations proved to have a greater sensitivity, incremental validity, and prognostic value than proton MRS."	Data suggest SPECT has better sensitivity than MRS in some types of patients with moderate head injuries which may help guide treatment and predict prognoses.

Maudsley 2015 (4.0)	MR Spectroscopy	Diagnostic	Sponsored by the National Institute of health research grants R01NS055107 and R01EB000822. No COI.	N = 69	Mean age was 28.239 males and 30 females	Whole brain	Closed-TBI TBI group 1 (n=20) TBI group 2 (n=20) Healthy controls (n=29)	Volumetric MSRI & DTI	MRI	-	+	+	-	-	-	-	+	-	The MRS-observed patients showed increases in Cho and Cho/NAA were broadly distributed. DTI group detected localized changes in major white matter tracts and adjacent tissues.	"The study demonstrates that MRSI and DTI have a complimentary nature."	Data suggest MRS I and DTS are useful in the detection of altered metabolism and injury post TBI but areas located by the 2 methods are different.
Govind (4.0) 2010	MR Spectroscopy	Diagnostic	Sponsored by National Institutes of Health grants R01NS055107 and R01EB000822. No COI.	N = 81	Mean age was 26.25 males and 4 females.	Whole brain	Closed-head TBI with brief loss of consciousness (<20min) TBI group (n=29) Healthy control (n=52)	MRSI EPSI	MRSI FLAIR Diffusion-weighted MRI	-	+	+	-	-	-	-	+	Mean: 20.5 days	MRS imaging shows a widespread decrease of NAA and NAA/Cre, and increases of Cho and Cho/NAA in all lobes. No significant correlation found between MSRI or NPT	"The results indicate that significant and widespread alterations of proton MRS - observed metabolites occur throughout the brain as a result of mild-to-moderate TBI."	Data suggest that in mild to moderate TBI patients there are significant and widespread metabolite alterations which correlate to cognitive

																			measures .		performance.

Evidence for the Use of Functional MRI

Author Year (Score):	*Category:*	*Study type:*	*Sample size:*	*Age/ Sex:*	*Sponsorship/COI:*	*Area of Body:*	*Diagnoses:*	*Type of MRI used:*	*Type of CT used:*	*T1 Weighted Images:*	*T2 Weighted Images:*	*X-ray:*	*Myelography:*	*More than one rater:*	*Surgery Performed:*	*Clinical Outcomes Assessed:*	*Long Term Follow-up (mean when noted):*	*Results:*	*Conclusion:*	*Comments:*
Zuniga 2014 (5.0)	fMRI	Prospective	N=19	9 males, 10 females; mean Age 22.29 ±7.57	No sponsorship or COI.	frontal, middle line, and occipital regions.	Mild Head injury	1.5 T MRI System	Yes	No	Yes	No	No	No	No	Yes	6 & 12 months	No significant results using spectroscopy.	"The majorly affected groups were pediatric and young individuals. We consider them the most vulnerable. Through our study of PCS, we identified physical and neuropsychological	Data suggest that fMRI can detect PCS in mild head injured patients via frontal lobe changes evidenced in neurometabolic alterations

																			anomalies affecting the areas of memory and learning.”	which affect memory and learning.
Dettwiler 2014 (4.5)	fMRI	Longitudinal	N=15 (w/Concussion) vs 15 (w/o concussion)	12 males, 3 femals; Mean age of 19.8	No sponsorship or COI.	Axial plane	Concussion	3T Siemens	No	Yes	No	No	No	No	No	Yes	Follow-up at 2 days, 2 weeks, & 2 months	Participants with concussion showed a significantly larger amount of activation at 2 days vs 2 months, and between control groups. Blood oxygen level dependent increased in	“The longitudinal nature of this study advances our understanding of the neural correlates of SRC by demonstrating alteration of brain activation subsequent to a return to normal	Data suggest brain activation functions persist 2 months post-TBI but the working memory is comparable to

																	concussed participant during working memory load tasks.	scores on NP tests."	controls.
Palacios 2012 (4.0)	fMRI	Cross-Sectional	N=38 (19 w/ TBI)	22 males, 16 females; control group mean age 27.47 ±6.04. TBI group mean age 26.78 ±5.55.	Authors supported by a fellowship from the Institute of Biomedical Research August Pi I Sunyer. No COI.	All planes and regions of brain.	Traumatic Brain Injury.	3T Siemens	No	Yes	No	No	No	No	No	Yes	None	Activation pattern IC1, showed TBI decreased activation in cerebral regions in comparison to control group within the default network ($p<0.009$). No difference in visual system activation.	"The present study provides strong evidence of the role of structural damage in dysfunctional patterns of working memory and default mode networks in TBI	Data suggest reduced memory performance is likely related to structurally changed white matter alterations in chroni

																		Lower white matter integrity showed a decreased Functional acuity scores (p=0.006). Significant correlation found in TBI patents in the default mode and working memory networks with the accuracy measure p=0.009).	patients. Both structural and functional alterations contribute to working memory deficits.”	c TBI patients seen with fMRI images.

Evidence for the Use of Diffusion Tensor Imaging (DTI)

Author Year (Score):	*Category:*	*Study type:*	*Sample size:*	*Age/Sex:*	*Sponsorship/COI:*	*Area of body:*	*Diagnoses:*	*SPECT or SPET:*	*MRI or CT:*	*T1 weighted images:*	*T2 weighted images:*	*More than one rater:*	*Clinical outcomes assessed:*	*Long term follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Lange 2015 (4.5)	DTI	Diagnostic	N=108	78 males, 30 females; Mean age Group 1: 34.1± 11.3. Group 2 34.1± 10.4 Group 3: 31.6± 10.2	This work was primarily supported by the Canadian Institutes of Health Research. No COI.	genu, body,and splenium of corpus callosum; (b) pontine crossing tract, fornix, and middle cerebellar peduncle, corticospinal tract, medial lemniscus, inferior cerebellar peduncle, superior cerebellar peduncle, cerebral peduncle, anterior limb of internal	Group 1: N=52 patients with TBI with post-concussion syndrome (PCS). Group 2: N=20 patients with TBI, no PCS. Group 3: N=36 Control.	1.5	3T Philips Achieva scanner	No	Yes	No	5 hour neuropsychological assessment which included neurocognitive functioning, self reported mental health, and post concussion symptoms.	No follow up, DTI taken 6-8 weeks past injury.	Significant Differences Tract-based spatial statistics (TBSS) between groups 1 vs 3 in DTI measures of Mean Diffusivity (MD), radial diffusivity (RD) increased in TBI group ($p<0.05$). TBSS revealed significant white-matter differences between the Group 1 vs group 3.	"In this study, symptoms of depression and anxiety differentiated patients with MTBIs who met criteria for the postconcussion symptom versus those who did not. In contrast, these groups did not differ on diverse metrics of DTI."	Data suggest changes in white matter did not serve as a significant PCS predictor in mild TBI patients.

						capsule, posterior limb of internal capsule, retrolenticular part of internal capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation, sagittal stratum, external capsule, cingulum (cingulate gyrus), cingulum (hippocampus), fornix/stria terminalis, superior longitudinal fasciculus, superior fronto-occipital fasciculus,											

						uncinate fasciculus, and tapetum.											
Sidaros 2008 (4.5)	DTI	Prospective	N = 60	23 males, 7 females; Mean age of 23.	Study supported by a grant from the Elsass Foundation. No COI.	Posterior limb of internal capsule (PLIC), posterior corpus callosum (PCC), cerebral peduncle (CP), centrum semivale [188], Putamen (PUT), and cerebrospinal fluid (CSF).	Traumatic brain injury (n=30), healthy controls (n=30).	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity, and radial diffusivity	12 months	At initial scan fractional anisotropy (FA) significantly decreased in regions of interest versus controls (p=0.00001).	"Our findings indicate microstructural alterations during the chronic stage of severe TBI, which may represent structural reorganization relevant to clinical recovery. DTI non-invasively provides quantitative pathophysiological information in vivo, and the prospect of tracking white matter microstru	Data suggest DTI is a TBI biomarker.

																ctural changes over time holds the promise of measuring neuroplasticity and repair following TBI, which eventually may offer a way of monitoring therapeutic response. ”	
Betz 2012 (4.5)	DTI	Retrospective	N = 59	43 males, 16 females; Mean Age 37.2± 16. 8	No sponsorship or COI.	Internal capsule, genu, splenium, and body of corpus callosum	Severe closed-head trauma. Compared scores to mild traumatic injury controls (n=18)	1.5 Tesla	MRI 1.5 T	Yes	Yes	No	Apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial and radial diffusivity, and Glasgow Coma Scale (GCS).	No	Favorable outcomes associated with higher mean ADC in whole brain white matter (p=0.011). higher axial diffusivity had a strong relationship with favorable	“Our study demonstrated that DTI parameters at the whole-brain level and regional level can provide prognostic information about the discharge	Data suggests that prognostic ability is improved when DTI is adjusted for age, gender and GCS.

															outcomes (p<0.00001). Poor patient outcome (death or severe injury) was associated with greater heterogeneity in DTI values measured by the coefficient of variation of ADC (p<0.0001) and axial diffusivity (p<0.0001). The genu of the corpus callosum had lower average of ADC (p=0.0068) and axial diffusivity (p<0.0001) which was significantly correlated	status of a patient, while circumventing many problems associated with currently used clinical measures, including the GCS."	

															with poor outcomes . DTI at whole brain and regional level correlated with GCS ratings and patient discharge status.		
Murugavel 2014 (4.0)	DTI	Longitudinal	N= 37	37 males, 0 females; Mean ages, Group 1: 20.19 ±1.03 Group 2: 19.9± 1.67.	This work was funded by the New Jersey Commission for Brain Injury Research, the American Medical Society for Sports Medicine AMSSM Foundation, the Goldstein Family Fund, and the	The regions implicated are all in the right hemisphere, posterior limb of the internal capsule (IC), retrolenticular part of the IC, sagittal stratum (inferior longitudinal fasciculus and inferior fronto-occipital	(N=21) male collegiate thletes that play contact sports (Concussion) (N=16) noncontact sport male athletes.	3.0 T MRI	3.0 T MRI	Yes	No	No	athletic history, physical exam, and baseline NP testing, including SCAT2and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT).	2 days, 2 weeks, 2 months.	Radial Diffusivity (RD) 2 days vs 2 wks showed descread in concussed group (p=0.025). RD higher in concussed group @ 2 days (p=0.002). fractional anisotropy (FA) values lower in concussed group at 2 days (p=0.0008), and at 2	"This study provides support for the hypothesis of increased RD and reduced FA within 72 h post injury followed by patterns of recovery. …RD was found to be a sensitive marker of SRC with potential for	Data suggest RD is a sensitive measure of sports-related concussion injuries and shows reduced RD as well as FA within 72 hours post-TBI.

					Peter & Cynthia Kellogg Foundation. No COI.	fasciculus), and anterior thalamic radiation									months (p=0.044).	personalized imaging-based diagnosis. ”	
Perlbarg 2009 (4.0)	DTI	Prospective	N = 30	28 males, 2 females; mean Age of 37±12	No mention of sponsorship or COI.	Inferior longitudinal fasciculus (ILF), posterior limb of internal capsule (PLIC), posterior corpus callosum (PCC), cerebral peduncle (CP)	Severe traumatic brain injury (n=30), split by unfavorable outcome at 1-year (n=15) and favorable 1-year outcome (n=15)	DTI 1.5 T	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	FA was significantly lower ($p<0.05$) for the unfavorable outcome group compared to favorable in the ILF, CP, PLIC, and PCC. No ADC differences were seen between both outcome groups ($p>0.05$). Authors concluded that FA was a relevant biomarker for predicting TBI outcomes.	“This article confirms that FA measured in several specific brain areas is a relevant biomarker for early outcome prediction in TBI.”	Data suggest ADC is not a good marker for the 1 year prognostic outcome reduced FA is associated with a poorer outcome and FA measurements show good sensitivity and specificity.

Kumar 2009 (4.0)	DTI	Diagnostic	N = 83	62 males, 21 females; Mean Age 34.25 ±10.28	Sponsored by Indian Council of medical Research. No COI.	Corpus Callosum; Frontal, temporal, parietal, and occipital	Mild (n=26) and moderate(n=57) traumatic brain injury	1.5 T	1.5 T MRI	Yes	Yes	No	Neuropsychological tests: figure connection, picture completion, digit symbol test, block design test, picture arrangement, object assembly	6 months	Across all neuropsychological tests healthy controls compared to mild and moderate brain injury performed significantly better (p=0.00). Diffusion tensor imaging abnormalities in the corpus callosum for those with moderate brain injury were positively correlated with worse outcome after 6 months.	"It is concluded that DTI abnormalities in the regions of CC (Corpus Callosum) were more in patients with moderate TBI compared to mild TBI and predicted a trend towards worse outcome at 6 months, as suggested by neuropsychological scores."	Data suggest DTI abnormalities more prevalent in CC regions of moderate TBI patients vs mild TBI patients and these finding were associate with a poor outcome 6 months post injury.
Farbota 2012 (4.0)	DTI	Prospective	N = 21	14 males, 7 females; TBI	This study was supported by a	Superior longitudinal fascicule (SLF),	Traumatic brain injury (n=12) and	DTI 3.0 T	MRI 3.0 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity	Visit 1 (mean =63 days), visit 2	TBI patients had a significant decrease	"In this study, we show that TBI patients	Relatively small sample. Data suggest

				mean age 35.0± 12.8 vs 29.2± for control.	Merit Review Grant from the Department of Veterans Affairs, NIH, and by William S Middleton Memorial Veterans Hospital. No COI.	interior longitudinal fascicule (ILF), internal/ external capsule, fornix, corpus callosum, ucinate fasciculus (UF), cerebral peduncle.	healthy controls (n=9).						(AD), radial diffusivity (RD), visuomotor speed (SS), neuropsychological tests, Glasgow Coma Scale (GCS)	(mean =318 days), and visit 3 (mean =1187 days).	in FA in the corpus callosum from visit 1 to 2. There was no significant correlation between GCS scores and regional white matter FA during any of the time points. The TBI group did not have greater FA during any of the time points of regions.	exhibit longitudinal WM changes that continue for at least four years post-injury."	TBI patients exhibit WM changes for at least 4 years post-injury. Suggesting TBI is a prolonged disease state.
Rutgers 2008b (4.0)	DTI	Prospective	N=50	27 males, 12 females; Mean 34±12	This work was supported by the Institut pour la Recherche sur la Moelle	Corpus callosum: genu, body, and splenium.	Mild traumatic brain injury (n=24), moderate TBI (n=9), severe TBI (n=6)	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	Compared to healthy controls patients with mild traumatic injury showed no significant difference	"Our study shows that there are local differences in DTI characteristics within the corpus	Data suggest that mild TBI is associate with DTI abnormalities in the

					e´pinie`r e et l'Ence´ph ale,. No COI.		and healthy controls (n=11)								between FA, ADC, and number of fibers in genu, body and splenium of the corpus callosum. Moderate TBI had lower FA ($p<0.001$) and significant ly higher ADC ($p<0.01$) in the genu compared to controls and mild traumatic brain injury ($p<0.05$). Severe TBI patients had significant ly lower FA ($p<0.001$) and higher ADC ($p<0.01$)	callosum, which are related to the clinical severity of head trauma. Mild TBI is associate d with DTI abnormali ties in the genu _3 months posttrau ma."	period up to 3 months post injury. Patient s with modera te and severe TBI had significa nt reducti ons in FA and increas es in ADC.

															compared to controls and compared to mild ($p<0.05$; $p<0.01$). DTI and fiber tracking was not significantly different between any groups.		

Evidence for the Use of Single-Photon Emission Computerized Tomography (SPECT) or Single-Photon Emission Tomographic (SPET)

Author Year (Score):	*Category:*	*Study type:*	*Sample size:*	*Age/Sex:*	*Sponsorship/COI*	*Area of head:*	*Diagnoses:*	*SPECT or SPET:*	*MRI or CT:*	*More than one rater:*	*Surgery Performed:*	*Clinical outcomes assessed:*	*Long term follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Newton 1992 (7.5)	SPECT	Prospective	N = 19 with severe head injury	Mean age of 29 years old. 4 Females, 15 Males	No mention of sponsorship or COI	Coronal, transverse, and sagittal plane imaging	Closed head injury	SPECT TC-99m Tc-HMPAO	CT - GE 9000 and MRI-0.8 Tesla	No	No	Yes	No	In the nineteen patients 43 perfusions were detected using SPECT, 21 focal lesions were shown by MRI, and 13 by CT scan. Both CT and MRI did not show a left hemisphere lesion, but SPECT showed a perfusion defect	"We conclude that SPECT reveals areas of cerebral damage, which may be either contusional or ischaemic, frequently not shown by CT or MRI. Defects on SPECT may correlate with focal neurolo	Pilot study. Data suggests SPECT detects cerebral damage undetected by either MRI or CT. The most neurologically disabled patient show the greatest number of lesions.

														in the left parietal region.	gical deficit. The most disabled patients tend to show the most number of lesions on SPECT."	
Joglekar 2014 (7.0)	SPECT	Retrospective	N = 63 patients who had undergone SPECT	Mean age of 59 years old. 40 Females, 23 Males	No mention of sponsorship or COI.	Brain	Head trauma, tinnitus, vertigo, or a combination	SPECT	Both	Yes	No	No	Not mentioned	Abnormalities were found in 15 of 63 SPECT scans, 16 of 62 MRIs, and 14 of 60 CTs. Out of the three test, MRI was the most sensitive for all three diagnoses. 13 of 60 exhibited areas of cerebral	"We conclude that SPECT may be a valuable complementary diagnostic modality for making a comprehensive neurotologic evaluation and that it may detect abnormalities in some	Data suggest SPECT may be useful as an adjunct test combined with MRI or CT.

														hypofusion on SPECT, but their MRI and CT scans were normal.	patients whose other imaging is read as normal. However, we did not find that SPECT was the most sensitive of the three modalities in neurotologic evaluation, as we had previously found in a preliminary study that the senior author (R.T.S.) published in 1996."	
Munari 2005 (6.5)	SPECT	Prospective Study	N = 20 clinically brain	Mean age of 43.3 years	No sponsorship or COI.	Brain	Brain Dead	SPECT – Triple-	CT	No	No	No	Not mentioned	Both angiography and SPECT	"Our results confirm the	Data suggest SPECT is a

			dead patients	old. 10 Females, 10 Males				headed gamma-camera (IRIX)						confirmed all 19 patients with BD. Contrast angiography showed slight and late filling of the cerebral arteries. SPECT showed weak perfusion of the brain stem and posterior part of the brain.	reliability of SPECT in the diagnosis of BD; because SPECT is noninvasive, it is a good candidate for the "gold standard" of diagnosis."	useful non-invasive imaging tool for diagnosing brain death.
Bavetta 1994 (6.5)	SPECT	Prospective	N = 10 with significant head injury	Mean age of 29.4 years old. 2 Females, 8 Males	Sponsored by the Saint Bartholomew's Joint Research Board. No mention of COI.	Temporal, frontal, basal ganglia, parieto-occipital, parietal, extracerebral	Severe closed-head injury	SPET 99m-Tc HMPAO	Non-enhanced CT and MRI 0.08 Tesla	No	No	Yes	No	In SPET 32 lesions were detected 10 patients, 10 lesions in CT, and 14 lesions in MRI. Of the 32 detected	"The results suggest that lesions in the temporal lobes, frontal lobes and basal ganglia are related to poor	Small sample. Data suggest SPET yields more useful prognostic data than either MRI or CT followi

														by SPET, 22/32 were only found on SPET, 6/32 were found on CT or MRI.	prognosis and that SPET yields more useful prognostic data than the other methods."	ng severe close head injury.
Roper 1991 (6.0)	SPECT	Prospective	N = 15 patients with acute closed-heady injury	Mean age of 32 years old. 1 Female, 14 Male	No mention of sponsorship or COI	Frontotemporal, parietal, frontal, occipital	Acute closed-head injury	SPECT ^{99}m-Tc HMPAO	X-ray CT scan	Yes	No	Yes	No	There were a total of 44 focal lesions found in 15 patients. 15/44 were found on both CT and SPECT. 12/44 were seen on CT only and 17/44 on SPECT.	"This study shows that SPECT can detect focal disturbances of cerebral blood flow That are not seen on x-ray tomography. It also suggests that there are two types of contusions: those with a	Small sample. Data suggest SPECT can detect focal disturbances with cerebral blood flow not seen with CT.

															decreased cerebral blood flow (i.e., detectable on SPECT) and those with a cerebral blood flow equal to that of the surrounding brain."	
Jacobs 1994 (5.5)	SPECT	Prospective	N = 67 closed cranial trauma	Mean age of 35 years old. 26 Females, 41 Males	No mention of sponsorship or COI.	Transaxial, coronal and sagittal plane imaging.	Closed cranial head trauma	SPECT 99mTc HMPAO	CT	No	No	Yes	3 months	For those with moderate head trauma the initial SPECT revealed abnormalities in 25/42, CT found 10/42, and 17/42 had normal SPECT evaluati	"Our results show that:[170]SPECT alterations correlate well with the severity of the trauma; (2) a negative initial SPECT study is a reliable predicto	Data suggest SPECT alterations correlate with the severity of head trauma and negative SPECT results suggest a favorable

														ons. For those with middle head trauma SPECT revealed 9/25 had abnormalities and 16/25 were normal.	r of a favorable clinical outcome; (3) in cases with a positive initial SPECT, a follow-up consisting of a combination of SPECT and clinical data is necessary; (4) in patients suffering from post-concussive symptoms, SPECT offers an instrument to objectivate sequalae”	patient outcome.

Lorberboym 2002 (5.5)	SPECT	Prospective	N = 16 with head injury	Mean age of 31.6 years old. 4 Females, 12 Males	No mention of sponsorship or COI.	Transaxial, coronal, and sagittal plane imaging.	Mild to moderate head trauma	SPECT 20mCi of 99mTc HMPAO	No	No	No	Yes	No	All patients had no abnormal CT scan. SPECT revealed that 12/16 had regional perfusion abnormalities and 8/12 had more than one abnormality. SPECT results significantly predicted amnesia severity ($p<0.001$) and accounted for 84% of the amnesia variation.	"Amnesia after mild head injury is associated with a high incidence of early regional cerebral perfusion abnormalities. Amnesia lasting more than half an hour is associated with bilateral cerebral hypoperfusion. SPECT evaluation in the ED may be a useful additional tool in the objective	Small sample. Data suggest SPECT may be useful in the assessment of post-traumatic amnesia.

															assessment of PTA."	
Romero 2015 (5.5)	SPECT	Case Control	N = 84 patients with mTBI	Mean age of 32.1 years old. 29 Females, 55 Males	Sponsored by the Canadian Institute for Health Research. No mention of COI.	Brain	TBI	SPECT – Prism 3000 XP	Neither	Yes	No	No	Follow up 1 year after baseline.	There was a negative association (P = 0.03) between SPECT perfusion and Stroop scores at baseline and follow up. SPECT scans categorized as normal or abnormal had no difference on any cognitive measure or symptom scale.	"SPECT scans categorized as normal or abnormal by radiologists did not differentiate cognitively impaired from intact subjects. These results demonstrate the clinical utility of SPECT in mild TBI, but only when data are subjected to blood flow quantification	Data suggest SPECT may be useful in predicting cognitive traction.

															analysis. ”	
Stamatakis 2002 (5.5)	SPECT	Prospective	N = 61 head injured	Mean age of 27.6 years old. No mention of sex distribution	Sponsored by the Chief Scientist Office. No mention of COI.	L/R frontal gyrus, L/R cingulate, L/R parietal lobule, corpus callosum	Acute head trauma	SPECT ^{99}mTc-HMPAO	MRI 1.5T T1 and T2-weighted	No	No	Yes	6 months	SPECT detected more abnormalities than MRI. The average lesion volumes of focal (56.31 vs. 53.93) and diffuse (12.61 vs 5.68) on SPECT and MRI. The volume was not significant at acute ($p<0.32$), but was significant at follow-up (30.39 vs 18.82; $p<0.001$).	“ SPM has a role in SPECT image interpretation because it allows better visualization than other methods of quantitative analysis of the spatial distribution of abnormalities in focal and diffuse head injury. Frontal lobe blood flow abnormality (particularly	Data suggest statistical parametric mapping (SPM) has some role in the interpretation of SPECT imaging as it enhances the visualization of abnormalities.

															anterofrontal regions and mesiofrontal areas) is common after head injury."	
Jacobs 1996 (5.5)	SPECT	Prospective	N = 136 patients with closed-cranial trauma	Mean age of 36 years old. 51 Females, 85 Males	No mention of sponsorship or COI.	Left temporal/frontotemporal Left temporoparietal L/R frontal L/R parieto-occipital	Closed-cranial trauma	SPECT ^{99}m-Tc HMPAO	No	No	No	Yes	12 months	At the 3-month follow-up 37/136 (27%) had positive clinical evaluations and 45/139 (33%) had positive SPECT. At 6-months 18/136 (13%) had positive clinical evaluation and 29/136 (21%) had positive SPECT.	"A normal ""Tc-HMPAO SPECT scan is a reliable tool in the exclusion of clinical sequelae of mild head injury. At 12 mo. post injury, a positive SPECT study is also a reliable predictor for clinical	Data suggest that at 12 months post mild head injury a positive SPECT result is a reliable predictor for outcome.

														At the final 12-month follow-up 9/136 (7%) had positive clinical evaluation and 12/136 (9%) had positive SPECT results.	outcome.”	
Ichise 1994 (5.5)	SPECT	Prospective	N = 46 with TBI or control	Mean age of 30.9 years old. 21 Females, 25 Males	Sponsored by Sterling-Winthrop Imaging Research Institute Grant. No mention of COI.	Frontal, temporal, parietal, and occipital lobes, cerebellum and subcortical grey matter	Minor traumatic brain injury (n=15) and major traumatic brain injury (n=14). Normal control (NC) group had (n=17).	SPECT ^{99}m-Tc HMPAO	CT non-enhanced and MRI 1.5 Tesla T1 and T2-weighted	No	No	Yes	No	3/17 in the NC had abnormalities. In the TBI patients 19/29 (66%) had abnormal SPECT, 13/29 (45%) abnormal MRI, and 10/29 (34%) had abnormal CT scan. SPECT detected 42	“ In evaluating chronic TBI patients, HMPAO SPECT, as a complement to CT or MRI, may play a useful role by demonstrating brain dysfunction in morphologically intact	Data suggest SPEC complements either CT or MRI to assist in determination of the morphology of brain dysfunction.

														abnormalities in 19/29 TBI patients, 33/42 (79%) were focal cortical perfusion deficits with no CT or MRI shard findings. CT and MRI detected diffuse cortical atrophy in 7/29 TBI patients that SPECT did not detect. All CT lesions were detected by MRI.	brain regions and providing Objective evidence for some of the impaired NP performance"	
Gray 1992 (5.0)	SPECT	Prospective	N = 53 with TBI	For Controls (N = 14): Mean age of	No mention of sponsorship or COI.	L/R frontal, temporal lobes, corpus callosum, L/R parietal and	Traumatic brain injury (in the last 6 months).	SPECT ^{99}m-Tc HMPAO	X-ray CT scan	No	No	Yes	No	The healthy controls did not reveal any	"In the evaluation of TBI patients,	Data suggest SPECT more sensitive than

				32 years old. 7 Females, 7 Males. Gender and age not given for TBI Group.		occipital regions.	Minor TBI (n=20) Major TBI (n=33) Excluded those with more than one TBI, drug/alcohol abuse, and neuropsychiatric problems. Health control group (n=14)							abnormalities. In the TBI patients regional cerebral blood flow (rCBF) was not abnormal, but focal and/or diffuse deficits were found in 42/53 (80%). CT scan revealed 29/53 patients had morphological abnormalities. The CT and SPECT concordance was 11/20 (55%) in the minor TBI and 27/30 (82%)	HMPAO SPECT is a useful technique to demonstrate regional brain dysfunction in the presence of morphological integrity as assessed by CT."	CT for detection of abnormal finding in patient with a history of mild TBI.

														for major TBI.7/33 major TBI patients had abnormalities on SPECT, but normal CT scan.		
Amen 2015 (5.0)	SPECT	Retrospective Study	N = 20746 neuropsychiatric patients	Mean age of 39.5 years old. 10100 Females, 10646 Males	No sponsorship. COI: Author TH is President and owner of Dr. Theodore Henderson, Inc. and the Synaptic Space and co-owner of Neuro-Luminance Corp. DA is the owner of Amen Clinics Inc and	Brain	TBI	High resolution Picker (Philips) Prism XP 3000 triple-headed camera.	None	Yes	No	No	Not mentioned	All PTSD regions were more active than the TBI regions. The two TBI/PTSD model produced similar sensitivity, specificity, and accuracy that ranges from 1% to 11%. PTSD shows an increased in perfusion,	"This study demonstrates the ability to separate PTSD and TBI from healthy controls, from each other, and detect their co-occurrence, even in highly comorbid samples, using SPECT. This	Data suggest SPECT may be beneficial in distinguishing PTSD from TBI.

					KW and DT are employed by Amen Clinics Inc									particularly in the frontal lobe. TBI showed a decrease in perfusion compared to PTSD.	modality may offer a clinical option for aiding diagnosis and treatment of these conditions"	
Mitchener 1997 (5.0)	SPECT	Prospective	N = 32 patients with a closed head injury	Mean age of 31 years. 5 Females, 27 Males	No mention of sponsorship or COI	Frontal, anterior/posterior temporal, occipital, parietal	Closed-head injury.	SPECT ^{99}m-Tc HMPAO	CT and MRI 1.5 Tesla T1 and T2 weighted	No	No	Yes	6 months	CT identified 45 lesions in 27/32 patients. SPECT showed 49 perfusion deficits in 30/32 patients. 22/49 perfusions appeared normal on CT scans. 48 lesions were detected by late MRI (4-6 months	" Our study has shown that, although on some occasions the presence of lesions on SPECT, MRI, or both can help to explain a poor clinical outcome, it is not necessarily an indicatio	Data suggest that at 6 months post head injury SPECT abnormalities correlate with clinical outcome.

														post injury).	n of poor outcome. We have shown that about 30% of patients were graded in the top band of recovery despite having lesions on SPECT or MRI. This may reflect insensitivity of the clinical outcome scale or indicate that these lesions had minimal functional	

															impact. This is the subject of further investigation."	
Gowda 2006 (5.0)	SPECT	Prospective	N = 92 with mTBI	Mean age of 27.6 years old. 17 Females, 75 Males	No mention of sponsorship or COI	Temporal lobe, temporal lobe, basal ganglia and thalamus, parietal lobes, cerebellum, occipital lobe.	Mild traumatic brain injury (mTBI).	SPECT ^{99}mTc-ECD	CT	No	No	Yes	No	All underwent SPECT and CT. 58/92 had perfusion abnormalities. 29/58 had positive and 29/28 had negative CT scan. 34/92 had negative findings and of those 2/34 had positive and 32/34 had negative CT scan.	"Tc99m-ECD SPECT can be used as a complementary technique to CT in initial evaluation of patients with MTBI. It is particularly useful in patients having PCS, LOC, or PTA with normal CT scan."	Data suggest SPECT may be used in addition to CT in the evaluation of patient with mild TBI.

Kant 1997 (5.0)	SPECT	Prospective	N = 43 with TBI	Mean age of 34.9 years old. 12 Females, 31 Males	No mention of sponsorship or COI	Frontal, parietal, and temporal lobes.	Mild closed head injury (loss of consciousness less than 20 minutes)	SPECT ^{99}mTc-HMPAO	CT, MRI and EEG.	No	No	Yes	No	23/23 had abnormal SPECT findings with 37 lesions detected. 39/43 underwent MRI scans that found abnormalities on 3/39. 21/43 underwent CT scan with 2/21 having abnormalities. 33/43 had EEG and 3/33 had abnormal findings. 2/3 abnormal EEG findings had normal MRI, CT, and	"We conclude that SPECT scan is more sensitive than MRI or CT scan in revealing the number of cerebral lesions after mild head injury in patients who are suffering PPCS. It could be a useful investigational tool in patients with PPCS who have normal MRI and/CT scan of the brain."	Data suggest SPECT is more sensitive in imaging the number of brain lesions in mild head injured patient compared to both MRI and CT.

														SPECT scans.		
Abu-Judeh 1999 (4.5)	SPECT	Prospective	N = 32 patients with mTBI	Mean age of 42 years old. 17 Females, 15 males	No mention of sponsorship or COI	Frontal lobe, thalami and basal ganglia, temporal lobes, parietal lobes.	Mild traumatic brain injury (mTBI).	SPET ^{99}Tc-HMPAO	Neither	No	No	Yes	3 months	19/32 had abnormal SPET with 17/19 having a total of 48 focal lesions. Frontal lobes. 26/32 had headaches. Patient complaints: 15/32 memory deficits, 13/32 dizziness, sleep disorders 8/32, generalized weakness 7/32, visual complaints 5/32, depression 2/32, and hearing	"Our findings suggest that there are significant brain perfusion abnormalities in symptomatic patients who sustain an mTBI injury without loss of consciousness in the absence of X-ray CT abnormalities. We also stress the importance of early SPET brain perfusio	Data suggest SPET imaging is more sensitive than CT for evaluating cerebral perfusion post mild TBI.

														difficulties 1/32.	n imaging in these patients because the incidence of brain perfusion abnormalities was higher in patients imaged less than 3 months post-injury compared to those imaged more than 3 months from the date of the accident.”	
Nedd 1993 (4.5)	SPECT	Prospective	N = 16 with TBI.	Mean age of 37.44 years old. 4 Femal	No mention of sponsorship or COI	Frontal hemisphere	Mild to moderate traumatic brain injury	SPECT ^{99}mTc-HMPAO	CT 9800	No	No	Yes	No	SPECT detected regional cerebral blood flow	The results in this indicated that in patients	Small sample size. Data suggest SPECT

				es, 12 Males										(rCBF) differences in 14/16 (87.5%) patients. CT scan revealed abnormalities in 6/16 (37.55), all patients with abnormal CT scan had abnormal SPECT. Half the patients had rCBF changes on SPECT, but normal CT scans. 8/16 had skull fractures yet CT scans did not detect any brain lesions in those areas.	with mild to moderate TBI: SPECT scans showed areas of contrecoup changes more often than CT scans, changes in rCBF were more frequent and more extensive on SPECT scans as compared with lesions on CT scans."	appears more sensitive than CT in evaluating axial lesions in mild to moderate TBI patient.

														SPECT detected decreases in rCBF for 5/8 with fractures.		
Hofman 2001 (4.5)	SPECT	Prospective	N = 21 with mTBI	Mean age of 22.8 years old. 9 Females, 12 Males	No mention of sponsorship or COI.	Temporal lobe and frontal lobe.	Mild traumatic brain injury (mTBI)-closed head injury	SPECT Tc99m-HMPAO	MRI 1.5 Tesla T2 FLAIR	No	No	Yes	6 months	21 underwent MRI and 18 SPECT. 11/28 (61%) had abnormal SPECT findings and 12/21 (57%) had abnormal MRI findings. 77% of patients had either an abnormal MRI or SPECT imaging.	" Brain lesions are common after mTBI; up to 77% of patients may have abnormal findings either on MR images or SPECT scans, and these lesions may lead to brain atrophy. The association between hypoperfusion	Data suggest approximately ¾ of TBI patient may have MRI or SPECT imagery showing abnormal finding which "may" lead to brain atrophy. Also, there is an association between hypoperfusion visualized on

															seen on acute SPECT and brain atrophy after 6 months suggests the possibility of (secondary) ischemic brain damage. There is only a weak correlation between neuroimaging findings and neurocognitive outcome."	acute SPECT and brain atrophy after 6 months suggesting there may be secondary ischemic brain damage.
Raji 2015 (4.5)	SPECT	Retrospective	N = 196 patients	Mean age of 42.1 years old. 28 Females,	No mention of sponsorship. No COI.	Brain	TBI and/or PTSD	SPECT – High resolution Picker (Philips) Prism	Neither	No	No	No	Not mentioned	Quantitative SPECT distinguished veterans with PTSD from	" This study demonstrates the ability to separate PTSD	Data suggest SPECT imaging can be used to differentiate

				168 Males				XP 3000 triple headed gamma camera						those with TBI with an accuracy of 87-94%. Distinguishing PTSD from those with PTSD and TBI has an accuracy of 85-92%. PTSD had increased perfusion in the brain while TBI had a decreased perfusion.	and TBI from each other in a veteran population using functional neuroimaging."	PTSD from TBI by examining DMN acuity.
Atighechi 2013 (4.5)	SPECT	Prospective Study	N = 63 with head injuries	Mean age of 32.5 years old. 18 Females, 44 Males	No mention of sponsorship or COI	Brain	Head trauma	SPECT – Double detector device	MRI – 1.5-T Siemens	Not mentioned	No	No	Not mentioned	MRI and SPECT had similar specificity and sensitivity for both anosmia	"According to our study, both brain MRI and SPECT have high	Data suggest both MRI and SPECT have good sensitivity and

				1 missing gender									and hyposmia (87.7, 82.1 vs 87.7, 85.7, 85.7, 66.7 vs 85.7, 81.25, respectively). Both have similar PPVs but SPECT has a higher NPV. When both are used together, it increases the accuracy.	sensitivity and specificity in the diagnosis of traumatic anosmia, although brain SPECT is slightly superior to MRI. If the two techniques are applied together, the accuracy will be increased."	specificity for detection of olfactory dysfunction post TBI but SPECT trended toward a slightly better result.
Dhandapani 2014 (4.5)	SPECT	Case Control	N = 53 patients with a closed head injury	Mean age of 33 years old. 9 Females, 44 Males	No sponsorship or COI.	Brain	Head injury	SPECT – Dual-headed rotating scintillation gamma camera	CT	No	No	No	Not mentioned	There was a non-significant association between SPECT and MRS findings (P = 0.81).	" To conclude, ECD-SPECT seems to have greater sensitivity, incremental validity and	Data suggest SPECT has better sensitivity than MRS in some types of patients with

														The more severe the injury, the greater number of patients with MRS and SPECT abnormalities. SPECT had more abnormalities than MRS.	prognostic value than single voxel proton MRS in select patients with head injury, with only severe hypoperfusion in SPECT significantly associated with unfavorable outcome independent of other confounding factors"	moderate head injuries which may help guide treatment and predict prognoses.
Masdeu 1994 (4.5)	SPECT	Prospective	N = 41 subjects with head trauma, HIV encephalopathy or are healthy.	Mean age of 39.3 years old. 15 Females, 26 Males	No mention of sponsorship or COI.	Inferior basal ganglia, upper thalamic, frontal lobe and posterior temporooccipital region.	Mild head trauma (n=14) HIV encephalopathy (n=12) Normal	SPECT ^{99m}-Tc HMPAO	All 14 head trauma had negative CT	2	No	Yes	No	In head trauma patients 4/14 were read by both raters as having HIV	"SPECT is more sensitive than CT in detecting brain injury after mild	Data suggest SPECT is a more sensitive imaging tool compar

							control (n=15)		scans					encephalopathy. 10/14 head trauma patients had abnormal scans. None of the normal controls were classified as having trauma, but 3/15 for rater 1 and 5/15 for rater 2 were classified as having HIV encephalopathy.	head trauma.”	ed to CT in the detection of brain injury post mild head trauma.
Abdel-Dayem 1987 (4.0)	SPECT	Prospective	N = 19	No mention of mean age or sex distribution	No mention of sponsorship or COI.	Left and right cerebral hemispheres	Acute traumatic head injury	SPECT ^{99}mTc-HMPAO	CT	Yes	No	No	No	14 trauma patients and 5 healthy volunteer (controls). SPECT detected 54 lesions	“Tc-99m-HM-PAO SPECT was shown to have the following advantages: It	Small sample. Data suggest cerebral perfusion changes correlated to

														on 14 of the trauma patients and 54 lesions with CT scan. All 54 lesions were correlated with clinical examinations and considered true-positive by both raters. 16/22 lesions found on CT were also found with SPECT.	reflected perfusion changes, was more sensitive than CT in demonstrating more lesions, and demonstrated lesions at an earlier stage than those demonstrated with CT."	lesions which then determined progress.
Prayer 1993 (4.0)	SPECT	Prospective	N = 18 with severe closed head injury	Mean age of 31 years old. 7 Females, 11 Males	Sponsored by Ludwig Boltzmann Institute for Radiological Tumor Diagnosi	Frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellar hemisphere	Severe closed head trauma	SPECT ^{99}m-Tc HMPAO	CT and MRI 1.5 Tesla T1 and T2-weighted	No	No	Yes	36 months	17/18 had cortical contusions and 9/18 diffuse axonal injury on MRI. 105 lesions	"Our results strongly suggest that in patients with subacute or chronic severe	Small sample size. Data suggest MR in combination with SPECT. Increas

					s. No mention of COI.								were found in 18 patients using MRI. With SPECT reduced cortical cerebral blood flow was seen in 16/18. Hypofusion of white matter was found in 13/18 patients.	closed head injury and normal cranial CT; MR imaging and SPECT will provide important information regarding posttraumatic brain damage. ”	es the ability to assess post-traumatic brain damage.

Evidence for the Use of Positron Emission Test (PET)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnosis:	Comparison:	Results:	Conclusion:	Comments
Coles 2004 (4.0)	PET	Case-Control	Sponsored by Medical Research Council, UK Government, Royal College of Anesthetists of Anesthesia, Research Training Fellowship, Wellcome Foundation and Veverley and Raymond Sackler Studentship award. No mention of COI.	22 Patients	Mean age of 30 years old 4 Females, 18 Males	Head Injury	Head Injury (N = 12) – Head injury within last 24 hrs. Vs Control (N = 10) – Healthy volunteers	The voxel-based technique suggests that a large portion of the cortex ipsilateral to the lesions is at risk for ischemic damage and neuronal loss. Statistically significant increases in IBV were produced in the control sets when comparing a mean CBF of 37 with reduced CBF of 20, 10 and 5 (All three were $P < 0.05$)	"This study shows that voxel-based analysis of PET OEF maps is sensitive at defining tissue at risk of ischemic injury after early head injury"	Data suggest PET maps are useful tools in defining and quantifing brain ischemia post TBI.
Steiner LA, 2003 (4.0)	PET	Cohort	Sponsored by Myron B. Laver Grant, Margarete and Walter Lichtenstein-Stiftung grant, Overseas Research Student Award, Wellcome	N=20	Mean age was 33 years old. Mean age of 33 years old. No mention of sex distribution.	TBI	All patients admitted to the Neurosciences Critical Care Unit with severe (admission Glasgow Coma Score [GCS] 8) or moderate (admission GCS 12)	TCD FVm correlated significantly with PET CBF in both hemispheres (CPP 70 mm Hg: left, r2=0.24, P< 0.03; right, r2=0.33, P<0.01; pooled, r2=0.23, P<0.002; CPP 90 mm Hg: left, r2=0.33, P 0.01; right, r2=0.36, P< 0.01; pooled, r2=0.34;	"[T]he static rate of autoregulation calculated from TCD data and PRx provide useful information on autoregulation in head-injured patients. Studies grading autoregulation	Data suggest some variability in autoregulation methods but $SROR_{PET}$ and PRx may be of some benefit in approximating auto autoregulation

			Research Training Fellowship, Beverley and Raymond Sackler Studentship, Codman grant, and the UK government. No mention of COI.				traumatic brain injury, with secondary neurological deterioration requiring intubation and mechanical ventilation, were eligible for included in the study.	P<0.0001). There was a significant correlation between SRORPET and SRORTCD (left, r2=0.53, P<0.001; right, r2= 0.32; P<0.01), suggesting that SRORTCD is a useful approximation of autoregulation within the MCA territory.	on that basis of changes in AJDO2 need to be interpreted with caution. PRx seems to be a more robust estimator of autoregulation than Mx. More data are needed to validate Mx. At least when our methods are used, all measurements may be influenced by flow-metabolism coupling."	in head injured patients.

Evidence for the Use of Vascular Imaging Tests

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Biffl, 2006 (6.0)	Vascular Imaging Tests	Diagnostic	No mention of industry sponsorship or COI.	N=313 patients	Mean age: 37.7±1.8 years. 225 males, 88 females.	Blunt cerebrovascular Injury	CTA: Computed Tomographic Angiography Vs. DSA: Digital Subtraction angiography	The GCS score averaged 12.9. Seventeen patients had C-spine injuries and 9 had BCVI. Eighteen patients had 20 blunt cerebrovascular injuries. Two patients had sign related to BCVI before diagnosis. Concordance between CTA and DSA was excellent. Four patients had false-positive CTA studies.	"CTA detected all clinically significant injuries during this study period. Liberal screening with 16-slice CTA is appropriate and is likely to miss very few significant injuries. A multicenter trial will help to clarify risk factors and the accuracy of noninvasive diagnostic modalities."	Data suggests 16 slice CTA is reliable fore detecting BCVI and is non-invasive.
Bodanapally, 2014 (6.0)	Vascular Imaging Tests	Diagnostic	No mention of sponsorship. No COI.	N=45 patients all had CTA and DSA.	Mean age: 31 years. 35 males, 10 females.	Penetrating Brain Injury	CTA: helical CT angiography Vs. DSA: digital subtraction angiography	Sensitivity of CTA for detecting arterial injuries was 72.7% (95% CI 49.8%–89.3%); specificity, 93.5% (95% CI 78.6%–99.2%); PPV, 88.9% (95% CI 65.3%–98.6%); and NPV, 82.9% (95% CI 66.4%–93.4%). CTA correctly identified all 7 TICAs. Sensitivity, specificity, PPV, and	"Computed tomography angiography had limited overall sensitivity in detecting arterial injuries in patients with PTBI. However, it was accurate in identifying TICAs, a subgroup of injuries usually managed by either	Data suggest CTA good for detection of TICAs but limited for detection of PTBI arterial injuries.

								NPV of CTA in detecting TICAs were 100%. To compare agreement with DSA, the standard of reference, confidence scores categorized as low, intermediate, and high probability yielded an overall effectiveness of 77.8% (95% CI 71.8%–82.9%).	surgical or endovascular approaches, and non-TICA injuries involving the first-order branches of intracranial arteries."	

Evidence for the Use of Brain Acoustic Monitor (BAM)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Dutton 2011 (4.5)	Brain Acoustic Monitor (BAM)	Diagnostic	No Mention of Sponsorship or COI.	N=369 suspected with mTBI Glasgow Coma Score (GCS) 13-15. N=79 healthy volunteers and Non-TBI patients;	Mean Age 41 (18-89)	Traumatic Brain Injury	Clinical Assessment as well as Computed Tomographic (CT).	25 patients had abnormal CT scan, 14 of the 25 patients had abnormal BAM (Sensitivity 100%, Specificity 30.06%). BAM vs Clinical Assessment: Final Diagnosis results, Sensitivity 0.71, Specificity 0.30. Among those initially categorized incorrectly, predictive power of abnormal BAM was 0.89.	"There is no gold standard for the diagnosis of mTBI. BAM screening is a useful diagnostic adjunct in patients with mTBI and may facilitate decision making. An abnormal BAM reading adds significance to LOC as a predictor of a new abnormality on head CT. In our study, opting not to CT scan patients with a normal BAM signal would have missed no new CT findings and no patients who required medical intervention for TBI, at a cost savings of $202,950."	Data suggest no single method for detecting mild TBI is adequate and using BAM as an adjunct method may be useful.
Dutton 2005 (4.5)	Brain Acoustic Monitor (BAM)	Diagnostic	John Sewell is the inventor and patent holder for the brain acoustic	N=206 patients who had blunt trauma, TBI symptoms, or visible	Mean Age 40.9	Traumatic Brain Injury	Computed Tomographic Scan (CT) and Glasgow Outcome Score (GOS)	Abnormal BAM with abnormal CT scan; Sensitivity 93%. Positive predictive value of 54% large	"BAM screening was highly sensitive to the presence of anatomic findings on CT scan, but not highly specific.	Data suggest BAM sensitive to CT imaging but not specific.

			monitor technology. Dutton et al hold no financial interest in BAM.	injury to the head;				number of false positive (14.3% Specificity). BAM screening compared to GOS, 100% Sensitivity as well as a 13% Specificity.	This may reflect oversensitivity of interpretation or transient perturbations in cerebral perfusion that were not associated with CT-detectable brain abnormalities. Early BAM screening of patients with TBI has the potential to guide diagnostic and therapeutic decisions prehospital and in the ED, but further refinement of specificity is required."	
Dutton 2002 (4.0)	Brain Acoustic Monitor (BAM)	Diagnostic	No Sponsorship or COI.	N=28 patients who had severe Traumatic Brain Injury;	Mean Age 35.7 years. 24 males, 6 females.	Traumatic Brain Injury	Brain acoustic monitor and Glasgow outcome score	BAM vs Clinical Status: Positive Predictive value (PPV) 83%, Negative Predictive Value 100%. Initial BAM recording predicted clinical status at discharge 25/28 cases ($p<0.01$). Initial BAM results and Continual BAM screenings did not different in 25/28 patients.	"It is possible that the BAM can be used to screen patients with TBI and indicate the need for more invasive care in much the same fashion that the pulse oximeter does for patients with thoracic injury or respiratory distress. Whether the BAM can be refined to the point of guiding clinical decision	Data suggest the BAM signal correlated with low GCS scores or death.

									making in the absence of direct determination of ICP is an open question and the subject of our continued research.”	

Evidence for the Use of Quantitative Electroencephalograph (QEEG) and Electroencephalograpghy (EEG)

Author Year (Score)	Category:	Study type:	Sponsorship and COI	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Ayaz 2015 (6.5)	EEG/QEEG	Diagnostic	Supported in part by funding from BrainScope Company, Inc, which covered expenses related to data acquisition. The device used for electroencephalogramdata acquisition is under development by BrainScope Company, Inc. COI, Leslie S Prichep is a scientific consultant to BrainScope Company, Inc, who provided the funds for this research. Brian J O'Neil discloses that BrainScope sponsored the study atWayne State University covering technical costs; however, BrainScope did not participate in the data analysis or writing of the	N = 152	(104 males, 48 females). Mean age is 36.6 years.	TBI	QEEG Vs. NOC Vs. CCHR VS. Nexus II	QEEG had a sensitivity of 92.3% and specificity of 57.1%. ; NOC sensitivity 96.1. Specificity: 15.8; CCHR sensitivity: 46. Specificity: 86.5; Nexus II sensitivity: 96.1. Specificity: 31.7.	"At a sensitivity of greater than 90%, QEEG discriminant score had better specificity than NOC and NEXUS II. Only CCHR had better specificity than QEEG discriminant score but at the cost of low(b50%) sensitivity."	Data suggest that when sensitivity was >90% of EEG had better specificity than NEC and NEXUS II for predicting intra-cranial lesions via head CT from mild TBI patients CCHR had better specificity than EEG but sacrificed a reduced sensitivity (50%)

			manuscript. No other financial relationships were present.							
Slobounov 2012 (4.0)	EEG/QEEG	Diagnostic	This work was supported by National Institutes of Health Grant RO1 NS056227-01A2 ‘‘Identification of Athletes at Risk for Traumatic Brain Injury’’. No mention of COI.	N = 380	(270 males, 110 females). Mean age is 21.0 years.	TBI	Alpha power suppression standing Vs. Sitting.	The magnitude of alpha power suppression predicted the rate of recovery of this measure in sub-acute and chronic phases of injury (r2 = 0.609, p < 0.01). Finally, 85% of MTBI subjects who showedmore than 20% of alpha power suppression in the acute phase of injury did not return to pre-injury status up to 12 months post-injury.	“Neurophysiological measures are excellent tools to assess the status and prognosis of patients with MTBI.”	Study demonstrates that use of a balance study with EEG over time in mild TBI patients helps identify residual cerebral dysfunction.

Evidence for the Use of Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Schatz 2006 (5.5)	ImPACT	Diagnostic	No mention of sponsorship or COI.	N = 138	(86 males, 52 females). Mean age is 16.9 years.	Concussion	ImPACT Vs. Post-Concussion Symptom Score (PCSS)	The combined sensitivity of ImPACT and PCSS is 81.9%. The specificity is 89.4%. Hotelling Trace (F=16.6; p=.001). Verbal Memory (F=32.4, p=.001). Visual Memory (F=34.9; p=.001). reaction time (F=43.6; p=.001). Processing speed (F=61.1; p=.001). Symptom Scale score (F=.3; p=87). Age didn't emerge as covariate (F=1.58; p.16).	"ImPACT is a useful tool for the assessment of the neurocognitive and neurobehavioral sequelae of concussion, and can also provide post-injury cognitive and symptom data that can assist a practitioner in making safer return to play decisions."	ImPACT provides post-injury cognitive and symptom data which could assist clinicians in clinical guidance post concussion.

Echemendia 2016 (4.0)	ImPACT	Diagnostic	No mention of sponsorship. No COI.	N = 187 athletes.	Mean age is 20.95 years. No mention of gender.	Concussion	ImPACT's indeces are composed of subscores from six cognitive modules: Word Discrimination Modules, Design Memory Modules, Symbol Matching, Color Match, and Three Letters module.	Speed index across multiple language two factor model is promising. Time composites from .52-.74. Speed composite of .73 for English. Visual motor=.65. Reaction time = .81. Speed composite (for Czech) =.82. Improvement in Memory composite is evident.	"The increased stability in test scores improves the test's ability to detect cognitive changes following injury, which increases the diagnostic utility of the test and allows for better return to play decision-making by reducing the risk of exposing an athlete to additional trauma while the brain may be at a heightened vulnerability to such trauma."	Data suggest that the 2-factor approach increases the one year reliability of ImPACT.
Nelson 2015 (4.0)	ImPACT	Diagnostic	One or more of the authors has declared the following potential conflict of interest or source of funding: This work was supported by the US Army Medical Research and Materiel Command under award number W81XWH-12-1-0004. This	N = 2063	(1584 males, 479 females). Mean age is 17.8 years.	Concussion	ANAM Vs. Axon Vs. ImPACT	ImPACT had the lowest invalid profile score of 2.7%. ANAM had 10.7%. Axon had 11.3%. ANAM vs Axon (OR=.95; P=.686). Axon and ANAM vs. ImPACT (OR=4.20; P<.001).	"The validity criteria for these CNTs may not identify the same causes of invalidity or be equally sensitive to effort. The validity indicators may not be equally appropriate for some athletes (eg, those with neurodevelopmental disorders)."	Data suggest ANAM, Axon Sports and ImPACT may be variable in terms of sensitivity to effort.

			publication was also supported by the Clinical and Translational Science Institute grant 1UL1-RR031973 (-01) and by the National Center for Advancing Translational Sciences (National Institutes of Health) grant 8UL1TR000055.					Axon vs ImPACT (OR=4.41; P<.001).		
Blake 2015 (3.0)	ImPACT computerized test.	Diagnostic	No mention of sponsorship. COI, a. Summer Ott has received honoraria from ImPACT Applications to conduct educational workshops. However, ImPACT Applications, Inc., had no role in the conceptualization of the study, the collection or analysis of the data, the writing of the article, or the decision to submit it for publication. b. Philip Schatz has served as a	N = 58	Mean age is 22 years. (13 males, 45 females).	Concussion	ImPACT Vs. Symptom Scale	English vs Spanish (F=.75, p=.59). English first vs. English second; English Composite (F=.56, p=.69), Spanish Composite (F=1.73, p=.16). Hotelling's Trace (F=3.05, p=.01). Verbal Memory (F=6.64, p=.013). Visual Memory (F=.46,	"Suggest a need for separate normative data for Spanish-speaking individuals completing the ImPACT battery if baseline data are not present."	Data suggest a need for separate normative data for Spanish speaking persons taking ImPACT of baseline data are unavailable.

			consultant to ImPACT Applications, Inc., however, ImPACT Applications, Inc., had no role in the conceptualizatio n of the study, the collection or analysis of the data, the writing of the article, or the decision to submit it for publication. c. Margaret Blake, Elizabeth Villanyi and Katia Kazhuro have no relevant conflicts of interest to disclose.					p=.50). Reaction Time (F=.47, p=.50). Total Symptoms scores (F=3.78, p=.057).		

Evidence for the Use of Military Acute Concussion Evaluation [318]

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:		Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
McCrea 2014 (4.5)	Other Military Acute Concussion Evaluation [318]	Diagnostic	The study was funded by a cooperative agreement with the United States Medical Research and Military Command (USAMRMC) (PT 073286) through USAMRMC Funding Opportunity Number W81XWH-07-TBI-CA (M. McCrea, Principal Investigator). No mention of COI.	N = 723 military personnel	Mean age: 23.62. 553 males, 54 females		Concussion/TBI	(N = 179) documented MACE data from day of mTBI vs. (N = 544) MACE normative control group	On the day of mTBI event, the mTBI group had significantly lower MACE scores than the control group (23.48 vs. 26.92, p <0.00001).	"Findings from the current study support the use o f the MACE as a valid screening tool to assess for cognitive dysfunction in military service members during the acute phase after mTBI."	Data suggest MACE may be used to evaluate mild TBI in U.S. military personnel.

Evidence for the Use of King Devick

Author Year (Score)	*Category:*	*Study type:*	*Conflict of Interest*	*Sample size:*	*Age/Sex:*	*Diagnoses:*	*Comparison:*	*Results:*	*Conclusion:*	*Comments:*
Galetta, 2015 (6.5)	TBI	Prospective-Diagnostic	No mention of sponsorship. COI, S.L. Galetta has received honoraria for speaking from Biogen-Idec, Vaccinex, and Genzyme.	N = 332 athletes (243 youth, 89 collegiate)	Mean age: Youth group 11±3, Collegiate group 20±1. Sex(M:F) 270:62	Concussion	Baseline scores of a 2min visual performance measure of rapid number naming (King Devick test) and post-injury or control scores.	Concussed athletes had significant mean change of -5.2 seconds from baseline in King-Devick (KD) scores in comparison to the control group who scores were improved by a mean of 6.2seconds (p=0.002). In comparison to timed tandem gait (TG), Standardized assessment of concussion (SAC), KD had the greatest capacity of distinguishing concussed vs control groups based on logistic regression models. (KD = 0.92, TG = 0.87, SAC = 0.68 (p<0.001)).	"Adding a vision-based performance measure to cognitive and balance testing enhances the detection capabilities of current sideline concussion assessment."	Data Suggest the addition of a vision-based performance measure to cognitive and balance testing increases concussion identification.
Fischer 2015 (5.0)	King Devick	Diagnostic	Sponsored by grants from Mission Connect, a program of TIRR Foundation. No COI.	(N=30)	21 males, 9 females; mean age for group M 33±16.5, group O 31±11.6, and group N 33±15.0.	Patients had a variety of injuries and were grouped accordingly, 10 mTBI patients (M), 7 orthopedic injury group (O), and 12 normal control (N)	Comparison between groups of a King-Devick tablet based test in controls, orthopedic injuries, and possible concussion (M) group.	KD task showed no significant difference between all three groups. Anti-Point response time with AUROC of 0.98 (0.96-1.00 (95%CI)). Pro-Point response time (RT) showed AUROC of 0.93 (0.84-1.00 (95%CI)).	"[I]n conclusion, these findings demonstrate that these quick tablet-based measures are able to reliably detect sensorimotor and cognitive impairments within hours after a mild traumatic brain injury and in the future may prove useful in	Data suggest tablet based tasks may provide a more sensitive metric for functional deficits leading to early detection and prognosis.

									evaluating interventions or predicting persistent post-concussion Symptoms at the time of injury onset."	
King 2015 (4.5)	King Devick	Observational Diagnostic	No sponsorship or COI.	(N=104)	104 males, 0 females; Mean age 23.7±5.0	Some patients had been diagnosed previously with concussions because of athletics	Comparison between individuals with witnessed concussive events during their season and those who did not receive a concussion during their season.	Baseline KD score vs Post match KD score, witnessed concussion group: 43.6 (31.1 – 54.3) vs 48.0 (38.8 – 58.6) ($p<0.05$), difference of 6.2 s. Baseline KD score vs Post match KD score, unwitnessed concussion group: 40.6 (34.2 – 48.6) vs 45.9 (38.1 – 53.3), difference of 4.6 s.	"The K–D and SCAT3 tests helped identify cognitive impairment in players without clinically observable symptoms post-match. The rate of undetected concussion was higher than detected concussions by using the K–D test routinely following matches."	Data Suggest K-D test detects a high number of undetected concussions following rugby matches.
Munce 2014 (4.0)	King Devick	Observational Study	Authors' received financial support from Sanford Research, South Dakota. No COI.	(N=10)	10 males, o females; Mean age of 13.04±0.7.	Patients were not diagnosed with any neurological impairment.	Compared adolescent football players before and after a 12-week season to investigate affection on cognitive function.	King-Devick test 1, pre vs post season (sec): 14.63±1.80 vs 13.18±1.31 ($p<0.05$). Balance with eyes closed, pre vs post season: 3.33±2.31 vs 1.72±1.38 ($p<0.05$). ImPACT composite score Reaction time pre vs post season: 0.58±0.04 vs 0.54±0.04 ($p<0.05$).	"In conclusion, selected clinical measures of neurologic function were not adversely affected in 10 youth football players tested before and after a 12-week season. There were, however, significant improvements in some measures of postural stability, oculomotor performance, and reaction time."	Data suggest all measures of neurological function remained unchanged.
King 2013 (4.0)	King Devick	Observational Diagnostic	No mention of sponsorship. No COI.	(N=37)	37 males, 0 females; Mean age 22.0±4.0.	(N=30) patients were previously diagnosed with concussion	Comparison between pre and post-match KD and SCAT tests as well as comparing	precompetition	"[T]he KD was able to identify players with a suspected concussion and players with a concussion that was not reported or	Data suggest K-D test good for rapid assessment of concussion and identified some players who had

						with clinical criteria.	athletes with previous concussion and no previous concussion pre match.		witnessed. The ease-of-use of the KD made it more acceptable to team management and players, as it provided immediate feedback to the player and coaching staff.	not previously reported any sign or symptoms of concussion.
Galetta, 2013 (4.0)	TBI	Prospective Diagnostic	No mention of sponsorship. COI, Dr. Galetta received honoraria from Biogen-Idec, Questcor, and Teva.	N = 27 hockey players	Mean age: 28±5 Sex(M:F) 27:0	Concussion	King-Devick Test and SCAT2 SAC test.	A 1 point reduction in SAC immediate memory score was associated with an average increase of 7.3 seconds in the K-D test (R^2=0.62, (p<0.001)). A reduction of 1 point in total SAC score was associated with an average increase of 2.2seconds in the K-D test (R^2=0.25, (p=0.01)).	"A composite of brief rapid sideline tests, including SAC and K-D (and balance testing for non-ice hockey sports), is likely to provide an effective clinical tool to assess the athlete with suspected concussion."	Data suggest a combination of rapid assessment tests such as K-D and SAC as well as balance testing may be effective for identification of concussion.
Galetta, 2011 (4.0)	TBI	Longitudinal Diagnostic Study	No mention of Sponsorship. COI, Dr.Devick is an employee of King-Devick Test, LLC. Dr. Galetta has received honoraria from Biogen-Idec, Teva, and Novartis.	N = 219 collegiate athletes	Mean age: 20.3±1.4 Sex(M:F) 182:37	Concussion	Baseline K-D test scores, post-season scores, and post-concussion scores when applicable.	K-D testing immediately after a concussion showed significantly worse median scores in comparison to median baseline scores (46.9 seconds vs 37.0 seconds (p = 0.009)).	"This study of collegiate athletes provides initial evidence in support of the K-D test as a strong candidate rapid sideline visual screening tool for concussion."	Data suggest K-D test may be a good rapid screening tool for concussion.
Alsalaheen, 2015 (4.0)	TBI	Diagnostic	Sponsored by Dr. Ben F. Bryer Foundation Research Fund. No COI.	N = 157 high school athletes	Mean age: 15.4 Sex(M:F) 157:0	Concussion	K-D test, Balance Error Scoring System (BESS), and Limits of Stability (LOS)	Faster Velocity of LOS was associated with better K-D score (r= -0.22, (p=0.024)). No significant differences were observed in median K-D scores from	"The K-D test was reliable over a short time interval, yet further research is needed to support the long-term reliability of the K-D test over clinically relevant periods."	Data suggest K-D test detects specific aspects of ocular motor brain function not detected in balance tests.

								participants with a concussion history, and those without (41.1sec vs 43.2sec; (p=0.438)).		
Leong D, 2015 (4.0)	King-Devick test	Diagnostic	Dr. Leong is an employee of King-Devick Test, LLC as a Director of Research. Dr. Balcer has served as a consultant for Biogen Idec, Questcor, and Novartis; and has received research support from the NIH/NEI and the National MS Society. Dr. Galetta has served as a consultant for BiogenIdec and Vaccinex. The work performed in this study was not funded by any of the above sources and the remaining authors have no disclosures.	N= 127 athletes	Mean age: 19.6 years	TBI	The King-Devick test Vs. Modified sport concussion assessment Tool 2(SCAT2) K---D testing was administered immediately on the sidelines for football players with suspected head injury during regular games and changes compared to baseline were determined. Post-season testing was also performed to compare non-concussed athletes' test performance.	Concussed athletes (*n* = 11) displayed sideline K---D scores that were significantly higher (worse) than baseline (36.5 ± 5.6 s vs. 31.3 ± 4.5 s, $p < 0.005$, Wilcoxon signed-rank test). Post- season testing demonstrated improvement of scores and was consistent with known learning effects (35.1 ± 5.2 s vs. 34.4 ± 5.0 s, $p < 0.05$, Wilcoxon signed-rank test). Test-retest reliability was analyzed between baseline and post-season administrations of the K-D test resulting in high levels of test-retest reliability (intraclass correlation coefficient (ICC) = 0.95 [95% Confidence Interval 0.85---1.05])	"The data show worsening of K---D test scores following concussion further supporting utility of the K---D test as an objective, reliable and effective sideline visual screening tool to help identify athletes with concussion."	Data suggest athletes with higher K-D scores, compared to baseline most likely have suffered a concussion.
Ventura R 2015 (4.0)	King-Devick test	Diagnostic	No COI or sponsorship mentioned	N= not mentioned	not mentioned	TBI	The King-Devick (K-D) test and	The King-Devick (K-D) test is a visual performance measure	"[A] combination of visual processing tasks, neuroimaging,	Data suggest a combination of assessment tools such as

							Sports Concussion Assessment Tool	that may increase the sensitivity of detecting concussions on the sideline when used in combination with tests of cognition and balance that are part of the Sports Concussion Assessment Tool (3rd ed.; SCAT3). Portable eye movement trackers and pupillometry may in the future improve our neuro-ophthalmic assessment after concussions. Combining visual tasks with neuroimaging and neurophysiology has allowed subtle changes to be detected, may refine our ability to make appropriate return-to-play decisions, and could potentially determine susceptibility to long-term sequelae of concussion	serum biomarkers, and electrophysiologic recordings may allow subclinical brain injury to be further studied, and may provide insights into those vulnerable to long-term sequelae."	neuroimaging and visual tasks allows for better concussion related decision making
Tjarks BJ 2013 (4.0)	King-Devick test	Diagnostic	No COI. No mention of sponsorship	N=35 concussed individuals	Age range: 12–19 y; 18 females, 17 males)	TBI	King-Devick test and impact	KD times improved with each visit (ΔV1–V2: 7.86 ± 11.82; ΔV2–V3: 9.17 ± 11.07; ΔV3–V4: 5.30 ± 7.87 s) and paralleled improvements in PCSS (ΔV1–V2: 8.97 ± 20.27; ΔV2–V3: 8.69 ± 14.70; ΔV3–V4: 6.31 ± 7.71), RT (ΔV1–V2: 0.05 ± 0.21; ΔV2–V3: 0.09 ± 0.19; ΔV3–	"Cognitive visual performance testing using KD has utility in concussion evaluation. Validation would further establish KD as an effective ancillary tool in longitudinal concussion management and research.	Data suggest both the King-Devick and impact have similar scores during concussion recovery. Data suggest use of King-Devick in acute health care settings as a tool in

								V4 0.03 ± 0.07) and VMS (ΔV1–V2: −5.27 ± 6.98; ΔV2–V3: −2.61 ± 6.48; ΔV3–V4: −2.35 ± 5.22). Longer KD times were associated with slower RT (r = 0.67; P < 0.0001) and lower VMS (r = −0.70; P< 0.0001), respectively		concussion assessment.
Silverberg N 2014 (4.0)	King-Devick test	Diagnostic	No COI. This study has been supported by the Medical Research Fund of Tampere University Hospital, the Maire Taponen Foundation and the Emil Aaltonen Foundation.	Participants with MTBI (n=26) and controls with non-head injuries (n=33)	Mean age: 38.6 years; 23 females, 36 males	TBI	Sport Concussion Assessment Tool 2 (SCAT2) vs. King Devick test (K-D)	The patients with MTBI differed from those without MTBI on components of the SCAT2, including the Symptom Scale (Cohen's d=1.02–1.15, p<0.001) and Standardized Assessment of Concussion (d=0.81, p=0.004), but not the K-D test (d=0.40, p=0.148). In a logistic regression analysis, the K-D Test did not contribute over and above these two measures in predicting group membership (MTBI vs. control), p=0.191. Low K-D Test scores in the MTBI group (<1 SD below controls) were not associated with poor SCAT2 performance, loss of consciousness or traumatic abnormalities on MRI, suggesting these cases may have been false positives.	"The present findings do not support the K-D Test for the assessment of civilian MTBI in an ED setting.	Data do not suggest use of K-D test for mTBI in an emergency department

Seidman D 2015 (4.0)	King-Devick test	Diagnostic	No COI. No mention of sponsorship	N= 343 athletes from local high school football teams	Mean age: 15.5 years; gender not specified	TBI	The King–Devick (KD) test	Of the 343 athletes, nine were diagnosed with concussions. In all concussed players, cumulative read times for the KD test were significantly increased (p b 0.001). Post-season testing of non-concussed athletes revealed minimal change in read times relative to baseline. Univariate analysis revealed that history of concussion was the only demographic factor predictive of concussion in this cohort.	"The KD test is an accurate and easily administered sideline screening tool for concussion in adolescent football players."	Data suggest K-D test is easy to administer as well as accurate.
Benedict P 2015 (4.0)	King-Devick test	Prognostic	Dr. S. Galetta has received speaking and consulting honoraria from Biogen, Genzyme, and Teva. Dr. Balcer has received consulting honoraria from Biogen and Genzyme, and has served on a clinical trial advisory board for Biogen. The authors have no financial	N= 206 with sport related injuries (concussions) and non-sports injuries	Mean age: 35 years, gender: no of females, males not reported	TBI	Standardized Assessment of Concussion (SAC), modified Balance Error Scoring System (BESS), and K-D	Symptom Evaluation scores showed a higher severity and a greater number of symptoms to be associated with older age (r=0.31, P=0.002), female gender (P=0.002, t-test), and longer time between the concussion event and first appointment at the concussion center (r= 0.34, P = 0.008). Performance measures of K-D and BESS also showed associations of worse scores with	"This study demonstrates a novel use of sideline concussion assessment tools for evaluation in the outpatient setting, and implicates age and gender as predictors of outcomes for these tests."	Data suggest age and gender are predictors of outcome for SCAT, SAC and KD and BESS

			interest in the SCAT3 or King–Devick tests; the work performed in this study was not funded by any of the above sources.					increasing patient age (r = 0.32–0.54, P ≤ 0.001), but were similar among males and females and across the spectrum of duration since the concussion event. Patients with greater Symptom Severity Scores also had the greatest numbers of referrals to specialty services in the concussion center (r=0.33, P=0.0008).Worse Immediate Memory scores on SAC testing correlated with slower K-D times, potentially implicating the dorsolateral prefrontal cortex as a commonly involved brain structure.		
Leong DF 2014 (3.5)	King-Devick test	Diagnostic	No mention of COI or sponsorship	N=34 amateur boxers	Mean age: not reported	TBI	Military acute concussion evaluation [318] vs K-D test	Post-fight KD scores were lower (better) than the best baseline score (41 vs. 39.3 s, P=0.34, Wilcoxon signed-rank test), in the absence of concussion. One boxer sustained a concussion as determined by the ringside physician. High levels of test-retest reliability were observed (intraclass correlation coefficient 0.9 [95% CI 0.84-0.97]. additionally 6 boxers who participated showed no worsening of their K-D times	"Results demonstrate that the K-D test is a rapid ringside screening tool for concussion that can be accurately and easily administered by non-medically trained sports parents to help identify athletes with concussions."	The K-D test is a concussion screening test, which doesn't require professionally trained personnel to administer.

								further supporting that scores are not affected by the fatigue associated with sparring.		
Van Wyk A 2014 (3.5)	King-Devick test	Diagnostic	No COI. Research funding to conduct the study was obtained from the Medical Research Council of South Africa.	N= 24 patients with Unilateral spatial neglect	Mean age: not reported.	TBI	The effect of saccadic eye movement training with Visual scanning exercises (VSEs) integrated with task-specific activities on USN post stroke. King-Devick Test vs Star Cancellation Test	Statistical significant difference was noted on the King-Devick Test (*P* = .021), Star Cancellation Test (*P* = .016), and Barthel Index (*P* = .004).	" Intensive saccadic eye movement training with VSE integrated with task-specific activities has a significant effect on USN in patients post stroke. Results of this study are supported by findings from previously reviewed literature in the sense that the effect of saccadic eye movement training with VSE as an intervention approach has a significant effect on the visual perceptual processing of participants with USN post stroke. The significant improved visual perceptual processing translate to significantly better visual function and ability to perform activities of daily living following the stroke.	Data suggest improved visual processing read to increased visual function and performance.
Walsh D 2016 (3.5)	King-Devick test	Diagnostic	This research was funded by the Military Operational Medicine	N= 200 active duty military personnel with diagnosed	Mean age: 26.31 years; all males	TBI	K-D test	The mTBI group had approximately 36%mean slower performance time with significant differences between	" Significant differences in KD test performance were seen between the acute mTBI and control	Data suggest K-D test may be utilized for acute mTBI .

			Research Program of the U.S. Army Medical Research and Materiel Command (USAMRMC), and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). No mention of COI.	acute mTBI (≤72 h) and age-matched controls				the groups (p< 0.001) in both tests. There were significant differences between the two KD test administrations in each group, however, a strong correlation was observed between each test administration	groups. The results suggest the KD test can be utilized for screening acute mTBI. A validated and rapidly administered mTBI, screening test with results that are easily interpreted by providers is essential in making return-to-duty decisions in the injured warfighter."	
Vernau B 2015 (3.5)	King-Devick test	Diagnostic	No mention of COI or sponsorship.	N=108 youth ice hockey players	Mean age:12.5 years, gender: not specified	TBI	King-Devick (K-D) Test, Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Sport Concussion Assessment Tool 3 (SCAT3), and convergence	Pearson correlation analysis did not identify any relationship between baseline convergence, ImPACT or K-D times. Worse (higher) K-D times were associated with worse [341] scores on the ImPACT visual motor speed and reaction time subtests. There was no association between K-D score and SCAT3 memory score. Of the 10 patients who took the K-D test post-injury, eight scored faster and two scored one second slower than their baseline	" Further research is needed to determine which combination of concussion assessments provides the most clinically useful, non-overlapping information in managing pediatric concussion. In addition, our exploratory study may indicate that annual baseline assessments in children may not be frequent enough in light of their ongoing neurodevelopment."	Data suggest no correlation between ImPACT and K-D scores where higher K-D scores were associated with lower ImPACT scores

								(range 2–19 days, M = 8, SD = 5.4). Six patients took ImPACT after their injury (range 2–19 days, M = 10, SD = 1.4).		
Vartiainen M 2015 (3.0)	King-Devick test	Diagnostic	No mention of COI or sponsorship	N= 185 male ice hockey players	Mean age: 23.8 years, all males	TBI	Sport Concussion Assessment Tool – 3rd Edition and King-Devick test	The average K-D score was 40.0 s (SD = 6.1 s, range = 24.0–65.7 s). K-D test performance showed no association with age, education, or the number of self-reported previous concussions in this sample. The association between trials 1 and 2 of the K-D test was good (ICC = 0.92, Pearson = 0.93).	"Research is needed on the intra rater reliability, test-retest reliability over clinically relevant intervals (e.g., 1 day, 1 week, 1 month, and 3 months), validity, and clinical usefulness of the test in athletes with concussions before health care professionals can have more confidence in using it. In our sample, each athlete performed the test without errors. Compared with the SCAT3, the test measures different aspects of functioning, so it may prove to have value as an additional method for assessing the acute effects of Concussion."	Data suggest King-Devick test results do not vary by age, education or concussion history
King, 2015 (3.0)	TBI	Prospective observational study	No mention of sponsorship or COI.	N = 19 junior league rugby team	Mean age: 10.4 ± 0.9 Sex(M:F) 14:5	Concussion	Pre-season baseline K-D test scores and Post-season or post-	Concussed athletes experience a mean change of 7.4seconds from baseline in post-match K-D times (p=0.018).	"The K-D test was quickly and easily administered making it a practical sideline tool as part of the continuum of	Data suggest K-D test is a quick concussion detection test.

							concussion scores.		concussion assessment tools for junior rugby league players."	
Rizzo 2016 (3.0)	King Devick	Diagnostic	Sponsored by 5K12HDOO1097 NICHD and NCMRR, National Institutes of Health Rehabilitation Medicine Scientist Training Program (JRR) and Empire Clinical Research Investigator Program (ECRIP). No COI.	N=67	24 males, 43 females; Mean age of 32.	N=25 individuals who were diagnosed with a concussion by the BYU concussion center.	Comparison between patients with a history of concussion and healthy controls with no history of concussion.	Total KD time (s), concussion patient vs nonconcussion patients: 53.4±14.04 vs 43.8±8.55 ($p<0.004$). Intersaccadiac interval analysis (ISI) (msecs), concussion vs non concussion patients: 324.4±85.6 vs 286.1±49.7 ($p=0.027$). Saccade spatial analysis, incorrect direction percentage of concussed vs non concussed participant: 14.43±8.26 vs 10.13±5.33 ($p=0.028$).	"Despite a wealth of literature noting prolonged KD test times following concussion, mechanisms explaining these findings have not been formally examined. We report on a number of eye movement findings in subjects with chronic concussion during performance of the KD test. Prolonged KD test times were associated with prolonged ISI values, an increased number of saccades (particularly at smaller amplitudes), and increased saccadic dysmetria.	Data suggest that in chronic concussion there may be disruption of the network which mediates visual function.

Evidence for the Use of SCAT

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Putukian 2013 (5.5)	SCAT	Diagnostic	Sponsored by American Medical Society for Sports Medicine Foundation and the New Jersey Commission on Brain Injury Research. COI: Putukian has nonfinancial support from National Football League Head Neck and Spine Committee, US Lacrosse Sports Science Safety Commission and National Collegiate Athletics Association. Echemendia has personal fees from Princeton University	N = 263 Athletes	Mean age of 20.3 years old. 87 Females, 176 Males	Concussion	Concussed Athletes (N = 32) Vs. Non-concussed Athletes (N = 231)	Concussed athletes have increased post concussive symptoms from baseline to post-injury testing for SCAT-2 ($P < 0.001$), symptom severity score ($P < 0.001$), total symptoms ($P<0.001$) and m-BESS ($P<0.05$). No significant change was seen in concussed athletes on the SAC.	"The SCAT-2 total composite score and each subcomponent are useful in the assessment of concussion."	Data suggest assessment of concussion is aided by SCAT-2 and subcomponents.

			and nonfinancial support and personal fees from National Hockey League and Major League Soccer. Bruce reports personal fees from Princeton University, National Hockey League and Archives of Clinical Neuropsychology.							
Luoto 2014 (5.0)	Neuropsychological Assessment	Cohort Study	No mention of sponsorship. No COI.	82 Patients meeting inclusion criteria (TBI or Control).	Mean age of 37.5 years old. 32 Females, 50 Males	mTBI	TBI Group (N = 49) Vs Control Group (N=33) Follow up one month after enrollment.	Patients with TBI had more symptoms and worse symptoms severity than the controls. SAC alone has a sensitivity of 34% and 94% specificity. Adding SCAT2 Symptom Score with the SAC increased the sensitivity to 64% while the specificity stayed at 94%.	"Emergency and military clinicians evaluating a patient with an mTBI within the first few days postinjury should consider including the SCAT2/SCAT3 or its key components as part of their assessment."	Data suggest SCAT 2 better than MACE in the detection of acute mTBI symptoms and cognitive impairment.
Snyder 2014 (5.0)	SCAT	Diagnostic	No sponsorship or COI.	N = 761 patients	Mean age of 14.8 years old. 105	Concussion	No comparison group mentioned	There is a significant effect of age on SCAT2 total score ($P < 0.001$).	"[F]indings suggests that the SCAT2 may have less	Data suggest SCAT-2 is useful for assessment of baseline function

					Females, 656 Males			Younger ages are associate with lower SCAT2 total score. Games-Howell analyses showed that the youngest age group (9 and 10) scored significantly lower on the SCAT2 compared to the older age group (17 and 18.	clinical utility in children under the age of 11 since variance in component scores for these children may be too limited to detect changes after a concussion has been sustained."	of adolescents but clinical utility may be best for children <11 years old.
Benedict 2015 (4.0)	SCAT	Diagnostic	Sponsored by the NYU School of Medicine. No mention of COI.	N = 206 with concussion	Mean age of 35 years old. No mention of sex distribution	Concussion	K-D Test Vs. SCAT3	Symptom severity scores were associated with a high K-D score (P = 0.002) and a low SAC (SCAT) score (P = 0.03). Low SAC scores were associated with high K-D scores (P = 0.005)	"This study demonstrates a novel use of sideline concussion assessment tools for evaluation in the outpatient setting, and implicates age and gender as predictors of outcomes for these tests."	Data suggest age and gender are predictors of outcome for SCAT, SAC, K-D and BESS.

Evidence for the Use of MMPI

Author Year (Score)	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
LaChapelle 2005 (7.0)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 49 individuals with TBI and spinal cord injury (SCI)	39 males, 10 females Mean age: 30.3 for TBI group, 43.4 years for SCI	TBI (n= 32) Vs. SCI (n=17)	MMPI VS. Center for epidemiological studies depression scale (CESD) VS. Revised neurobehavioral scales of the MMPI	The group with TBI scored significantly higher on the Cognitive scale and significantly lower on the Inactivity scale than the group with SCI (with or without depression as a covariate). The Glasgow Coma Scale correlated significantly and negatively with the Cognitive scale in the group with TBI. Discriminant function analysis revealed that together the scales correctly classified individuals with sensitivity and a positive predictive value (with respect to TBI) of 87% and 81%, respectively. Specificity and a negative predictive value (with respect to SCI) were 68% and 76%, respectively. The overall rate of correct classification of individual cases was 80% (with or without depression in the analysis). The	"Concurrent validation of specific TBI-related MMPI items against objective indexes of neurocognitive function, for example, might lead to the derivation of a more valid neurocorrective index than simple deletion of the items from the profile. Although an earlier effort to correlate MMPI neurocorrective factors with performance on neuropsychological tests in TBI met with little success (see Brulot et al., 1997), the results of this study suggest that such an approach be further examined in light of the high sensitivity and specificity for TBI of the Cognitive scale identified in this study."	Data suggest the revised neurobehavioral scales of the MMPI correctly classified TBI patients with a sensitivity of 87% and a PPV of 81% giving support for use of MMPI-2.

								Cognitive scale alone correctly classified individuals in the group with TBI with a positive predictive value of 84%.		
Greve K 2006 (6.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 259 participants with traumatic brain injury and N=133 general clinical patients.	137 females, 255 males 42.9 mean age.	Mild TBI Mod/severe TBI Vs. Clinical diagnoses CVA, Memory disorder Psyc, Tumor, Encephalopathy Infection Seizure Multiple sclerosis Substance abuse Academic problems Lupus	Scales and indicators examined in this study included: Infrequency (F), Infrequency-back (Fb), Infrequency, psychopathology (Fp), Fake Bad Scale, Dissimulation revised (DS-r), F minus K (F-K raw), Obvious minus Subtle (O-S raw), Lie (L), Correction (K), Ego Strength (ES), and the Meyers Composite Index (MI raw) The relevant indices of classification accuracy (and therefore error rate, the reciprocal of accuracy) are Sensitivity, Specificity, and Predictive Power	Significant group effects were observed for all scales except L. Generally, the No Incentive and Incentive Only groups did not differ (except for O-S) and the MND (Statistically Likely, Probable, Definite) groups generally did not differ. Thus, these results show a clear relationship between the amount of evidence suggestive of cognitive malingering and exaggeration on the MMPI-2	"A diagnostic system that does not take into account multiple modalities of disability presentation (i.e., focuses only on cognitive manifestations) likely misses important information. Thus, in the future, the system may benefit from modification and expansion to allow the diagnosis of malingering in its various behavioral and functional manifestations."	Data suggest diagnosing malingering is challenging and must consider disability presentation as well as cognitive manifestations or key information is missed.
Alkemade 2015 (6.5)	MMPI	Diagnostic	No COI. No mention of sponsorship	N= 259 TBI patients	162 males, 97 females Mean age: 35.7 years	TBI	Exploratory factor analysis (EFA) vs. confirmatory factor analysis (CFA) vs.	Results showed that the MMPI-2 RF was able to differentiate across the groups with the MMPI-2 RF specific problem scale	"In summary, the four-factor model of MMPI-2 Hs defined in this study was found to satisfy the criteria for partial measurement	Data suggest continued use of MMPI-HS items to determine

							invariance testing, vs. MMPI-2 Scale Hs	Anxiety adding incrementally to MMPI-2 Restructured Clinical scales in predicting PTSD. Both MMPI-2 RC1 (Somatic Complaints) and MMPI-2 RF head pain complaints predicted mTBI screen but did not add incrementally to each other. Of note, all of the MMPI-2 RF validity scales associated with overreporting, including Symptom Validity—Revised (FBS-r), were not significantly elevated in the mTBI group.	invariance across a TBI sample and a gender-matched subset of the MMPI-2 normative sample. None of the items from the Gass correction model that are included in the Hs scale were found to fail the test of invariance. In addition, practical impact analysis of the four-factor model supports retaining all items of the Hs scale when assessing patients with a TBI. Furthermore, while this study assessed the factormodel with a TBI sample, additional groups from the spectrum of neurological impairments require evaluation because patients experiencing diverse illnesses and injuries may also endorse physical and neurological symptoms potentially complicating interpretation of the MMPI-2."	the health of TBI patients.

Jones A 2016 (6.0)	MMPI	Diagnostic	No COI. No mention of sponsorship.	N=300 participants from a military sample with traumatic brain injury	248 males, 52 females mean age: 31.6 years	non-malingering group (NM) (n=145) Vs. Three malingering groups (NM) (n=155)	Response Bias Scale (RBS) Vs. the Symptom Validity Scales (FBS, FBS-r) vs Infrequent Somatic Responses scale (Fs), vs. the Henry–Heilbronner Indexes (HHI, HHI-r).	Cutoffs were developed by comparing a psychometrically defined non-malingering group (NM) with three psychometrically defined malingering groups (probable PM, probable to definite PDM, and definite malingering DM) and a group that combined all malingering groups. RBS had the largest mean effect size (d) when the malingering groups were compared to the non-malingering group (d range = 1.23–1.58).	"This research examined the performance of MMPI-2 and MMPI-2-RF C-S SVTs in a military sample of mostly closed head-injured patients with mTBI. The results indicate that RBS had the largest "mean" effect size (d = 1.58) in distinguishing the NM and the three malingering groups used for this research. This was followed by HHI and HHI-r; d was 1.50 for both scales. The lowest mean effect size was for Fs (1.23). These results suggest that there is not much difference in the C-S SVTs based on this metric, and that they all have utility. For the CM group, the results indicated that RBS, HHI, and HHI-r performed in a very similar fashion (d range = 1.39–1.42) with RBS having the largest effect size."	Data suggest Response Bias Scale (RBS) was lost at discriminating malingering from non-malingering.

Whitney 2013 (6.0)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 194 participants	Age 21 to 77 181 males, 13 females 50.67 years mean age.	Patients with TBI referred to the author for neuropsychological testing within a VA Medical Center.	Pass TOMM (N=149) RBS VS F VS Fb VS Fp VS FBS VS HHI Against Fail TOMM (N=45) RBS VS F VS Fb VS Fp VS FBS VS HHI TOMM=Test of Memory Malingering;	There was a statistically significant difference between passed TOMM (N=149) and failed TOMM (N=45) at for Pass TOMM (N=149) M: (11.4, 67.8, 66.2, 53.2, 20.6, 8.1) and SD: (4.1, 18.9, 22.2, 13.1, 5.6, 3.7) VS failed TOMM (N=45) M: (14.6, 82.1, 82.4, 61.5, 23.8, 10.7) and SD: (4.0, 20.8, 25.1, 17.0, 5.8, 3.2)	"Although the TOMM and the MSVT were used to classify individuals as demonstrating performance invalidity in the present study, it should be emphasized that the diagnosis of invalid presentation, especially if malingering is in question, is a clinical judgment that cannot be made on the results of symptom validity tests alone, but must be made in consideration of other psychometric, behavioral, and collateral data (Slick et al., 1999)."	Data suggest RBS and HHI show poor performance in predicting malingering.
Arbisi 2011 (5.5)	MMPI	Diagnostic	No mention of COI. This research was supported by grants from the University of Minnesota Press and U.S. Department of Defense Congressionally Directed Medical Research Program.	N= 229 National Guard soldiers, who were also administered questionnaires to identify posttraumatic stress disorder (PTSD) and mild traumatic brain	Mean age: 32.1 years Gender: not specified	Controls (n=166) PTSD (post-traumatic stress disorder) only (n=21) TBI only (n=33) PTSD and TBI (n=9)	Minnesota Multiphasic Personality Inventory–2 Restructured Form for PTSD Vs Minnesota Multiphasic Personality Inventory–2 Restructured Form for TBI	On the basis of responses to the screening instruments, the National Guard soldiers who produced a valid MMPI-2 RF were classified into four groups: 21 soldiers who screened positive for PTSD only, 33 soldiers who screened positive for mTBI only, 9 soldiers who screened positive for both conditions, and 166 soldiers who did not screen positive for either	"In sum, this study is the first of its kind to examine the utility of the MMPI-2 RF in discriminating between recently returned soldiers who screened positive for PTSD and mTBI from those who did not report symptoms consistent with those conditions. Generally, conceptually related scales such as RC7 and ANX from the	Data suggest MMPI-2RF is useful in assessment of PTSD in non-treatment seeking veterans and was able to differentiate between mTBI, PTSD and normal.

				injury (mTBI)				condition. Results showed that the MMPI-2 RF was able to differentiate across the groups with the MMPI-2 RF specific problem scale Anxiety adding incrementally to MMPI-2 Restructured Clinical scales in predicting PTSD. Both MMPI-2 RC1 (Somatic Complaints) and MMPI-2 RF head pain complaints predicted mTBI screen but did not add incrementally to each other. Of note, all of the MMPI-2 RF validity scales associated with overreporting, including Symptom Validity—Revised (FBS-r), were not significantly elevated in the mTBI group.	MMPI-2 RF were found to be effective in identifying the PTSD group. However, the MMPI-2 RF scales associated with somatic concerns were also significantly elevated in the PTSD group, suggesting that beyond symptoms commonly associated with PTSD, veterans returning from the war in Iraq who screen positive for PTSD report poor health and a range of somatic concerns."	
Peck CP 2013 (5.5)	MMPI	Diagnostic	No mention of COI. No mention of sponsorship	N= 100 patients with TBI with invalid TBI, valid TBI and patients with psychogenic non-epileptic seizures (PNES)	Mean age: 40.9 years 39 males 61 females	Valid TBI (n=27) Vs. TBI invalid (n=18) Vs. PNES (n=55)	the Symptom Validity Scale vs. Response Bias Scale (RBS) from the Minnesota Multiphasic Personality Inventory-2	Results indicate that a >30 raw score cutoff for the Symptom Validity Scale accurately identified 50% of the invalid traumatic brain injured group, while misclassifying none of the valid traumatic brain injured group and 6% of the psychogenic non-epileptic seizure disorder group. Using a >15 RBS raw cutoff score accurately classified 50% of the invalid traumatic	"Findings from this preliminary study suggest that the conjunctive use of the Symptom Validity Scale and the RBS from the Minnesota Multiphasic Personality Inventory-2 may be useful in differentiating probable malingering from individuals with brain injuries and conversion disorders."	A litigating sample. Data suggest RBS and FBS (both from the MMPI-2) help to distinguish those individuals who are malingerers from those with brain injuries and

								brain injured group and misclassified fewer than 10% of the valid traumatic brain injured and psychogenic non-epileptic seizure disorder groups. These cutoff scores used conjunctively did not misclassify any members of the psychogenic non-epileptic seizure disorder or valid traumatic brain injured groups, while accurately classifying 44% of the invalid traumatic brain injured individuals.		conversion disorders.
McCusker 2003 (5.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 63 participants	59 males, 4 females mean age was 30.8 years	Diagnoses included (not mutually exclusive): psychotic disorders (40%), affective disorders (52%), anxiety disorders (14%), substance abuse disorders (54%), personality disorders (40%), dissociative disorders (5%), sexual disorders (5%), organic mental disorders (6%), impulse control	Structured Interview of Reported Symptoms (SIRS) scores Vs. Minnesota Multiphasic Personality Inventory—2 (MMPI-2)	Despite differences between facilities in terms of seriousness of subjects' offenses, mean scores on the malingering tests were similar. Cutting scores for F(p) and F resulting in substantial correspondence between these scales and the SIRS were derived. Use of the cut score for F(p) proposed by Arbisi and Ben-Porath (1995) resulted in less agreement with the SIRS than did a lower cut score. No substantial difference between F(p) and F in each scale's overall agreement	"It is an experience that malingering and genuine psychopathology are by no means always mutually exclusive. Clinicians who perform assessments to rule out malingering are encouraged to establish local norms for F(p), F, and the SIRS in their assessment settings, using clinical ratings as the criterion for malingering and choosing cut scores that would reflect the relative importance of positive	Data suggest test scores in addition to interviews and clinical information.

						disorders (3%), and no or unclear diagnoses (9%)		with the SIRS was observed. A principal components analysis of the SIRS primary scales produced two factors, interpreted as Overreporting of Symptoms and Implausible Symptoms. F(p) was observed to correlate significantly with Implausible Symptoms but not with Overreporting of Symptoms; F was significantly correlated with both factors.	or negative predictive power in those settings."	
Ross 2004 (5.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 59 participants with head injury.	25 males, 34 females. Meang age is 40 years.	Traumatic Brain Injury with clinical scales of Hypochondriasis, Depression, Hyysteria, Psychopatic-Deviate, Masculinity-Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania, Social Introversion.	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs. Recognition Memory Test (RMT)	A cutoff score of 65 on the F scale provided a sensitivity of 66% and specificity of 64% for and overall correct classification rate of 65%, p<.001. A cutoff score of -6 on F-K index resulted in a sensitivity of 58% and specificity of 56% for an overall classification rate of 57%, p<.05. A cutoff greater than or equal to 21 for FBS resulted in 90% correct classification, p<.001. A cutoff score of 20 had a specificity of 85% and sensitivity of 95% A cutoff score of 25 had a sensitivity of 81% and specificity of 95%.	"The FBS appears to provide rather unique – and powerful – predictive power in identifying likely malingering in MHI, over and above traditional MMPI-2 validity indices and relevant clinical scales."	Data suggest the MMPI-2 FBS has the excellent sensitivity and specificity for accurate identification of effort in mild head injured persons.

Larrabee 2003 (5.0)	MMPI	Diagnostic	No mention of sponsorship or COI	N = 26 litigants performing worse significantly (p<.05).	14 males, 12 females. Mean age is 34.72 years.	Traumatic Brain Injury	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs Portland Digit Recognition Test (PDRT)	MMPI-2 validity scales for malingering and closed head injuries in the order of scale, malingerers, closed head injury, p value and effect size. F, 64.81, 57.10, p=.052, 0.54. Fb,66.19, 55.28, p=.051, 0.54. F(p), 54.00, 58.73, p=.151, -0.39. FBS, 26.15, 15.67, p=.001, 1.81, FBS, 26.15, 15.67, p=.001, 1.81. Meyers' Index, 3.31, 0.79, p=.001, 1.01. F-K, -7.15, -8.48, p=.519, 0.18. Ds-r, 57.52, 53.96, p=.320, 0.27. Subtle-obvious, 81.50, 35.47, .018, 0.66. Es, 28.05, 41.77, p=.001, -1.05.	"The sensitivity of the FBS to malingering in neuropsychological settings is superior to any other MMPI-2 validity or standard clinical scale and F, Fb, and F(p) are generally insensitive to malingering of neuropsychological symptoms."	
Nelson 2011 (4.5)	MMPI	Diagnostic	Supported by Grants funded by the Congressionally Directed Medical Research Programs (number PT074550, contract W81XWH-08-2-0038) to Scott R. Sponheim Ph.D. and the Minnesota Veterans Research Institute (MVRI) to Nathaniel W. Nelson, Ph.D.	N = 128. Divided into three groups of forensic (N=42), clinical (N=43), and research (N=43) with combat related traumatic brain injury.	123 males, 5 females. Mean age is 31.8 years.	Psychological Function with respect to Traumatic Brain Injury	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs Minnesota Multiphasic Personality Inventory -2 – Restructured From (MMPI-2-RF)	Analyses of MMPI-2/RF scales resulted in significant overall models. Fp, p=.323, Fp-r p=.021 were the only scales that did not show significant differences. RCd p=<.001, RC1 p<.001, RC2 p<.001, MLS p<.001, GIC p<.001, HPC p<.001, COG p<.001, STW p<.001, AXY p<.001 and ANP p<.001. Particpants with active disability claims were four times more likely to elevate on FBS p=.001; OR=3.86, 95% CI=1.73-8.63. Also 3 more times likely to elevate on FBS-r p=.018; OR=2.64, 95%	"The current findings suggest that rates of possible symptom exaggeration, particularly over-endorsement of somatic and cognitive symptoms, increases dramatically in forensic and clinical contexts relative to settings in which primary and secondary gain issues are less salient to OEF/OIF concussion groups."	Data suggest litigation significantly influences injury severity reporting as reflected in the MMPI-2.

			No mention of COI.					CI=1.16-6.04 and RBS, p=0.15; OR=3.07, 95% CI=1.19-7.92.		
Youngjohn 1997 (4.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 60 patients with vary levels of head injury.	42 males, 18 females. Mean age is 33.15 years.	Traumatic Brain Injury	Two groups of head injury compared using Minnesota Multiphasic Personality Inventory-2 (MMPI -2). Moderate/Severe head injuries (N=30) vs. Minor/mild head injury (N=30).	Significant differences were found on the basic scales Hs, D, Hy, Pt, and Sc. On scales Hs, all three groups were significantly different from one another. LOC for group 1 was 653, group 2 was 470, group 3 was .01. GCS group 1:6.9, group2: 7.27, group 3: 15.00. PTA for group1: 1,238, group 2: 774, and group 3:2. Large subset of patients completed the MMPI-2 content with 13 supplemntary scales including F Back (fb) Variable Response Inconsistensies (VRIN), and True Response Inconsistensies (TRIN).	"The virtually 100% prevalence of litigation in symptomatic minor/mild head injury gives rise to the obvious hypothesis that persisting symptoms and disability in this population are entirely determined by involvement in litigation."	Data suggest litigation significantly influences injury severity reporting as reflected in the MMPI-2.
Greiffenstein 2002 (4.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 68 patients with moderate-severe closed-head injury.	Mean age is 33.14 years.	Moderate/severe traumatic brain injury.	Claimants and all participants were administered the MMPI-2. FBS raw scores were tabulated.	AMHI and MSCHI groups had a significant difference in FBS group means p<.0001. No significant difference between groups on MMPI-F scale (t=-.833) or F-K index (t=-.907). Improbability ranking with FBS scores within the AMHI group	"FBS appears to be superior to the standard MMPI infrequency scales in differentiation of atypical versus better-documented neurological injury when litigation status is held constant. Correlational analyses	Data suggest FBS is superior to MMPI-2 F and F-K scalesfor distinguishing atypical vs real brain injury outcomes.

								obtained a significant r of.305 (p<.001). FBS had significant correlations with other MMPI scales with; Hs, Hy, D, Pt, Si, Sc, Pa, Pd, and Gough in descending magnitude. No significant correlations with L, K, Mf or Ma.	showed the FBS is not a pure validity construct measuring one type of spurious symptom over reporting."	
Van Dyke S, 2013 (4.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 120 participants	Age 17 to 85 94% male, 6% female 32.6 years mean age.	Patients with TBI from the urban Department of Veterans Affairs Medical Center	2-factor I SA VS VA 2-factor II C VS SR 3-factor I CP VS PV VS SR 3-factor II C VS SS VSS SV 4-factor PV VS SS VS SV	There was a statistically significant difference on individuals performing better on the MSVT (M = 96.48, SD = 6.55) when compared to other referrals (M = 92.36, SD = 12.94), t(118) = 2.30, p = .023.	"Overall, the current study contributes to the clarification of relationships between the constructs underlying cognitive performance measures, performance validity measures, symptom self-report measures, and symptom validity measures. The findings extend the consensus that forensic and clinical neuropsychological assessments should include a multifactorial assessment of effort (Bush et al., 2005; Heilbronner et al., 2009) to also encourage separate assessment of performance validity and symptom validity."	Data suggest performance validity should be evaluate separately from symptom validity.

Bolinger 2015 (4.5)	MMPI	Diagnostic	No COI No mention of sponsorship.	N= 79 Young adults with a history of mild head injury	Mean age: mean 18.97 years.	Those randomly assigned to simulate head injury and who showed evidence of following simulator directions by failing at least one PVT, as described above (n = 32) vs. Those randomly assigned to perform with their best effort and who showed no evidence of poor performance on any PVTs (n = 46).	Neurological Complaints (NUC) vs Cognitive Complaints [366] scales of the Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF)	Results showed that both scales, but especially NUC, are elevated in individuals simulating head injury, with medium to large effect sizes. Although both scales were highly correlated with all MMPI-2-RF over-reporting validity scales, the relationship of Response Bias Scale to bothNUCandCOG was much stronger in the simulators than controls. Even accounting for over-reporting on the MMPI-2-RF, NUC was related to general somatic complaints regardless of group membership, whereasCOGwas related to both psychological distress and somatic complaints in the control group only. Neither scalewas related to actual neuropsychological performance, regardless of group membership.	"The present results support the need for further examination of self-reported cognitive and neuropsychological complaints using objective cognitive tests (including PVTs). Clinicians need to remember that self-reported cognitive symptoms can be due to many causes, not necessarily cognitive impairment, or can be exaggerated in a non-credible manner. It remains imperative that clinicians interpret high scores on cognitive symptom scales in light of measures of non-credible symptom report, PVT performance, actual cognitive test performance, evidence of everyday functioning, and overall psychological distress."	Data suggest self-reported cognitive symptoms result from many causes not simply or necessarily cognitive impairment and may be exaggerated.

Kim JS 2013 (4.0)	MMPI	Diagnostic	No mention of COI. The study was supported by the 2009 Yeungnam University Research Grant	N= 219	Mean age: 37.87 years 161 males, 58 females	Participants with mild brain injury	Korean Wechsler Adult Intelligence Scale (K-WAIS) Vs. Korean Memory Assessment Scale (K-MAS) Vs. Korean Boston naming test (K-BNT) Vs. Symptom Checklist-90-revised (SCL-90-R) Vs. Minnesota Multiphasic Personality Inventory (MMPI	Over a quarter (26.9%) experienced severe psychopathological symptoms and 43.4% experienced mild or moderate psychopathological symptoms, and all of the mild TBI patients showed a significant relationship between neurocognitive functions and subjective and/or objective psy-chopathic symptoms, but the degree of this relationship was moderate. Variances of neurocognitive function were explained by neurotic and psychotic symptoms, but the role of these factors were different to each other and participants did not show intelligence and other cognitive domain decrement except for global memory abilities compared to the non-psychopathology group	"In this study, we demonstrated a relationship between the neuropsychological performance of patients with mild TBI and their psychopathological characteristics assessed in the DE process. We examined the variables that influenced psychopathological characteristics in neuropsychological performance among patients with mild TBI via statistical clustering of the same characteristics in mild TBI. Certain patients with mild TBI displayed psychopathological symptoms, but these were not directly related to cognitive decrement, and psychopathology and cognitive decrement were discrete aspects in patients with mild TBI."	Data suggest some mild TBI patients showed psychopathological symptoms but they did not appear to be directly related to cognitive decrement.

Youngjohn 2011 (4.0)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 82 participants with claimed TBI.	54 males, 28 females. Mean age is 45 years.	Diagnoses were categorized into Mild traumatic brain injury, complicated mild traumatic brain injury, and moderate/severe traumatic brain injury.	Minnesota Multiphasic Personality Inventory—2 Restructured Form (MMPI-2RF) vs. Portland Digit Recognition Test (PDRT) vs. Word Memory Test (WMT) vs. Dot Counting Test (DCT) vs.	Two way MANOVA comparing validity scales profiles of MMPI-2-RF showed no significant differences p=0.07. Somatic/cognitive scales using MANOVA did not indicate significant differences p=.32. The resulting function of somatic/cognitive scales classified 70.7%	"MMPI-2-RF scales FBS-r, RC1, and the Somatic/Cognitive scales (MLS, GIC, HPC, and NUC) can be useful tools in assessing symptoms, disability, and over-reporting in TBI litigants."	Data suggest the use of MMPI-2 RF is effective in neuropsychological assessment of TBI litigants in an attempt to identify poor effort, somatization or over reporting of symptoms.
Thomas 2009 (4.0)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 83 patients with claimed TBI.	55 males, 28 females. Mean age is 45 years.	Diagnoses were categorized into Mild traumatic brain injury, complicated mild traumatic brain injury, and moderate/severe traumatic brain injury.	Minnesota Multiphasic Personality Inventory—2 Restructured Form (MMPI-2RF) vs. Portland Digit Recognition Test (PDRT) vs. Word Memory Test (WMT) vs. Dot Counting Test (DCT) vs.	Two way MANOVA comparison of TBI severity groups indicated no significant differences; p=.31. Profiles of SVT status differed significantly p=.01. TBI severity and SVT status were not significantly different p=.08. MANOVA comparing RC scales were not significantly different p=.29. RC scales of SVT status differed significantly p=.02.	"RC scales of the MMPI-2-RF will perform functionally comparable to the traditional clinical scales of the MMPI-2 in litigating TBI populations. The MMPI-2 validity, clinical, and RC scales all appear to be accurate and effective means by which to identify somatization and malingering."	Unequal sample size for TBI severity categories. Data suggest MMPI-RC scales help diagnose malingering in TBI patients.

Evidence for the Use of Wechsler Adult Intelligence Scale (WAIS)

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Reid-Arndt, 2011 (score=5.0)	WAIS III	Diagnostic	No mention of COI or sponsorship.	N=176 individuals with a history of TBI.	Mean age: 34.3±12.2 years; 102 males, 74 females.	Traumatic brain injury	All patients completed 7 subtests of WAIS-III. (Short-form 1-7: SF1-7)	Estimated FSIQ from all WAIS-III short forms correlated with actual WAIS-III FSIQ (allrs>.91, ps<.001). ANOVA results showed highest validity for both short forms. Short-form 1 showed highest percentage of estimated FSIQ ±5 points of actual FSIQ (75.6%). Short-form 4 resulted in next highest percentage within ±5 pts of actual FSIQ (71.6%). SF-1 provided 71% correct classification of individuals while, SF-4 resulted in 73.9% correct classification.	"Thus, two tetrad versions were consistently superior to others in accuracy of estimating FSIQ; these may be helpful when time constraints or other issues necessitate use of an abbreviated battery for estimating FSIQ among individuals with TBI."	Data suggest two tetrad versions consistently accurately estimated FSIQ which may be beneficial when there are time constraints in TBI individuals as the estimated FSIQ correlated well to the actual FSIQ.
Greve, 2003 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=65 traumatic brain injury patients.	Mean age: 36.6 years; 43 males, 22 females.	Traumatic brain injury	All or most patients completed WAIS, WMS, and one SVT.	Group effect was observed for DFS (F[1, 57]=10.93 p<.01), Significant group	"This study has added to the literature by reporting sensitivity and	Data suggest the DFS and V-DS in combination does not result in improved

							Probable: (n=28) vs Control: (n=37)	(F[1, 57]=6.601, p<.05), and FSIQ level (F[1, 57]=5.360, p<.05) for VDS. Cutoffs were used to determine sensitivities and specificities.	specificity of Mittenberg's WAIS formula in the diagnosis of malingering as applied to both the revised and third edition of the WAIS, to different levels of brain injury severity, and to different IQ levels. These results indicate that a positive finding in the presence of substantial external incentive is associated with malingering."	diagnostic accuracy. Additionally, a positive finding in the presence of substantial external incentive was associated with malingering.
Miller, 2004 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=100 persons with either a history of alcohol abuse, polysubstance abuse, or TBI.	Mean age: 42.5 years; 86 males, 14 females.	Malingering Alcohol abuse, polysubstance abuse, head trauma	Alcohol abuse group: (n=30) vs polysubstance abuse: (n=43) vs TBI group: (n=27)	Vocabulary (WAIS)-Digit Span (DS or WMS) called V-DS score misclassified 0% of alcohol group, 2% of polysubstance group and 0% of TBI group. Overall V-DS score correctly classified 99% of cases. RMI misclassified 3% of alcohol group, 5% of polysubstance	"The specificities of the screening indexes in the present investigation, 99% (V-DS) and 95% (RMI), support the conclusions of previous investigators. In addition, the index cutoff scores do not represent prevalent test patterns produced by	Mixed population of alcohol abuse, polysubstance abuse, and TBI patients. Data suggest both the V-DS and the RMI detected symptom exaggeration with high accuracy 99% for V-DS and 95% for RMI.

								group, and 7% of TBI group. Overall RMI correctly classified 95% of cases.	individuals diagnosed with AA or PA, indicating that among individuals with these clinical diagnoses, the test patterns under investigation are not characteristic of these disorders, despite frequent patient complaints of attention and memory problems."	
Mathias, 2002 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=54 traumatic brain injury patients.	Mean age: 35.96 years; 38 males, 16 females.	Traumatic brain injury	All patients completed WAIS, WMS, and SVT tests. Probable group: (n=24) vs Control group: (n=30)	Group effect was observed for RDS score F (1, 52) =44.77, p<.01. Sensitivity and specificity were measured at specific cutoffs of 5, 6, 7, 8. Only cutoff 8 showed greatest sensitivity of 88 with specificity of 80. Cutoff 5 showed sensitivity of 21, but specificity of 100. Issues of false positives/negativ	"This study has replicated previous work in demonstrating that the RDS test is sensitive to MND in TBI while maintaining excellent specificity and extends previous work by classifying patients in terms of Slick et al.'s (1999) proposed criteria for MND."	Data suggest RDS is sensitive to MND in TBI patients and has very good specificity.

								es were observed.		
Wilbur 2008 (score=4.5)	WAIS-III	Diagnostic	No mention of sponsorship. No COI.	N=214 patients. 42 with diagnosed traumatic brain injuries, 42 with diagnosed learning disabilities and 40 with emotional diagnoses.	Age and gender not reported.	Traumatic brain injury (TBI)	Participants' self-predicted and observed standardized sub-test scores (R) on 17 WAIS-III subtests and participants' predicted and observed sub-tests scores (B).	Significant relationship among the WAIS-III and self-monitoring measures, $p<0.0001$. No differences among the groups on the FSIQ, VIQ, POI and WMI measures, $p>0.05$.	"The R and B measures are two valid and reliable indices of self-monitoring that can be conveniently estimated from the WAIS-III."	Mixed population of TBI, emotionally disabled and learning disability patients. Data suggest that 2 measures are useful in measuring self-monitoring and discriminating between the 3 different groups.
Walker 2009 (score=4.5)	WAIS-III & WMS	Diagnostic	No sponsorship or COI.	N=200 patients. 100 patients with moderate to severe traumatic brain injury (TBI). 100 controls.	Mean age: TBI 30.68 years. Controls 40.07 years. TBI: 81 males/19 females. Controls: 70 males/30 females.	Moderate to severe traumatic brain injury (TBI).	Wechsler Adult Intelligence Scale-III (WAIS-III) and Wechsler Memory Scale-III (WMS-III) indices vs. age corrected indices.	Age corrected indices correctly classified 77% [154385] of all participants, with 82% sensitivity and 72% specificity. Demographically corrected indices correctly classified 74% [148385] of participants, with 76% sensitivity and 72% specificity.	"[F]or mostly younger white individuals with lower levels of education, the demographic corrections for the WAIS-III and WMS-III do not provide an advantage in the classifi cation of moderate to severe TBI over and above age corrected indices."	Data suggest demographically corrected WAIS-III and/or WMS-III indices did not provide better diagnostic accuracy than age corrected indices in TBI patients.
Strong 2005 (score=4.5)	WAIS-III	Diagnostic	Supported by a grant from the Campbell Foundation and was based in part on	N=200 patients. Mild TBI (n = 53), Moderate-Severe TBI (n = 47) and standardization	Mean age: Mild TBI 35.94 years, 33 males/ 20 females. Moderat	Traumatic brain injury (TBI).	Demographically corrected norms vs. traditional age-corrected norms	Demographically corrected norms were not clearly advantageous or disadvantageous for use in	"[D]emographically corrected WAIS–III norms do not offer a clear advantage or disadvantage	Data suggest there is no advantage for using demographically corrected WAIS III norm

			standardization data derived from the Wechsler Adult Intelligence Scale. No mention of COI.	controls (n = 100)	e-severe: 31.64 years, 33 males/ 14 females. Controls 34.29 years, 33 males/ 20 females.		Evaluation with the WAIS–III. Mild TBI (n=53), Moderate-Severe TBI (n=47), controls (n=100)	the diagnostic classification of moderate-severe TBI in a primarily Caucasian sample.	compared to traditional age-corrected norms in the assessment of patients with TBI who are Caucasian and who have at least a middle school level of education."	compared to traditional age corrected norms in the assessment of Caucasian TBI patients with a minimum of a middle school level of education.
Langeluddecke, 2003 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=150 subjects with mild TBI.	Mean age: 35.2 years; 130 males, 75 females.	Moderate to severe traumatic brain injury	All patients interviewed and tested via GCS score, then tested with WAIS-III. Extremely severe TBI: (n=41) vs Severe: (n=74) vs Moderate: (n=35) vs Controls: (n=50)	Greatest effect size between controls and TBI groups was observed for PSI (F=21.0). Moderate TBI group mean differences in most of IQ and Index scores were small, averaging <5 IQ points. PSI was the only measure that moderate TBI group differed with p<.03 from control group. Differences between severe TBI and control group were observed for all measures with an effect size of -.57 for WMI to -.96 for PSI. For extreme TBI	"Findings for the entire moderate to extremely severe TBI sample in the present study indicate a significant ''dose response'' relationship between WAIS-III IQ/Index scores and TBI severity."	Data found a significant dose-response relationship between TBI severity and all WAIS-III index/IQ scores.

								group similar results to moderate group with difference in all measure and effect size of -.78 for WMI to -1.5 for PSI. Effect size for controls vs combined TBI group were highest (d≥0.9) for similarities, digit symbol, picture arrangement, and symbol search.		
Greve 2008 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=211 TBI patients. Not-Malingered Neurocognitive Dysfunction (MND) (n=87), Indeterminate (n=68), and MND (n=56).	Mean age 38.3 (SD=13.6) . 60 females, 151 males.	Traumatic Brain Injury (TBI)	WAIS-III, VIQ, PIQ, and FSIQ.	No difference in latency as a function of injury severity (eta^2=0.02) or malingering status (eta^2=0.00) PIQ differential was accurate in mild TBI but did not differentiate MND from Not-MND in moderate-severe TBI.	"This study indicates that VIQ declines of greater than 24 points are rare except in very severe TBI. Particularly in mild TBI, such differentials likely indicate intentional suppression of WAIS-III performance consistent with MND."	Data suggest verbal IQ declines of more than 24 points are uncommon except in rare cases of severe TBI. If such decline is found in M-TBI it is possibly due to intentional suppression of WAIS-III performance and is likely malingered neurocognital dysfunction.
Curtis 2009 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=83 total TBI patients. Mild TBI not-malingered neurocognitive	Mean age 37.4 (SD=12.8) . 23	Traumatic Brain Injury (TBI)	WAIS-III, Verbal IQ, Verbal Comprehension Index, and	VIQ, VCI, and WMI scores differentiated malingerers	"Overall, a dose–response relationship between injury severity and all	Data suggest V-DS and the Mittenberg formula failed in

				dysfunction (MND) (*n* = 26), mild TBI MND (*n* = 31), moderate/severe (M/S) TBI not-MND (*n* = 26).	female/ 60 males.		Working Memory Index.	from nonmalingerers with a high degree of accuracy, detecting ≥26% of malingerers with an FP rate of ~5%.	WAIS-III scores was observed, with PSI showing the largest effect size."	the differentiation of malingerers from non-malingerers.
Fischer, 2000 (score=3.5)	WAIS-III	Diagnostic								Data suggest WAIS-III results showed IQ and index scores of MTBI patients were similar to controls but moderate-severe TBI patients had significantly lower mean scores across all measures.
Donders, 2001 (score=3.5)	WAIS-III	Diagnostic								Data suggest letter-number-sequencing and symbol search have moderate criterion validity but should be used with other metrics in neuropsychological evaluations. Additionally, Matrix Reasoning show little of any

										sensitivity to TBI sequalae.
Ryan, 2005 (score=3.5)	WAIS-III	Diagnostic								Mixed population of TBI, stroke, Parkinson's disease, dementia, or Alzheimer's disease. Data suggest the MR subtest is not sensitive to TBI, but sensitive to stroke and dementia.
Kennedy, 2003 (score=3.0)	WAIS-III	Diagnostic								Data suggest TBI patients reflect WAIS-III PSI scores involving perceptual processing speed and working memory. However, motor speed had had a very small effect on WAIS-III PSI scores.

Evidence for the Use of Automated Neuropsychological Assessment Metrics [1]

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Nelson 2016 (Score=5.5)	ANAM	Diagnostic	No COI. Sponsorship provided by the U.S. Army Medical Research, Materiel Command, the Clinical and Translational Science Institute, and the National Center for Advancing Translational Sciences, National Institutes of Health.	N = 165 concussed high school and collegiate athletes and N = 166 matched non-injured controls	Mean age: Concussed group – 17.46, Non-injured group – 17.64; 276 males and 55 females	Concussion qualifying as a mTBI	Three computerized neurocognitive tests (CNTs): ANAM, Axon Sports/Cogstate Sport, and ImPACT. Testing occurred 24 hours post-injury, as well as 8, 15, and 45 days post-injury. Each subject only participated in two CNTs.	Sensitivity to concussion at 24 hr: 6.0–23.8% for ANAM, 6.8–48.6% for Axon, and 24.4–39.5% for ImPACT. Sensitivity diminished at day 8 (median difference between hit and false positive rate at day 8 for ANAM, Axon, ImPACT: 0.4%, 4.9%, and 2.4%, respectively).	"Analyses of group effect sizes, discrimination, and sensitivity and specificity suggested that the CNTs may add incrementally (beyond symptom scores) to the identification of clinical impairment within 24 hr of injury or within a short time period after symptom resolution but do not add significant value over symptom assessment later."	Data suggest ANAM, AXON and ImPACT are time limited in detecting concussion and of little use, if any, performed after 8 days post injury. They are best performed within the first 24 hours.
Luethcke C 2010 (4.5)	ANAM	Retrospective Study	No sponsorship or COI.	N = 82 military personnel and civilians	Mean age of military personnel 26.62 years with all male population. Age range no provided. Follow-up duration not provided.	Acute and mild stages of Traumatic brain injury	(N = 38) Non-blast Group vs. (N= 39) Blast Group. No follow-up analysis were conducted.	No significant results difference was found in return to duty (RTD) after treatment for TBI clinic in both groups. Blast injuries were less frequently associated with loss of consciousness (LOC) when compared to non-blast injuries (54.8%) P=0.604	"Despite this limitation, these results have important clinical implications and provide a solid foundation for future research, since this is the first study that we could identify to capture symptom expression among deployed military personnel within 72 hr of mTBI."	Data suggest few differences exist between concussive symptoms of acute blast versus nonblast mild TBI individuals.

								for RTD and p=0.035 for LOC. No significant differences were found from blast and non-blast injury type p=0.650.		
Cernich 2007 (4.5)	ANAM	Case Control Study	Funded by Cooperative Agreement #DAMD17-00-1-0056 from the US Army Medical Research Materiel Command to the National Rehabilitation Hospital. No COI.	N = 122, high school and college aged; this study looked at the use of the ANAM-sports-medicine battery (ASMB) for use in concussion surveillance and management.	High school and college aged 15-27 with mean of 17.2 years	Concussions	(N = 68), cadets were concussed vs. (N= 18) cadets were not concussed.	MTH scores showed the greatest specificity for concussive injury; SRT and CPT showed a decline between the baseline assessment and the first post-injury assessment.	"Future development of the ASMB is discussed as it relates to interpretation of ASMB, development of appropriate norms, and defining adequate baseline assessment."	Data suggest ANAM may be valuable as a clinical tool for tracking cognitive recovery.
Bryan 2012 (4.0)	ANAM	Retrospective Study	No mention of sponsorship or COI.	N=116 service members referred to a TBI clinic in central Iraq for a TBI evaluation	92.2% males with an average age 27.74 years	Mild traumatic brain injury with any period of loss of or decreased level of consciousness, any loss of memory for events immediately before or after the injury, any alteration in	(N = 96) with TBI vs. (N= 20) without TBI.	Results indicate that service members with TBI demonstrate greater declines in speed and throughput as compared both those service members without TBI regardless of timing of the assessment.	"Assessment of cognitive impairment following TBI in a combat zone may assist providers in making treatment recommendations for service members with mild TBI."	Data suggest TBI cognitive impairment from a combat zone may aid clinicians in making treatment recommendations for military personal with mild TBI.

						mental state at the time of the injury, neurological deficits that may or may not be transient, and intracranial lesion.				
Kelly MP, 2012 (4.0)	ANAM	Case Control Study	Sponsored by U.S. Army Medical Research Acquisition Activity Project W81XWIH-09-2-0057. No COI	N= 212 Male participants only	Aged 18-55 years old with a mean of 25	Traumatic brain injury	(N = 66) Cases vs. (N= 146) Controls. Two control groups were used: healthy group of U.S. Army soldiers from deployed units volunteering for participation, acutely injured U.S. Army soldiers presenting for outpatient care who were neither head-injured nor exposed to a blast.	Cases reported more headaches, blackouts, confusion, and flashbacks. Cases also endorsed more frequent alcohol problems. ANAM, particularly SRT, can detect changes in cognition following a concussion incurred in the combat environment that are both "statistically and clinically significant"; cases performed more poorly than controls on multiple ANAM subtests.	"Results clearly demonstrate that ANAM, and particularly SRT, is more effective than the traditional brief sports medicine neuropsychological battery in differentiating concussed from non-concussed participants in the combat environment when administered within 72 h of injury."	Data suggest ANAM SRT if administered within 72 hours post-TBI has good sensitivity and specificity and can distinguish between concussed and non-concussed individuals.
Vincent 2012 (4.0)	ANAM	Retrospective Study	No sponsorship or COI.	N = 107,500 active duty service member 17-65 years of age with	17-65 years of age with mean age of 27.4 years	Previous brain injury with ongoing TBI related symptoms	The following tests were compared to each other; CDD (N=107523)	Analyses examining the influence of age and gender indicate statistically	"Future research should examine the effects of other potential intervening factors on performance, such as	Data suggest ANAM-4 established a comprehensive age and gender

				97067 males and 10604 females.			vs CDS (N=107546)vs M2S (N=10767) vs MTH (N=107651)vs PRO (107353) vs SR2 (N=107413)vs SRT (N= 107662)	significant effect of both "below average" and "clearly below average" on ANAM scores.	military service, ethnicity/race, education, and rank."	stratified set of norms useful for chemical practice.
Norris J 2014 (4.0)	ANAM	Retrospective Study	Sponsored by the Navy Bureau of Medicine and Surgery, under Work Unit No. N24LB. No COI.	N=210 patients with blast-related Mild Traumatic brain injury	Aged 18-50 years with Mean age of cadets 24.80 years with all male population. Follow-up 48-72 hours following visit.	Concussion or Mild Traumatic brain injury	(N = 142) No LOC (LOC is Loss of Consciousnes s no more than 30 mins) Group vs. (N= 39) LOC Group. Follow-up 48-72 hours after initial visit	A difference in ASRs between no LOC and LOC patients (9.2% vs. 23.5% p<=0.01). At follow-up, LOC reported sleep difficulty 30.3% to 48.5% no LOC p<=0.01. A significant main effect ASR at intake p<=0.001 but not for LOC at p=0.09.	"Computerized neuropsychological tests such as ANAM, when combined with the computer classrooms available at many schools, make it possible to do baseline testing of large numbers of athletes rapidly and inexpensively."	Data suggest ASR from ANAM may partially mediate cognitive dysfunction and symptoms presentation in the acute phase of mTBI post blast.
Vincent 2008 (4.0)	ANAM	Retrospective Study	Sponsored by the DVBIC and Cooperative Agreement DAMD17-00-1-0056 with the US Army Medical Research and Materiel Command and the National Rehabilitation Hospital. No COI.	N= 5,247 aged 18-51 years old with 4773 males and 474 females.	aged 18-51 years old with mean age of 26.0	Traumatic brain injury	The following tests were compared to each other using the following logarithmicall y transformed processes MCRT, PC, TP, & LTP. Test are CDD vs CDS vs MSP vs MTH vs CPT vs SRT. N= 5247	Overall, the data suggest that a general decline in performance with age should be expected on most tests in the ANAM TBI battery.	"This article presents reference data for a military population tested with the ANAM TBI battery."	Data suggest ANAM may have utility in analyzing TBI patients in the general population.

Norris J 2013 (4.0)	ANAM	Retrospective Study	Sponsored by the Navy Bureau of Medicine and Surgery, under Work Unit No. N24LB. No COI.	N=165 concussed active duty personnel (active 176oncussio n)	Aged 19-41 years with Mean age of patients 22.00 years with all male population. Follow-up not conducted	Concussion or Acute concussions	Session 1 N=165 vs Session 2 N=165 Test were against each other SRT vs CDS vs PRO vs MTH vs M2S vs CDD vs SR2.	The reaction time-based subtests SRT, and PRO at 0-25% and RTD time of 19 days for SRT, SR@, and PRO. The upper 0-25% had a median RTD time of approximately 7 days for SR2 AND PRO. No statistically significant results, Session 1 SRT p=0.37, and PRO p=0.35, and Session 2 SRT p=0.50, and PRO p=0.50.	"This study of 165 cases shows that computer-based testing is able to capture useable data that otherwise would have required over 80 hours of clinician time for test administration." "This report supports the CRCC clinician use of the SRT tests in their initial and follow-up assessments of concussion."	Data suggest the ANAM4 TBI battery has prognostic value.

Evidence for the Use of Memory and Malingering Tests

Author Year (Score)	Category:	Study type:	Sponsorship / COI:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Hall 2014 (6.5)**	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	48	27 female, 21 male Mean age 39 years	Minimal to mild head injury, in acute stages post-injury	Trail Making Test vs.Verbal Fluency (FAS) test vs. Colour Word Interference Test vs. Word Memory Test vs. Test of Malingering Memory (TOMM) vs. Reliable Digit Span vs. PDI vs. MSPQ Processing Speed Index [419] from WAIS-III vs. Word List Recognition	At the 82.5% cutoff for WMT, the false positive rate (FPR) was 18%. Those who failed the IR or DR also failed the WMT, resulting in a joint failure rate of 18%. In the IR the FPR was 8% and 3% for the DR. The difference between those who passed and failed the WMT was also significant in regards to the verbal fluency test ($p<0.05$, effect size $d \leq 0.7$). Sensitivity for various subtests: RDS = 0.41, TOMM = 0.61; WLR = 0.81; PSI = 0.55; PDI = 0.59; MSPQ = 0.9.	"[T]he results of this study suggest that the WMT consistency index cut-off may be too aggressive with minimal to MHI individuals within the early stages post-injury."	All participants were not involved in litigation and this did not fit malingering criteria. Data suggest WMF may be the result of a specific verbal processing deficit in the acute phase of mild head injury.
Armistead-Jehle 2013 (6.0)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	280	12 female, 268 male Mean age 32 years	U. S. military service members on active duty with history of mild TBI	Word Memory Test (computer administered verbal memory test with multiple subtests designed to assess verbal memory, effort, and response consistency)	106 participants (37.9%) failed WMT. 18 (6.4%) failed ACS subtests at 10% base rate level and 23 (8.2%) failed at 15%. 173 (62%) passed both tests at 10% and 17 (6%) failed both. 89 (32%) passed ACS subtests but failed WMT. 1 participant (0.4%) failed ACS tests but passed WMT.	"Despite these limitations, the current data replicate previous studies demonstrating the limited sensitivity of embedded effort measures relative to standalone	Primarily Caucasian male population. Data suggest ACS has adequate specificity but poor sensitivity

							vs Embedded indices testing/subtests: Advanced Clinical Solutions package – WAIS-IV, WMS-IV, RDS, LM-rec, VPA-rec, and VR-rec subtests All participants underwent both testing	170 (61%) passed both at 15% base rate level, along with 19 (7%) failing both, 87 (31%) failing WMT, and 4 (1%) failing ACS subtests. At 10% and 15% base rate levels ACS subtest specificity high (0.99, 0.98, respectively) but sensitivity low (0.16, 0.18). Positive predictive power (0.91, 0.85) and likelihood ratios (16.0, 7.80) high, but negative predictive power (0.66, 0.66) and likelihood ratios low (1.18, 1.19). At 25% base rate level specificity = 0.94, but sensitivity = 0.27.	instruments designed to gauge respondent effort on neuropsychological testing."	compared to WMT.
Das Nair 2012 (6.0)	Memory and Malingering	RCT	Sponsored by grants from The Stroke Association, Remedi (2006/05), Universities UK (Overseas Research Students Award Scheme), and the University of Nottingham. No COI.	N = 72 with memory problems following traumatic brain injury, stroke or multiple sclerosis.	Mean age 47.7, (10.2) years; 32 males and 40 females.	Compensation, 10 sessions (N = 24) vs Restitution treatment programmes, 10 sessions (N = 24) vs A self-help group control 10 sessions (N = 24).	7-months	No significant effect of treatment on the Everyday Memory Questionnaire, (p = 0.97). At 7-months, mean score for compensation vs restitution vs self-help; 41.0 vs 36.6 vs 44.1. Internal memory Aids questionnaire, (p = 0.002). Treatment groups used more internal memory aids vs to self-help, (p < 0.01). Measure of mood / adjustment / and activity of daily living, (p > 0.05).	"These results show few statistically significant effects of either compensation or restitution memory group treatment as compared with a self-help group control."	Dissimilar time since diagnosis between groups. Mixed population of TBI, MS and Stroke patients. At 7 months data suggest similar efficacy between all groups for mood, memory functions and dialing living activities although the compensation

										and restitution groups used significantly more internal memory aids than did the self help group.
Barhon 2015 (6.0)	Memory and Malingering	Diagnostic	No mention of sponsorship or COI	N = 92	Mean age: 19.7 years; 25 males, 67 females.	TBI	Word Choice Test (WCT) vs. Test of Memory Malingering (TOMM) Full-Effort Group (N=46) vs. Distraction Group (N=46) vs. Uncoached Group (N=22) vs. Coached Group (N=24)	Statistical significance found between full effort group and uncoached group (p<.0005) and between full effort group and coached group (p<.0005), and no statistical significance between full effort group and distraction group (p<.0005). At a cut score of 48, TOMM had a sensitivity of 91.3, specificity of 89.13. At a cut score of 48, WCT had a sensitivity of 86.96, and a specificity of 78.26.	"The WCT was found to be as effective as the TOMM in differentiating simulators from participants applying full effort. The WCT is primarily a measure of effort rather than cognitive ability."	Data suggest similar efficacy between TOMM and WCT in the detection of cognitive impairment. Both TOMM and WCT are primarily tests of validating poor effort.
Iverson GI 2002 (5.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	N= 571 participants presenting to the trauma service with a known or suspected head injury	405 males, 166 females Mean age: 35.8 years	Traumatic brain injury	Trail making test And tests of effort were Computerized Assessment of Response Bias Word Memory Test	The hospital patients with more severe traumatic brain injuries performed more poorly than the patients with less severe brain injuries on Trails A and Trails B. The performances of the head injury litigants who exaggerated on at least one well-validated symptom validity test were compared to these cutoffs. Very high positive predictive values for individuals with very mild head injuries on Trails A and B	"In conclusion, the results of this study do not support the use of the TMT as a reliable predictor of deficits during neuropsychological testing. Based on individual patient comparisons in this study, the TMT's clinical utility as means of identifying poor effort was	571 patients non-litigated and 228 patients involved in head trauma litigation. Data do not support the use of TMT as a reliable predictor of either poor effort or exaggerated effort. Brain injury severity was not

								were identified (i.e., both 100%); lower positive predictive values were obtained for individuals with more severe head injuries (55.6–60%). The negative predictive values were only moderate (range=66.4–78.2%), and the sensitivity was very low (range=7.1–18.5%) for all groups.	extremely limited. Thus, they may be indicative of deliberate exaggeration. Typically, this process relies on multiple test results and sources of information. The TMT has a very limited value in this process due to its low sensitivity."	necessarily correlated with effort.
Lange 2010 (5.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	63 individual with mild TBI who were receiving financial compensation from the Workers' Compensation Board	Mean age: not specified; 40 males, 23 females.	Mild TBI	TOMM pass (n = 48) vs. TOMM fail (n = 15). All participants underwent the following tests: Post-Concussion Scale (PCS), British Columbia Cognitive Complaints Inventory (BC-CCI), selected test from Neuropsychological Assessment Battery Screening (S-NAB)	Between TOMM pass and fail groups: significant main effects and large effect sizes for PCS (d=0.79, p=0.002), BC-CCI (d=0.98, p=0.011). Those in TOMM fail group scored higher for both measured compared to TOMM pass group. TOMM fail group scored lower on attention (d=1.26, p=0.004), memory (d=1.16, p=0.006), and executive functioning (d=0.70, p>0.05) indexes	"These results highlight the importance of considering the influence of poor effort, in conjunction with a growing list of factors that can influence, maintain, and/or mimic the persistent postconcussion syndrome."	All participants receiving financial compensation . Data suggest poor effort must be considered in addition to multiple other factors which can mimic post-concussion syndrome.
Flahert y 2015 (5.5)	Memory and Malinger ing	Diagnostic	No COI. No mention of sponsorship.	257 veterans with possible mild TBI	Mean age: 29.5 years; 248 males, 9 females.	Possible mild TBI	Rey Fifteen-Item Memory Test (FIT) (n = 257). Out of the 257 participants that underwent the FIT, some completed the Digit Span (n = 148) and some completed	Four (1.6%) participants failed the FIT (according to standard cut-off of <9 items), three (1.2%) failed the FIT (cut-off of <8 items), and 198 (77%) obtained perfect scores.	"Despite its popularity, the FIT is not supported as an appropriate measure of performance validity in veterans	Data suggest FIT is not a good tool for performance validity in veterans being evaluated for mTBI.

							the Digit Span and the TOMM (n = 109)		undergoing evaluation for possible mTBI. Therefore, inferences regarding neuropsychological data reliability with adequate statistical certainty require use of other measures of performance validity with greater sensitivity."	
Schroeder 2013 (5.5)	Memory and Malingering	Retrospective	No sponsorship or COI.	62 consecutive forensic cases, with complaints related to TBI	Mean age 40.83 years for pass MND, 44.08 years for fail MND; 38 males, 24 females.	Mild TBI, complicated mild TBI, moderate-to-severe TBI, or a number of other conditions including major depressive disorder, frontotemporal dementia, and mental retardation to name a few.	Malingered Neuropsychological Dysfunction Criteria (MND) Pass group (n = 26) vs. MND Fail group (n = 36). All participants underwent TOMM trial 1, TOMM trial 2, TOMM retention, and the Albany Consistency Index tests.	Group performances between pass and fail MND groups, respectively (mean score, mean rank, Mann-Whitney U, p-value) - TOMM trial 1: 47.17 vs. 35.92, 41.89 vs. 17.12, 94.00, ($p < 0.01$), TOMM trial 2: 49.86 vs. 41.96, 41.08 vs. 18.23, 123.00, ($p < 0.01$), TOMM Retention: 49.69 vs. 39.88, 41.35 vs. 17.87, 113.50, ($p < 0.01$), ACI: 46.89 vs. 30.15, 42.57 vs. 16.17, 69.50, ($p < 0.01$)	"Evidence was provided for convergent and divergent validity for all TOMM indices, which increases confidence for the clinical utility of both the new and traditional indices. Although each index well differentiated patients passing and failing MND criteria, the ACI was found to be the superior index."	Data suggest both the new and the traditional TOMM indices are valid and have good clinical value. However, the ACI was found to be the superior index.
Guise 2010 (score= 5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	N=176 TBI patients (archival data).	Mean age mild TBI/good effort: 38.1 (SD=9.7). 26	Mild to severe TBI	Mild TBI/Good Effort (n = 40) vs. Mild TBI/Poor Effort (n = 42) vs. Moderate-severe	Effort was found to have a greater effect on test performance (0.79) than injury severity (0.47).	"Moderate-severe TBI produced overall worse	Data suggest effort has a greater effect on text performance

					males, 13 females mild TBI/good effort group.		TBI/Good Effort (n = 40) vs. Moderate-severe TBI/Poor Effort (n = 14) vs. Control (n=40). Portland Digit Recognition Test vs. Test of Memory Malingering (TOMM).		performance than mild TBI patients and control subjects. Mild TBI showed some effect on test performance, but deficits were likely due to secondary factors including financial incentive, psychological overlay, and poor effort."	than does injury severity.
Teichner 2004 (score= 5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	N=78 elderly cognitively intact, cognitively impaired (non-dementia), and with dementia	Mean age was 70.5 (SD=8.5). 33 males and 45 females.	Cognitively intact, cognitively impaired (non-dementia), and with dementia.	Test of Memory Malingering (TOMM) vs. Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) vs. Wechsler Memory Scale—Third Edition (WMS-III) vs. Mini-Mental State Examination (MMSE).	100% of normals and 92.7% of the cognitively impaired group made fewer than five errors (the suggested cut-off) on Trial 2 or the Retention trial of the TOMM.	"Results suggest that the TOMM is an useful index for detecting the malingering of memory deficits, even in patients with cognitive impairment, but only when dementia can be ruled out."	Data suggest TOMM is a useful test for the detection of malingering and memory defects even in those with cognitive impairment if and only if dementia can be ruled out.
King 1999 (5.0)	Memory and Malingering	Cross-validation sample	No mention of sponsorship or COI.	N = 57 with mild to moderate head injuries.	Mean age 32 (13) years; 43 males and 23 females.	TBI	Short Orientation Memory and Concentration Test (SOMC), Rivermead Post-Concussion Symptoms Questionnaire (RPQ)	At 3 months, SOMC scores accounted for 74%of the variance in RPQ Scores, combination of IES and SOMC scores accounted for 55% of the variance in RPQ scores at 7±10 days.	"[T]he results from this study largely support the previous findings and confirm that it is a combination of measures – emotional, organic and neuropsychologic	Data suggest combining HADS and IES are useful for prognostic screening and predicting PCS.

									al – which best predict early on post –injury those most likely to suffer persisting PCS."	
Sherer M 2015 (5.0)	Memory and Malingering	Diagnostic (prospective cohort, observational study)	No COI. Supported by the National Institute on Disability and Rehabilitation Research, U.S. Department of Education [grant number H133B090023], [grant number H133A120020]	491 medically documented participants with TBI	369 males, 122 females. Mean age: 38 years.	TBI	Word memory test (WMT) vs. performance validity test (PVT)	117 participants showed poor performance validity using the standard cutoff. Variable cluster analysis was conducted as a data reduction strategy. Findings revealed that the 10 cognitive tests and questionnaires could be summarized as 4 indices of emotional distress, speed of cognitive processing, verbal memory, and verbal fluency. Regression models revealed that verbal memory, emotional distress, age, and injury severity (time to follow commands) made unique contribution to prediction of poor performance validity	"Poor performance validity was common in a research sample of persons with medically documented TBI who were not evaluated in conjunction with litigation, compensation claims, or current report of symptoms. Poor performance validity was associated with poor performance on cognitive tests, greater emotional distress, lower injury severity, and greater age. Many participants expected to have residual deficits based on initial injury severity showed poor performance validity."	Secondary analyses using a subset from (Sherer et al 2015). Data suggest that persons with medically documented TBI commonly exhibited poor performance validity and thus increasing age, lower injury severity and increasing emotional distress.

Hegedish Hall 2015 (5.0)	Memory and Malingering	Diagnostic	No mention of COI and sponsorship	N=81 participants: 21 healthy control, 20 coached simulators, 40 patients with acquired brain injury	Mean age was 27.4 years	TBI	TMST=Temporal Memory Sequence Test Vs. TOMM=Test of Memory Malingering Vs. WMT=Word Memory Test	One-way ANOVA revealed significant differences between healthy controls (TMST IR, M=97.12% correct, SD=2.81; TMST DR, M=98.81% correct, SD=2.57) and coached simulators (TMST IR, M=62.88% correct, SD=17.45; TMST DR, M=61.25% correct, SD=16.06), on TMST IR, F(1, 39)=78.74, p < .001, and TMST DR, F (1, 39)=111.84, p < .001. The TMST correctly classified 100% of the healthy controls and 95% of the coached simulators. Thus, the TMST yielded 100% specificity, 95% sensitivity, and a 98% overall hit rate.	"To further establish the TMST as a valid test of NRB detection, the suggested cutoff should be cross-validated, and larger samples of patients with ABI should be examined. To broaden its external validity, the TMST should be administered to "extreme" populations, such as young children, schizophrenics, and patients with dementia. The paradigm of temporal order can also be applied in a recognition method by presenting alternative threesomes for the response choice."	Data suggest the TMST showed high negative correlations with GCS supporting an association between mild TBI and probable malingering.
Boone KB 2002 (5.0)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	N=178	80 males, 98 females mean age: 44.6 years	Presenting diagnoses included: head trauma, ``stress'' or depression,	Rey 15 item Memorization test was followed by Rey 15 item recognition trial	A free recall score <9 was found to have excellent specificity (97-100%), although sensitivity was modest (47%). However, use of a combined recall and recognition score (i.e., free	"[T]he data from the current study suggest that the addition of a recognition trial to the standard administration	All controls were paid to participate and all study participants with "suspect effort" were in litigation,

						learning disability, toxic exposure, psychosis or bipolar disorder, stroke, somatoform or factitious disorder, dementia , chronic fatigue syndrome, anoxia, narcolepsy, and decreased memory from ECT clinic referrals included Patients were excluded from the study if they were in personal injury litigation learning disabled college students (who due to their		recall.[recognition -false positives] <20) substantially increased sensitivity (71%) while maintaining high specificity (≥92%).	format may enable the test to meet standards for ``probable'' certainty in identifying suspect effort (defined as 75% correct classification of individual subjects). It may be possible to modify the test through brief additions to existing test administration format, thereby enabling it to approach this standard	seeking to maintain obtain disability. Data suggest combining recall and recognition scores substantially increases sensitivity and specificity is maintained.

						disability might be expected to have difficulty in processing and recall of the Rey 15-item stimuli), and normal controls.				
Greve KW 2002 (5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	N= 89 TBI referrals for comprehensive neuropsychological evaluation	58 males, 32 females Mean age: 35.8 years	Traumatic brain injury	4 potential Wisconsin card sorting test malingering indicators (Unique Responses Perfect Matches-Missed; Bernard; Suhr)	Individual Sensitivities were greater than .33 with acceptable Specificity. Combined Sensitivity for two of the indicators was greater than .60.	"In summary, this study indicated three relatively independent approaches or strategies used by malingerers on the WCST. Two reflect attempts to appear impaired while one appeared to reflect valid, unimpaired performance. It should be noted that one False Negative was impaired on the WCST.	Participants were derived from workers compensation population. Data suggest detection of malingers with WCST were derived from 3 different approaches and attempts to maximize sensitivity should be carefully evaluated so as to not decrease specificity.
Bashem 2014 (5.0)	Memory and Malingering	Diagnostic	Supported by grants from Wayne State University, the Del Harder	109	No gender distribution described	Those with TBI, ranging from mild complicated to severe	Premorbid intelligence, measured via Wechsler Test of Adult Reading	TOMM highest hit rate (68%). TOMM highest sensitivity (50%) and MSVT highest specificity (94%). RDS smallest	"The findings should be generalized with caution, but if	Participants were each compensate $30. Data suggest use of

			Foundation, and the National Institute on Disability and Rehabilitation Research. No mention of COI.		Mean age 44.0 years	(n=51) vs Neurologically healthy controls (n=58) All participants underwent all testing	(WTAR) vs Performance Validity Test (PVT) - Test of Memory Malingering (TOMM) vs PVT – Word Choice Test (WCT) vs PVT – Medical Symptom Validity Test (MSVT) vs Embedded indices – Forced Choice Recall (CVLT-II) vs Embedded indices – Reliable Digit Span (RDS)	hit rate (54%), specificity (77%), and sensitivity (35%). TOMM and CVLT highest agreement within TBI participants (86% passed both, 2% failed both, 88% overall agreement rate). RDS and WCT had lowest overall agreement rate (68%) in those with TBI. Overall agreement highest between TOMM and MSVT (84%) in controls. 40% failed both tests and 45% passed both.	only one index will be employed, this study provides support for administering the TOMM alone and reserving the MSVT as an equivalent, alternate measure for future assessment."	TOMM with CVLT or use of MSVT with CVLT for the best diagnostic accuracy to assess TBI associated memory function. Any more than 2 tests does not significantly increase diagnostic accuracy.
Krishnan M 2011 (5.0)	Memory and Malingering	Diagnostic	The authors' clinical practice, as employees of a non-profit hospital, includes about 15% of medicolegal referrals, which are	155 participants were referred for neuropsychological examinations for traumatic	76 males, 39 females Mean age: 40.7 years	TBI	Performance on the Test of Memory Malingering (TOMM) Vs. Word Memory Test (WMT)	Individuals who failed the TOMM or WMT were almost six times more likely to fail the CVMT validity criteria than those who passed the TOMM or WMT. The addition of compensation seeking increased this odds ratio to 9.80. The area under the curve for the latter	"[T]his supports the conclusion that the CVMT SVT is useful clinically as an embedded measure of negative response bias in	Data suggest CVMT may be useful if used in conjunction with other established tests.

			predominantly of defense origin. They do not receive any extra benefits from such referrals as compared to clinical referrals. This work was supported by a grant from the Campbell Foundation.	brain injury				classification was 0.74. Maximum likelihood ratio optimization of the CVMT validity test cutoff score indicated sensitivity of 0.25 and specificity of 0.99 at a revised cutoff of ,12 items. Classification accuracy was 91%. The original cutoff score of ,14 items also performed acceptably, with a classification accuracy of 88%.	neuropsychological assessments. It is best used as an adjunct to other measures of symptom validity, such as in combination with a stand-alone measure and one or more other embedded measures of response bias, as well as other clinical information about the patient, in order to obtain a reasonable overall sensitivity."	
Hampson 2013 (4.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	47	15 female, 32 male Mean age for those with acute brain injury 54.6 years, for community brain injury 47.0, and for epilepsy 36.6	Acute brain injury (n=11) vs Community brain injury (n=20) vs Intractable epilepsy (n=16)	Word Memory Test (WMT) Coin-in-Hand Test Autobiographical Memory Index Digit-Symbol Coding Mental Control Short Recognition Memory Test for Faces	Community injuries scored lower memory results than epilepsy in WMT paired associated (t(32)=2.43, p=0.021) and the Free Recall tests (t(32)=3.14, p=0.004). Overall failing rates on WMT Immediate or Delayed Recognition portions: 27.3% in acute, 35.0% in community, and 18.8% in epilepsy group.	"The WMT was able to identify failures associated with significant cognitive impairment through the application of profile analysis and=or lowered cutoff levels. Implications for clinical assessment, effort test interpretation,	A significant proportion of study participants were either currently receiving benefits risking malingering or had prior litigation benefits which could bias responses. Data suggest

									and future research are discussed."	WMT able to identify significant cognitive impairment particularly in severe TBI patients via lowered cutoff pounds or profile analyses.
Constantinou 2004 (score= 4.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	N=69 litigants with mild TBI.	Mean age 42.41 (SD=12.45). 36 females and 33 males.	Mild TBI.	Test of Memory Malingering (TOMM) vs. general performance patterns on the WAIS-R vs. Halstead–Reitan Neuropsychological Battery for Adults (HRNB-A).	TOMM was associated (P <0.05/15 = 0.003 (Bonferroni method for control of Type I error) with decreased VIQ (Correlations r=0.47), PIQ (Correlations r=0.52), FSIQ (Correlations r=0.52) scores and decreased performance onWAIS-R subtests	"[I]t appears that a poor performance on the TOMM is predictive of a generalized poorer performance on standardized measures such as the WAIS-R and the HNRB-A."	Data suggest a poor performance on TOMM trial 2 was generally positively correlated to a poor performance on WAIS-R and HRNB-A.
Heyanka 2015 (4.0)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	160	9 female, 151 male Mean age 31.7 years	Mild TBI	Word Memory Test (WMT) – IR, DR, CNS trials vs TOMM vs California Verbal Learning Test-Second Ed. (CVLT-II)	Significant correlation (p<0.001) between CVLT-II and TOMM (0.40-0.68), CVLT-II and WMT (0.43-0.61), and WMT and TOMM (0.51-0.75) observed.	"Our findings support assertions that PVTs measure effort independent of memory in veterans with mild TBI."	Data suggest PVTs are measuring effort which is independent of memory in mild TBI veterans.
Lippa 2014 (4.0)	Neuropsychological Assessment	Cohort Study	No mention of sponsorship or COI.	44 Participants with TBI	Mean age of 38.4 years old. 12 Females, 32 Males	Moderate or severe TBI	No mention of comparison groups. All participants were examined with same tests.	The final model, which included years of education, PTA length, and RBANS effort index, showed that the variance accounted for by the	"Findings suggest that more in-depth analysis of validity test performance is	Data suggest that intense analyses of validity test performance

								predictors were statistically significant.	beneficial to gauge a patient's level of effort and is important to consider when interpreting results and in treatment planning."	is important when determining level of effort in acute TBI patients.
Zacks 2015 (4.0)	Neuropsychological Assessment	Longitudinal Study	Sponsored by training grant T32AG000030 and R01MH070674. No mention of COI.	157 Participants in the Vietnam Head Injury Study.	Mean age of 63.32 years old. 0 Females, 57 Males	Male veterans suffering from pTBI.	Veterans with pTBI (N = 123) Vs Non-injured control (N=23)	pTBI had a poorer segmentation agreement than NC (P<0.001). For recognition, pTBI group recognized fewer pictures than NC. However, most pTBI had large lesions (P<0.001). When large lesions were excluded, effect became non-significant. Likewise for order memory. Many individuals in pTBI group had large lesions which made the comparison significant. When large lesions were excluded, the comparison became non-significant.	"[P]atients with pTBI showed substantial impairments in comprehension and memory for movies of everyday activity."	Data suggest pTBI patients showed comprehension and memory defects and event segmentation interventions could improve memory.

Evidence for the Use of CVLT

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Curits 2006 (score=6.0)	CVLT-II	Diagnostic	No mention of sponsorship or COI	N=275 with TBI	Mean age: 40.82 years; 77 females, 198 males	TBI	Malingered Neurocognitive Dysfunction (MND) of four individual California Verbal Learning Test (CVLT) variables and eight composite CVLT malingering indicators	Within TBI, persons with the strongest evidence for malingering (Probable and Definite) had the extreme scores. Good sensitivity (approximately 50%) in the context of excellent specificity (> 95%) was found in the TBI samples	"[R]egardless of the severity of the injury, proper application of these findings requires that a given patient's data be interpreted based on the appropriate comparison groups. When appropriately used, the formulaic composites derived from the CVLT are powerful indicators of poor effort and malingering."	Data suggest CVLT is useful in the detection of malingering in mild TBI patients and is influenced by both cognitive capacity and effort.
Greve 2009 (score=5.5)	CVLT-II	Diagnostic	No mention of COI or sponsorship.	N=442 TBI patients, and =378 chronic pain patients	Mean age (TBI)= 38.7 years (Chronic pain)= 42.4 years;	TBI and chronic pain	2 versions of California Verbal Learning Test (CVLT 1 & 2)	Performance on the CVLT-2 was poorer than on the CVLT-1. The difference between CVLT-1 and CVLT-2 was larger in the pain patients than in the TBI patients. These findings mean that at the same cutoffs, malingering indicators on the CVLT-2 will be	"In summary, this study determined that the two versions of the CVLT are equally accurate in detecting malingering in TBI and chronic pain. However, they are not interchangeable. The use of CVLT-1 cutoffs with the CVLT-2 may result in an increased risk of FP error. The results of this study provide preliminary	Data suggest CVLT-II and CVLT-I are good for detecting malingering but are not interchangeable as current cutoff points may cause increased false positive rates.

								associated with a higher rate of FP errors than the CVLT-1. The difference between the two versions was most pronounced when cutoffs associated with lower FP rates were examined. CVLT-1 cutoffs associated with FP error rates of approximately 10% (a conservative upper bound) always resulted in CVLT-2 FP error rates of 15% or more, even in TBI. In the TBI patients, cutoffs associated with a 5% FP error rate in the CVLT-1 resulted in similar FP rates in the CVLT-2. In the pain sample, Recognition Hit accuracy was comparable but the cutoffs for the Linear Shrinkage score needed to be adjusted upward to maintain a comparable FP rate.	data for the use of some CVLT-2 indicators for the detection of invalid performance and malingering in TBI and chronic pain."	

Davis 2016 (score=4.5)	CVLT-II	Diagnostic	No COI. No mention of sponsorship.	N= 104 participants with different TBI severity	Mean age: 40.26 years; 28 females, 76 males.	TBI	Word Memory Test (WMT) vs. California Verbal Learning Test-Second Edition (CVLT-II).	Participants grouped by TBI severity significantly differed on the CVLT-II but not WMT. Post-traumatic amnesia (PTA) significantly correlated with the CVLT-II but not WMT. In a non-medicolegal sample subset (N = 61), TBI severity groups significantly differed on CVLT-II and WMT free recall (FR); PTA significantly correlated with the CVLT-II and WMT FR. CVLT-II impairment groups differed on all WMT variables. Participants grouped by neuroimaging findings differed on CVLT-II but not WMT. WMT FR predicted two-level TBI severity using logistic regression but did not contribute in a model including the CVLT-II.	"Overall, WMT memory subtests appeared less sensitive to TBI severity than the CVLT-II. The current findings provide preliminary support that, at least, FR on the WMT may have some utility as a memory measure. Cross-validation of the preliminary regression results presented here would be helpful for refining the model and comparing WMT memory indices with other measures."	Data suggest that overall the CVLT-II is more sensitive than the WMT for memory measures in TBI patients.

Donders 2007 (score=4.5)	CVLT-II	Diagnostic	Study was supported in part by a grant from the Campbell Foundation. No mention of COI.	N= 46 healthy controls and patients with moderate-severe TBI	Mean age: 34.9 years; 16 females, 30 males	TBI	California Verbal Learning Test, Second Edition (CVLT II)	Patients with traumatic brain injury recalled fewer correct words, and also made more intrusive errors, on CVLT-II short and long delay, free and cued recall trials ($p < .02$ for all variables after Stepdown Bonferroni correction). However, recall discriminability indices yielded a classification of clinical versus control participants (72%) that was not significantly different from one based on traditional variables (74%).	"CVLT-II recall discriminability indices do not routinely provide an advantage over traditional variables in patients with traumatic brain injury."	Data suggest CVLT-II provides no advantage over established recall discriminability tests.
Moore 2004 (score=4.0)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N= 132 individuals (referrals) from a 3 year series	Mean age: 35.77 years; 50 females, 82 males	TBI	Test of Memory Malingering (TOMM) and the California Verbal Learning Test-Second Edition (CVLT-II)	Twenty patients (15%) performed in the invalid range when held to a priori specified criteria for invalid test performance (i.e. TOMM <45/50 on Trial 2 or CVLT-II <15/16 on Forced-Choice	"The TOMM and CVLT-II are sensitive to the potential impact of current financial compensation seeking and prior psychiatric history on neuropsychological test performance after TBI"	Data suggest both TOMM and CVLT-II are sensitive to financial incentive and previous psychiatric history post TBI.

								recognition trial). Both psychiatric history and financial compensation seeking were associated with an almost 4-fold increase in likelihood of invalid responding.		
Bauer 2005 (score=4.0)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N= 120 head injured patients	Mean age: 28.43 years; gender: not specified.	TBI	five California Verbal Learning Test–Second Edition (CVLT–II) variables	The discriminant function seemed to best predict those who put forth adequate effort while testing (95.6% correct) but not those who failed to put forth adequate effort during testing (only 13.8% correct). Hence, although the overall classification rate was moderately impressive (75.8%), the model's sensitivity in classification of the incomplete effort group was low.	"In sum, this study provides some evidence that recognition variables in the CVLT–II show promise in their ability to supply information about effort during neuropsychological testing. Therefore, using CVLT–II performance to measure effort in larger and more diverse populations needs to be examined."	Data suggest some information regarding recognition variables in CVLT-II ut the test did not show great sensitivity in discriminating those with incomplete effort.
Jacobs 2008 (score=4.0)	CVLT-II	Diagnostic	The study was supported by a grant from the Campbell	N= 114 Patients with TBI, selected from a 5-year series of consecutive	Mean age: 38.24 years; 51 females, 63 males	TBI	Seven California Verbal Learning Test–Second Edition CVLT-II	Various performance contrasts (i.e., proactive interference, retroactive	"It is concluded that performance discrepancies on the CVLT-II should never be used in isolation to	Data suggest CVLT-II should not be used as a standalone test to determine the

			Foundation. No mention of COI.	rehabilitation referrals			variables of interest	interference, rapid forgetting, and retrieval problems) were evaluated. Initial analyses revealed higher rates of rapid forgetting in the TBI group as compared to the standardization sample. There were 10 patients (8.77%) who had PI effects−1.5; 14 patients (12.28%) who had RI effects≤−1; 24 patients (21.05%) who had RF1 effects≤−1; 15 patients (13.16%) who had RF2 effects≤−1; 5 patients (4.38%) who had RP1 effects≥1.5; and 3 patients (2.63%) who had RP2 effects≥1.5. Only for the RF1 Contrast was the difference with the respective prevalence in the CVLT-II standardization sample statistically significant ($z = 2.22$, $p < 0.013$; $p > 0.10$ for	determine the presence or absence of acquired cerebral or memory impairment. However, regardless of the cause, such discrepancies may still be relevant for clinical treatment recommendations."	presence or absence of acquired cerebral or memory dysfunction.

								all other comparisons).		
Donders 2011 (score=3.5)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N=100 patients with TBI	Mean age: 37.5 years; 55 females, 45 males	TBI	California Verbal Learning Test – Second Edition (CVLT–II) and World memory test(WMT	Although the CVLT–II logistic regression formula demonstrated a statistically significant level of agreement with results from the Word Memory Test, it was associated with an unacceptably high proportion of false positives. The component variables of the logistic regression were sensitive to length of coma but did not covary with psychosocial complicating factors (e.g., unresolved prior psychiatric history) that were associated with a higher relative risk of failure of WMT validity criteria.	"we conclude that the Wolfe et al. CVLT–II response bias formula is not yet ready for routine application in general clinical settings where assessment of effort is used first and foremost to determine the validity of test results, as opposed to the detection of malingering in a medicolegal context. The current results do not suggest that the Wolfe et al. formula is useless. It is possible that it might have fared better if we had used a sample with a different balance of cases with sufficient vs invalid effort and who were seen several years post injury."	Data suggest multiple measures should be used in assessing effort testing to limit numbers of false positives.

Evidence for the Use of RBANS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Lippa 2017 (score=7.0)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 250 military service members	Mean age:28.4 years; 235 males, 15 females	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Test of Memory Malingering (TOMM)	Participants were divided into two groups based on their performance on the Test of Memory Malingering: PVT-Pass, *n* =193; PVT-Fail, *n* =57. For the EI, recommended cut-offs for extremely probable, highly probable, and probable poor effort were established. A cut-off score of >3 resulted in low sensitivity (.14), high specificity (.99) and positive predictive power (.94), and moderate negative predictive power (.68)	"the findings support the use of the EI over the ES to identify poor effort in mild TBI patients, but also suggest that additional PVTs are generally required to accurately rule poor effort in or out. The EI and ES should continue to be validated in various patient samples, as it appears their usefulness and ideal cut-offs vary by sample.	Data suggest the RBANS E1 and ES are useful for detecting possible poor effort in mild TBI but additional PVTs are recommended.

								and is recommended for identifying highly probable poor effort. For both the EI and ES, cut-offs for probable poor effort were identified.		
McKay 2008 (score=6.0)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 51 TBI cases and 34 non-head-injured controls	Mean age: 41.7 years; 44 females, 41 males.	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Across RBANS' Index Scores, the TBI group performed at a significantly lower level than the controls; sensitivity to TBI and likelihood ratios ranged from modest to strong; and specificity was high. Particularly efficacious was the clinical efficiency exhibited by the Total Scale Index (summary score) of the RBANS.	"In conclusion, the results of this study demonstrate the clinical utility of the RBANS within the TBI population, specifically in terms of its sound sensitivity and specificity. The RBANS has been found to be a clinically useful cognitive screening measure in dementia, Parkinson's disease, multiple sclerosis,	Data suggest RBANS is a sensitive and specific test for detecting TBI especially with the Total Scale Index Summary subtest.

									stroke, and with this current evidence, the TBI population."	
Novitski 2012 (score=5.5)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 25 mild TBI patients, 69 clinical subjects with amnestic MCI (n= 15) or probable Alzheimer's disease (n=54),	Mean age: 49 (mildTBI patients), 89 (clinical subjects); Gender: not specified	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Receiver-operating characteristic analyses demonstrated much better sensitivity and specificity of the ES (effort scale), with a marked reduction in false positive errors.	"Additional validation work is necessary to more firmly establish the clinical utility of the newly derived RBANS ES, and, as with any measure of effort, the ES should be considered in the context of clinical history, presentation, and pattern of performance across other measures. Specifically, it would be helpful to validate the ES in conjunction with stand-alone measures of effort. Once the calculation of	Data suggest ES is better than E1 demonstrating better sensitivity and specificity and reduced numbers of false positives but should only be used in cases where there is previous concern for impairment and/or lack of effort demonstrated on Digit Span or List Recognition subtests.

									an ES score is triggered by unusually low performance on one or more of these two subtests, ES scores ,12 should be considered suspicious for suggesting poor effort. Additional measures of effort should be examined under most circumstances in order to clarify the finding."	
Lippa 2013 (score=4.5)	RBANS	Diagnostic	No COI. No mention of sponsorship.	N=51 with acute TBI patients.	Mean age: 39.6 years; 13 females, 38 males.	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	In this sample of acute TBI patients (n=51), the mean index scores on the RBANS ranged from 1.59–2.36 SD below the mean of the standardization sample. Each WRAT-4 Reading sub-test score was above the corresponding RBANS Total Scale Index score (t (31) =10.32,	"The RBANS appears to be a useful tool in assessing the presence and severity of acute TBI."	Data suggest RBANS is a sensitive tool for detecting cognitive domains in TBI patients and could be useful in acute care settings.

								p<0.001). Regression analyses revealed that Delayed Memory (β=-0.365, p<0.007) and Total Score (β=-0.297, p<0.023) indices were significantly predicted by post traumatic amnesia (PTA) length after controlling for age and education.		
Couillet 2010 Score = 4.0)	RBANS	Diagnostic	Sponsored by grants from the Programme Hospitalier de Recherche Clinique and by Assistance Publique-Hopitaux de Paris. No mention of COI.	N = 12 patients in the stages of subacute or chronic after a severe TBI.	Mean age of AB group: 23.8 (N=5) BA group: 26.7 (N=7) No mention of Sexes	An AB vs. BA crossover design was used. Each phase was six weeks and consisted of four one-hour training sessions a week for a total of 24 hours of training. A phase was the control phase,	Follow up at 6 weeks, 12 weeks, and one month after the end of the trial.	Effect of time and the group x time interaction in Divided attention subtest of the TAP: Mean Reaction Time: AB group: F(3, 21) = 21.5, (p < .0001); BA group: F(3, 21) = 20.7, (p < .0001) Number of Omissions: AB Group: F(3, 18) =22.3, (p < .0001)	"In summary, these results suggest that the specific rehabilitation programme for divided attention had specific effects on divided attention and was useful and helped patients to deal more rapidly and more accurately with dual-task situations."	Small sample randomized crossover study. At 6 weeks, the data suggest specific divided attention training was better than control for most tasks. but executive function and working memory tasks improved to a lesser degree.

						consisting of cognitive tasks that did not use the patient's divided attention or working memory. B phase consisted of specific dual attention training.		BA group: F(3, 18) = 13.2, (p < .0001) Effect of time and the group x time interaction were both significant for the go–no go dual-task reaction times: AB group: F (3, 18) =12.3, (p <.0001). BA group: F(3, 18) = 17.5, (p <.0001,) Digit Span Dual Task: AB group: F(3, 18) =84.6, (p<.0001); BA group: F(3, 18)= 28.4, (p<.0001)		

Evidence for the Use of WMS-III

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Ord 2008 (Score = 5.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N = 208 patients with TBI	Mean age: 48.92 years; 118 males, 90 females.	TBI	All patients received WMS-III examination. Mild TBI non-malingering (N = 34) vs Mild TBI malingering (N = 31) vs Moderate/severe TBI non-malingering (N = 28) vs General clinical group (N = 93)	MTBI MND group preformed worse then MTBI groups on all eight indices (P < .01)	"This study indicates that the WMS-III primary indices can accurately identify malingered neurocognitive dysfunction in mild TBI when used as part of a comprehensive classification system."	The majority of study patients were financially incentivized. Data suggest the primary WMS-III induces can be used as an accurate measure to identify malingered neurocognitive dysfunction in mild TBI if used as a component of a comprehensive classification system
Glassmire 2003 (Score = 5.5)	Wechsler Memory Scale-III	Diagnostic	Sponsorship from The Defense and Veterans Head Injury Program and the Medical research Service of the Department of Veterans Affairs. David	N = 60 patients with TBI	Mean age: 33.3; 55 males, 5 females.	TBI	Both groups received the WMS-III Faces I subtest for assessment of Malingering. Nonlitigating traumatic brain injury (N =30) vs Control (N = 30)	(TBI vs. Control) by Testing Condition (SA vs. IM) interaction was significant, F(1, 58) = 8.70, (p = .005) Average raw Faces score in SA condition (M = 36.3, SD = 4.9) IM condition (M = 23.3, SD = 6.9), Difference	"The findings of the current study indicated that the Faces I subtest (Faces) provides important information when screening for the presence of malingered memory impairment on the WMS-III."	"Data suggest the WMS-III faces subset holds promise for validity in the measurement of malingering for memory impairment in TBI."

			Glassmire is currently affiliated with Patton State Hospital					, F(1, 58) = 150.95, (p<.001.)		
Langeluddecke 2003 (Score = 5.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N = 75 Patients with TBI	Mean age: 35.4 years; 54 males, 21 females.	TBI	Both groups received the WMS-III Malingerers (N = 25) vs Nonmalingerers (N = 50)	Malingerers vs Nonmalingerers Auditory immediate 70.2 vs 92.1 (t = 6.11) Visual immediate 62.4 vs 88.6 (t= 8.10) Immediate memory 60.2 vs 88.8 (t = 8.40) Auditory delayed 70.8 vs 94.2 (t = 7.12) Visual delayed 62.1 vs 90.2 (t = 8.71) Auditory recognition-delayed 67.4 vs 97.5 (t = 9.31) General memory 60.3 vs 92.1 (t = 9.03) Working memory 82.2 vs 100.0 (t = 4.44)	"The results of the present study suggest that the inclusion of auditory recognition memory subtests and indexes on the WMS-III is a major improvement on the WMS-R in facilitating the detection of malingering."	Data suggest <10% of sever TBI patients, only about 10% returned scores below the cut-off score for malingering in mild TBI patients.
Hacker 2009 (Score = 5.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship. No COI.	N = 27 patients with TBI mild to severe. N = 60	Mean age: 33.6; 27 males, 50 females, 10 not stated.	TBI	All groups received the WMS-III test, Wechsler test of Adult Reading, and Wechsler	Sensitivity to malingering: Difference between the word list	"Overall the findings provide preliminary evidence to support the use of the WLR as an embedded	Data suggest the WLR of the WMS-III discriminated between a simulator and TBI group which

				control group N = 87 total patient.			abbreviated Scale of Intelligence. TBI and control optimal group took test to best of their abilities. Analogue malingerer was instructed to take as if they had a brain injury. TBI (N = 27) Vs Control (N = 300 vs Analogue malingerer (N = 30).	recognition (WLR) performance of the AM group and the TBI group (t = -6.216; p<0.01) WASI FSIQ CO 116.13 vs TBI 85.13 vs AM 82.13. Difference TBI vs AM (p = .52)	symptom validity indicator. These findings, however, require further cross-validation with larger clinical samples in order to assess its ecological validity."	suggest it may have validity as an "embedded symptom validity indicator."
Walker 2009 (score=4.5)	WAIS-III & WMS-III	Diagnostic	No sponsorship or COI.	N=200 patients. 100 patients with moderate to severe traumatic brain injury (TBI). 100 controls.	Mean age: TBI 30.68 years. Controls 40.07 years. TBI: 81 males/19 females. Controls: 70 males/30 females.	Moderate to severe traumatic brain injury (TBI).	Wechsler Adult Intelligence Scale-III (WAIS-III) and Wechsler Memory Scale-III (WMS-III) indices vs. age corrected indices.	Age corrected indices correctly classified 77% [154385] of all participants, with 82% sensitivity and 72% specificity. Demographically corrected indices correctly classified 74% [148385] of participants, with 76% sensitivity and 72% specificity.	"[F]or mostly younger white individuals with lower levels of education, the demographic corrections for the WAIS-III and WMS-III do not provide an advantage in the classifi cation of moderate to severe TBI over and above age corrected indices."	Data suggest demographically corrected WAIS-III and/or WMS-III indices did not provide better diagnostic accuracy than age corrected indices in TBI patients.
West 2011 (Score = 4.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N=132 patients with TBI.	Mean age Mod/Sev TBI group: 29.9 (SD=10.1).	TBI	N=44 mild TBI patients with good effort vs. N=48 mild TBI patients with poor	Moderate–severe TBI group scored the lowest on WMS-III Visual indices. Effort	"[F]indings of this study are consistent with the TBI outcome literature and emphasize the	96% of patients had some sort of financial incentive. Data suggest effort

					91 males, 41 females.		effort vs. N= 40 moderate–severe TBI patients with good effort. WMS_III index scores were main outcome: Auditory Immediate, Visual Immediate, Immediate Memory, Auditory Delayed, Visual Delayed, Auditory Recognition Delayed, General Memory, and Working Memory.	had a larger effect than injury severity on WMS-III scores average Cohen's d =−1.27).	importance of controlling for effort in neuropsychological assessments."	had more impact on WMS-III scores than did injury severity. Additionally, a dose-response relationship was found between injury severity and WMS-III scores.
Langeluddecke 2005 (Score = 4.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N= 180 litigants with post-acute moderate to extremely severe TBI, classified.	Mean age of 35.5 Years. 117 males, 63 females.	TBI	Moderate TBI (N=44) vs severe-very severe TBI (N=86) vs. Extremely severe (N=50) vs. Normal Control Group (N=50). Main outcome was WMS-III indexes and core subtests.	Mean scores related to severity on all index measures, with lower scores in the more severely brain injured. Mean±SD Visual immediate comparing controls vs. moderate vs. severe vs. extremely severe: 101.3±15.3 vs. 88.8±14.0 vs. 85.3± 15.1 vs. 74.9±13.1, p=0.006.	"Differences between WMS-III memory indexes are unlikely to be of diagnostic utility although memory-intelligence discrepancies may be."	Data suggest a significant dose-response relationship exists between TBI injury severity and most WMS_III indices and subtests. Also, TBI effected results indices more than auditory indices. Also, revised Tulsky indices did not result in increased severity compared to the original ones.

Hawkins 1998 (Score 4.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N= 214 principal subjects are the clinical samples for whom complete WAIS-III and WMS-III data are presented in the Technical Manual. Only 22 patients had TBI.	Mean age of TBI patients: 26.9 (SD=5.9).14 males, 8 females among those with TBI.	TBI	Immediate Memory Index (WMS-III) vs. WMS-III General Memory Index. Details sparse.	WMS-III Visual Index may also prove highly sensitive to brain compromise. Verbal comprehension was the high point for five of the seven conditions (mean VCI-PSI difference = 14.23, *SD* = 7.6), with the exceptions being the TBI [66] and Korsakoff's samples (WMI). The VCI was 2.5 points lower than POI for the TBI group.	"[C]ompared with the Immediate Memory Index, the WMS-III General Memory Index (measuring delayed recall and recognition) does not exhibit greater sensitivity to the memory deficiencies of most of the patient samples for whom data are available"	Population included Alzheimer's Huntington's disease, Parkinson's disease as well as TBI patients, chronic alcohol abusers and Korsakoff's syndrome, and schizophrenia patients. Data suggest the WMS-III general memory Index does not have superior sensitivity to memory deficits in most patients compared to the immediate memory index.

Evidence for the Use of TOMM

Author Year (Score)	Category :	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Hall 2014 (6.5)	TOMM	Diagnostic	No mention of COI or sponsorship	48	27 female, 21 male Mean age 39 years	Minimal to mild head injury, in acute stages post-injury	Trail Making Test vs. Verbal Fluency (FAS) test vs. Colour Word Interference Test vs. Word Memory Test vs. Test of Malingering Memory (TOMM) vs. Reliable Digit Span vs. PDI vs. MSPQ Processing Speed Index [419] from WAIS-III vs. Word List Recognition	At the 82.5% cutoff for WMT, the false positive rate (FPR) was 18%. Those who failed the IR or DR also failed the WMT, resulting in a joint failure rate of 18%. In the IR the FPR was 8% and 3% for the DR. The difference between those who passed and failed the WMT was also significant in regards to the verbal fluency test ($p<0.05$, effect size $d \leq 0.7$). Sensitivity for various	"In conclusion, the results of this study suggest that the WMT consistency index cut-off may be too aggressive with minimal to MHI individuals within the early stages post-injury."	All participants were not involved in litigation and this did not fit malingering criteria. Data suggest WMF may be the result of a specific verbal processing deficit in the acute phase of mild head injury.

								subtests: RDS = 0.41, TOMM = 0.61; WLR = 0.81; PSI = 0.55; PDI = 0.59; MSPQ = 0.9.		
Whitney 2013 (6.0)	TOMM	Diagnostic	No mention of COI or sponsorship	N= 194 participants	Age 21 to 77 181 males, 13 females 50.67 years mean age.	Patients with TBI referred to the author for neuropsychological testing within a VA Medical Center.	Pass TOMM (N=149) RBS VS F VS Fb VS Fp VS FBS VS HHI Against Fail TOMM (N=45) RBS VS F VS Fb VS Fp VS FBS VS HHI TOMM=Test of Memory Malingering;	There was a statistically significant difference between passed TOMM (N=149) and failed TOMM (N=45) at for Pass TOMM (N=149) M: (11.4, 67.8, 66.2, 53.2, 20.6, 8.1) and SD: (4.1, 18.9, 22.2, 13.1, 5.6, 3.7) VS failed TOMM (N=45) M: (14.6, 82.1, 82.4, 61.5, 23.8, 10.7) and SD: (4.0, 20.8, 25.1, 17.0, 5.8, 3.2)	"Although the TOMM and the MSVT were used to classify individuals as demonstrating performance invalidity in the present study, it should be emphasized that the diagnosis of invalid presentation, especially if malingering is in question, is a clinical judgment that cannot be made on the results of symptom validity tests alone, but must be made in consideration of other psychometric, behavioral, and collateral data (Slick et al., 1999)."	Data suggest RBS and HHI show poor performance in predicting malingering.

Barhon 2015 (6.0)	TOMM	Diagnostic	No mention of sponsorship or COI	N = 92	Mean age: 19.7 years; 25 males, 67 females.	TBI	Word Choice Test (WCT) vs. Test of Memory Malingering (TOMM) Full-Effort Group (N=46) vs. Distraction Group (N=46) vs. Uncoached Group (N=22) vs. Coached Group (N=24)	Statistical significance found between full effort group and uncoached group (p<.0005) and between full effort group and coached group (p<.0005), and no statistical significance between full effort group and distraction group (p<.0005). At a cut score of 48, TOMM had a sensitivity of 91.3, specificity of 89.13. At a cut score of 48, WCT had a sensitivity of 86.96, and a specificity of 78.26.	"The WCT was found to be as effective as the TOMM in differentiating simulators from participants applying full effort. The WCT is primarily a measure of effort rather than cognitive ability."	Data suggest similar efficacy between TOMM and WCT in the detection of cognitive impairment. Both TOMM and WCT are primarily tests of validating poor effort.
Lange 2010 (5.5)	TOMM	Diagnostic	No mention of COI or sponsorship.	63 individual with mild TBI who were receiving	Mean age: not specified; 40 males,	Mild TBI	TOMM pass (n = 48) vs. TOMM fail (n = 15). All participants	Between TOMM pass and fail groups:	"These results highlight the importance of considering the	All participants receiving financial compensation.

				financial compensation from the Workers' Compensation Board	23 females.		underwent the following tests: Post-Concussion Scale (PCS), British Columbia Cognitive Complaints Inventory (BC-CCI), selected test from Neuropsychological Assessment Battery Screening (S-NAB)	significant main effects and large effect sizes for PCS (d=0.79, p=0.002), BC-CCI (d=0.98, p=0.011). Those in TOMM fail group scored higher for both measured compared to TOMM pass group. TOMM fail group scored lower on attention (d=1.26, p=0.004), memory (d=1.16, p=0.006), and executive functioning (d=0.70, p>0.05) indexes	influence of poor effort, in conjunction with a growing list of factors that can influence, maintain, and/or mimic the persistent postconcussion syndrome."	Data suggest poor effort must be considered in addition to multiple other factors which can mimic post0concussion syndrome.
Flaherty 2015 (5.5)	TOMM	Diagnostic	No COI. No mention of sponsorship.	257 veterans with possible mild TBI	Mean age: 29.5 years; 248 males, 9 females.	Possible mild TBI	Rey Fifteen-Item Memory Test (FIT) (n = 257). Out of the 257 participants that underwent the FIT, some	Four (1.6%) participants failed the FIT (according to standard cut-off of <9 items), three	"Despite its popularity, the FIT is not supported as an appropriate measure of performance	Data suggest FIT is not a good tool for performance validity in veterans being

							completed the Digit Span (n = 148) and some completed the Digit Span and the TOMM (n = 109)	(1.2%) failed the FIT (cut-off of <8 items), and 198 (77%) obtained perfect scores.	validity in veterans undergoing evaluation for possible mTBI. Therefore, inferences regarding neuropsychological data reliability with adequate statistical certainty require use of other measures of performance validity with greater sensitivity."	evaluated for mTBI.
Schroeder 2013 (5.5)	TOMM	Retrospective	No sponsorship or COI.	62 consecutive forensic cases, with complaints related to TBI	Mean age 40.83 years for pass MND, 44.08 years for fail MND; 38 males, 24 females.	Mild TBI, complicated mild TBI, moderate-to-severe TBI, or a number of other conditions including major depressive disorder, frontotemporal dementia, and mental retardation to name a few.	Malingered Neuropsychological Dysfunction Criteria (MND) Pass group (n = 26) vs. MND Fail group (n = 36). All participants underwent TOMM trial 1, TOMM trial 2, TOMM retention, and the Albany Consistency Index tests.	Group performances between pass and fail MND groups, respectively (mean score, mean rank, Mann-Whitney U, p-value) - TOMM trial 1: 47.17 vs. 35.92, 41.89 vs. 17.12, 94.00, (p < 0.01), TOMM trial 2: 49.86 vs. 41.96, 41.08 vs. 18.23, 123.00, (p <	"Evidence was provided for convergent and divergent validity for all TOMM indices, which increases confidence for the clinical utility of both the new and traditional indices. Although each index well differentiated patients passing and failing MND criteria, the ACI was found to be the superior index."	Data suggest both the new and the traditional TOMM indices are valid and have good clinical value. However, the ACI was found to be the superior index.

								0.01), TOMM Retention: 49.69 vs. 39.88, 41.35 vs. 17.87, 113.50, ($p < 0.01$), ACI: 46.89 vs. 30.15, 42.57 vs. 16.17, 69.50, ($p < 0.01$)		
Guise 2010 (score= 5.0)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=176 TBI patients (archival data).	Mean age mild TBI/good effort: 38.1 (SD=9.7). 26 males, 13 females mild TBI/good effort group.	Mild to severe TBI	Mild TBI/Good Effort (n = 40) vs. Mild TBI/Poor Effort (n = 42) vs. Moderate-severe TBI/Good Effort (n = 40) vs. Moderate-severe TBI/Poor Effort (n = 14) vs. Control (n=40). Portland Digit Recognition Test vs. Test of Memory Malingering (TOMM).	Effort was found to have a greater effect on test performance (0.79) than injury severity (0.47).	"Moderate-severe TBI produced overall worse performance than mild TBI patients and control subjects. Mild TBI showed some effect on test performance, but deficits were likely due to secondary factors including financial incentive, psychological overlay, and poor effort."	Data suggest effort has a greater effect on text performance than does injury severity.
Teichner 2004 (score=5.0)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=78 elderly cognitively intact, cognitively impaired (non-dementia), and with dementia	Mean age was 70.5 (SD=8.5). 33 males and 45 females.	Cognitively intact, cognitively impaired (non-dementia), and with dementia.	Test of Memory Malingering (TOMM) vs. Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) vs. Wechsler Memory Scale—	100% of normals and 92.7% of the cognitively impaired group made fewer than five errors	"Results suggest that the TOMM is an useful index for detecting the malingering of memory deficits, even in patients with cognitive impairment, but	Data suggest TOMM is a useful test for the detection of malingering and memory defects even in those with cognitive

							Third Edition (WMS-III) vs. Mini-Mental State Examination (MMSE).	(the suggested cut-off) on Trial 2 or the Retention trial of the TOMM.	only when dementia can be ruled out."	impairment if and only if dementia can be ruled out.
Haber 2006 (5.0)	TOMM	Retrospective Study	No mention of sponsorship or COI	50 Cases with head-injury.	Mean age of 39.1 years old. 27 Females, 22 Males	TBI	TBI Group (N = 22) Vs IME Group (N=28)	The TBI group was moderately to severely impaired for memory performance. Nobody in the TBI group scored below 45 on Trial 2 despite being impaired visually.	"[T]he TOMM appears to have adequate sensitivity and excellent specificity vis-a`-vis traumatic brain injury, allowing the clinician to have high confidence that positive scores reflect incomplete effort."	Data suggest that TOMM is useful in the detection of suboptimal effort especially for those individuals with mild head trauma.
Bashem 2014 (5.0)	TOMM	Diagnostic	Supported by grants from Wayne State University, the Del Harder Foundation, and the National Institute on Disability and Rehabilitation Research. No mention of COI.	109	No gender distribution described Mean age 44.0 years	Those with TBI, ranging from mild complicated to severe (n=51) vs Neurologically healthy controls (n=58) All participants underwent all testing	Premorbid intelligence, measured via Wechsler Test of Adult Reading (WTAR) vs Performance Validity Test (PVT) - Test of Memory Malingering (TOMM) vs PVT – Word	TOMM highest hit rate (68%). TOMM highest sensitivity (50%) and MSVT highest specificity (94%). RDS smallest hit rate (54%), specificity (77%), and sensitivity (35%).	"The findings should be generalized with caution, but if only one index will be employed, this study provides support for administering the TOMM alone and reserving the MSVT as an equivalent, alternate measure for future assessment."	Participants were each compensate $30. Data suggest use of TOMM with CVLT or use of MSVT with CVLT for the best diagnostic accuracy to assess TBI associated memory function. Any more than 2 tests does not significantly

							Choice Test (WCT) vs PVT – Medical Symptom Validity Test (MSVT) vs Embedded indices – Forced Choice Recall (CVLT-II) vs Embedded indices – Reliable Digit Span (RDS)	TOMM and CVLT highest agreement within TBI participants (86% passed both, 2% failed both, 88% overall agreement rate). RDS and WCT had lowest overall agreement rate (68%) in those with TBI. Overall agreement highest between TOMM and MSVT (84%) in controls. 40% failed both tests and 45% passed both.		increase diagnostic accuracy.
Ashendorf 2004 (score=4.5)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=197 community-based older adults with mild-to-moderate depression and anxiety as measured by Beck Depression Inventory	Mean age 64.57 (SD=5.52). 101 females and 96 males.	Mild-to-moderate depression and anxiety.	Test of Memory Malingering (TOMM).	All TOMM Trial 2 scores were 48 or higher, suggesting an absence of malingering.	"These findings demonstrate that depression and anxiety levels in an older community-dwelling sample do not negatively affect performance on the TOMM."	Data suggest that although TOMM appears resistant to many conditions including TBI, depression and anxiety do not negatively affect TOMM performance.

				(BDI) and. State-Trait Anxiety Inventory (STAI).						
Constantinou 2004 (score=4.5)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=69 litigants with mild TBI.	Mean age 42.41 (SD=12.45). 36 females and 33 males.	Mild TBI.	Test of Memory Malingering (TOMM) vs. general performance patterns on the WAIS-R vs. Halstead–Reitan Neuropsychological Battery for Adults (HRNB-A).	TOMM was associated (P <0.05/15 = 0.003 (Bonferroni method for control of Type I error) with decreased VIQ (Correlations r=0.47), PIQ (Correlations r=0.52), FSIQ (Correlations r=0.52) scores and decreased performance onWAIS-R subtests	"[I]t appears that a poor performance on the TOMM is predictive of a generalized poorer performance on standardized measures such as the WAIS-R and the HNRB-A."	Data suggest a poor performance on TOMM trial 2 was generally positively correlated to a poor performance on WAIS-R and HRNB-A.
Heyanka 2015 (4.0)	TOMM	Diagnostic	No COI. No mention of sponsorship.	160	9 female, 151 male Mean age 31.7 years	Mild TBI	Word Memory Test (WMT) – IR, DR, CNS trials vs TOMM vs California Verbal Learning Test-Second Ed. (CVLT-II)	Significant correlation (p<0.001) between CVLT-II and TOMM (0.40-0.68), CVLT-II and WMT (0.43-0.61), and WMT and TOMM (0.51-0.75) observed.	"Our findings support assertions that PVTs measure effort independent of memory in veterans with mild TBI."	Data suggest PVTs are measuring effort which is independent of memory in mild TBI veterans.

Stenclik 2013 (4.0)	TOMM	Diagnostic	No mention of COI or sponsorship.		Mean age: 45.52 years; 20 males, 24 females	44 with history of mTBI (defined by the American Congress of Rehabilitation Medicine (ACRM) Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group)	All participants underwent the TOMM Trial 1, Trial 2, and Retention Trials. Comparison of standard TOMM cutoff values (n = 44) vs nonstandard cutoff of <49 on Trial 2 (n = 44) vs nonstandard cutoff of ≤39 on Trial 1 or Retention Trial (n = 44). Criteria for performance invalidity equal to failing two or more SVTs (Rey 15-ItemTest, Victoria Symptom Validity Test, Word Memory Test, and Reliable Digit Span)	Classification accuracy statistics for cutoffs (sensitivity, specificity, false negative rate, and false positive rate, respectively) - standard TOMM cutoffs: .4, 1.0, .6, .00. <49 on Trial 2/Retention Trial cutoff: .75, .92, .24, .08. ≤39 on Trial 1 cutoffs: .6, .96, .4, .04.	"These findings support the use of nonstandard cutoffs to increase the TOMM's classification accuracy."	Data suggest non-standard cutoffs likely to increase the classification accuracy of TOMM.

Evidence for the Use of Cognitive Event Related Potential

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Gosselin 2012 (4.0)	Cognitive Event Related Potential	Diagnostic	Study was supported by the Canadian Institutes of Health and Research and by the Defense Research & Development. No COI.	N=44 Patients w/ TBI. N=40 Controls.	44 females, 40 males; Mean age 30.3±11.1 (TBI group), 28.6±10.5 (Control group)	Individuals who had sustained an mTBI event within the last 36 months.	Comparison between healthy controls and TBI patients of frontal ERP (Event related potential) components (N200, N350). Working Memory (WM) processes an d partial ERP would have (P200, P300)	N350 amplitude showed smaller amplitude for mTBI group during the decision phase of WM ($F(1,80) = 6.11$ ($p=0.016$)). P300 amplitude in WM decision phase was smaller in mTBI stuff ($F(1, 80) = 9.33$ ($p<0.01$)).	"This study showed that abnormal ERP results are observed in patients in their post-acute and long-term stages after MTBI… Clinicians should be aware that patients with MTBI or sports concussion probably have underlying mild but persistent cerebral dysfunctions that require further investigation."	Data suggest patients with mild TBI exhibit abnormal ERP results including in the non-acute post injury stage which often goes undetected
Soldatovic 2014 (4.0)	Cognitive Event Related Potential	Diagnostic	No sponsorship or COI.	N=90 patients with varying severities of TBI.	No mention of sex; Mean age of 38.18±13.17.	Patients with mild, moderate and sever TBI within the past year.	(N=41) mild TBI, (N=27) moderate TBI, (N=22) Severe TBI groups we compared in P300 cognitive evoked potentials.	P300 ERPs latency was significantly different between mild and severe, 326.8 ±36.76 vs 350.55±31.71 ($p=0.03$). Mild and moderate, 326.83±36.76 vs 355.67±42.32 ($p=004$).	"As regards neuropsychological assessment of cognitive deficits, our data show that the WCST has a great significance for detecting cognitive impairment, as well as for assessing the severity of TBI."	Date suggest p300 ERP correlates to increased response latency and NCST useful for discriminating TBI severity and thus both tests have benefit in the detection of cognitive impairment.

Evidence for the Use of Attention Tests

Author Year (Score)	Category:	Study type:	Sponsorship / COI	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Twamley 2014 (4.0)	Attention Test	Randomized controlled trial	Sponsored by the DOD award. Dr. Delis received royalties from the sale of the CVLT-II and D-KEFS. No mention of other COI.	N = 50 Veterans with TBI.	Age and sex information only available for post-treatment sample. Mean age: 29; 32 males and 2 females.	TBI	Comparison data only available for post-treatment sample. Supported employment plus CogSMART (N = 16) vs Control group, received enhanced supported employment that controlled for therapist attention (N = 18). Attention and working memory measured with the Wechsler Adult Intelligence Scale-3rd Edition Digit Span scaled score, Verbal learning/memory measured with the CVLT-II. Follow-up for 12 weeks.	CogSMART-associated improvements in postconcussive symptoms / and prospective memory performance: NSI: p = 0.01 / and MIST 24 h probe: p = 0.05. CogSMART showed small-medium effect size improvements in psychiatric symptom severity / and HAM-D: CAPS: d = 0.43 / and HAM-D: d = 0.37 compared to controls.	"Results suggest that adding CogSMART to supported employment may improve postconcussive symptoms and prospective memory."	Pilot RCT. Data suggest Cog SMART "may" improve post concussive symptoms in Veterans with TBI.
Rogers 2014 (NA)	Attention Test	Prognostic	Sponsored by a University of Western Australia International Postgraduate Research Scholarship awarded to the	N = 10 with history of mild traumatic brain injury (mTBI) and	Aged 17–34 (18) and 18–30 (18.5) for controls. 12 males and 8 females.	mTBI and healthy subjects	Mild TBI, time since injury>2 months, completed Paced Auditory Serial Addition Task (PASAT) as a measure of attention process, at four separate sessions	Performance differences from the first (Session 1A) to the second experimental block (Session 1B) at each of the 4 inter-stimulus interval	"These preliminary results suggest sustained mental effort is required to achieve 'normal' performance	Data suggest practice of mental effort post TBI is important for improving functional recovery.

			first author. No COI.	10 healthy subjects.			(N = 10) vs Healthy matched controls completed PASAT at 4 sessions (N = 10).	rates or ISIs: F (1, 18) = 12.90, $p < 0.01$, $n^2p = 0.42$. The mean number of correct PASAT responses, the main effects of session: F (2.02, 36.43) = 91.16, $p < 0.01$, $n^2p = 0.84$ and ISI: F (1.35, 24.24) = 51.85, $p < 0.01$, $n^2p = 0.74$, were significant.	levels following mTBI and support the use of practice-related, ERP indices of recovery from mTBI as a sensitive correlate of persistent post-concussion symptoms."	
Wäljas 2014 (NA)	Attention Test	Prognostic	Sponsored by Competitive Research Funding of the Pirkanmaa Hospital District, Tampere University Hospital. No COI.	N = 109 with mTBI.	Aged 37.4 (13.2) yeas, 52 male and 57 females.	mTBI	Outcome measures; Self-report questionnaires, post-concussion symptoms, depression, fatigue, and general health, measured with the Rivermead Post Concussion Questionnaire (RPSQ). Attention and executive functioning were assessed with the Stroop Color Word Test (Golden version), Trail Making Test A and B, and 2 verabl fluency tasks: animal naming and single letter-based word generation.	RTW rates: 1 / 2 / 3 / and 4 weeks; 46.8% / 59.6% / 67.0% / and 70.6%. 2 months / and 1 year; 91.7% / and 97.2%. Significant predictors of the number of days to RTW: age, multiple bodily injuries, intracranial abnormality at the day of injury, and fatigue ratings (all, $p < 0.001$). Participants who returned to work fewer than 30 days after injury (n = 82,	"Return to work is one important marker of functional recovery following mTBI."	Data suggest time until RTW post mild TBI is correlated with the number of bodily injuries, age, intracranial injury and fatigue.

							Follow-up or 3 to 4 weeks.	75.2%) vs 30+ days (n = 27, 24.8%).		
Oldenburg 2015 (NA)	Attention Test	Prognostic	No mention of sponsorship. No COI.	N = 102 with mild traumatic brain injury (mTBI) with N = 35 controls.	Aged 15-65 years.	mTBI	Post-concussion symptoms (PCS) (N = 34) vs Recovered (N = 68) vs Control (N = 35). Self-report questionnaire and Neuropsychological test: The Paced Auditory Serial Addition Test (PASAT) processing speed, information processing and attention; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span, WAIS-R Block Span, The Selective Reminding Test The Stroop Color and Word Test	Only 102 subjects had PCS data and only 88 had neuropsychological assessment data. Recovered patients: WAIS-R Digit Span / WAIS-R Block Span / PASAT (2.4 sec) / and PASAT (1.6 sec); (N = 55) 9.8 (2.8) / (N = 28) 16.8 (2.8) / (N = 53) 55.4 (7.0) / and (N = 51) 54.3 (8.4). Controls; WAIS-R Digit Span / WAIS-R Block Span / PASAT (2.4 sec) / and PASAT (1.6 sec); (N = 28) 10.1 (2.9) / (N = 55) 17.0 (3.1) /	"mTBI may be linked to subtle executive memory deficits. Lower cognitive reserve appears to be a risk factor for PCS and indicates individual vulnerabilities."	Data suggest mTBI "may" be linked to deficits in working memory.

								(N = 28) 54.3 (7.0) / and (N = 26) 54.6 (5.8). Statistical significance between the 3 gropes above, for each of the 4 attention test domains; (p = 0.673) (p = 0.236). (p = 0.102). (p = 0.526).		
Nash 2014 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 207 seriously injured persons.	Aged at least 16 years.	mTBI	Moderate / severe group A (N = 48) vs Mild group (N = 89) vs Severe injuries without brain trauma (N = 70). Outcome measures: Questionnaire, Post-traumatic Stress Disorder Checklist Scale, Neurobehavioral Rating Scale, and	The most frequently observed symptoms (> 15%): anxiety (52.2%) / irritability (38.6%) / memory disorders (38.6%) / depressive mood (30.4%) / attention disorders (28.0%) / mood lability (26.6%) / and guilt feelings (16.4%). Memory and attention disorders were significantly more frequently found in the two	"The presence and the initial severity of a traumatic brain injury condition the nature and frequency of residual effects after one year."	Data suggest irritability or a depressive mood are not specific to TBI.

							The Trail Making Test, measurement of mental flexibility or attention-switching capability.	TBI groups than in the non-TBI group.		
Dockree 2015 (NA)	Attention Test	Prognostic	Sponsored by grants from the Health Research Board (PA-06-17) of Ireland, the National Rehabilitation Hospital Trust, University College Dublin Seed funding, and the National Disability Authority awarded to Dr. Simone Carton. No COI.	N = 62 with impaired self-awareness after TBI.	Mean age 34.37 (11.85), 49 males and 13 females.	Impaired self-awareness after TBI	All participants underwent the following testing: National Adult Reading Test (NART), Modified Six Elements Test (M-SET), Hospital Anxiety and Depression Scale (HADS), Sustained Attention to Response Test (SART), the Dual-task Attention to Response Test (DART), the Error Awareness Task (EAT), Cognitive Failures Questionnaire (CFQ), and the Frontal Systems Behaviour Scale (FrSBe).	Relationship between patient self-reports and SART no-go errors, (all $p > 0.1$). Positive relationship between CFQ ratings and SART errors ($r = 0.31$, $p = 0.01$). Relationships between FrSBe other reports vs SART errors ($r = 0.18$; $p = 0.1$) and PCRS other reports and SART errors ($r = -0.19$; $p = 0.08$). Self-other discrepancy measures derived from the CFQ, FrSBe & PCRS were inter-correlated: CFQ-FrSBe: $r = 0.48$; CFQPCRS: $r = 0.51$; FrSBe-PCRS: $r = 0.61$, (all $p < 0.0005$).	"This relationship supports the idea that the monitoring of errors in daily tasks will foster a growing self-awareness of daily functioning after brain injury, which, in turn, may necessitate a change in strategy or a commitment to rehabilitation to accomplish daily tasks more efficiently."	Data derived from diaries written by significant others. Data suggest emergent awareness was determined to be the only good predictor of performance on a modified 6 element test.
Johansson 2015 (NA)	Attention Test	Prognostic	Sponsored by grants from AFA Insurance, The Local Research and Development Board for	N = 76 with mild traumatic brain injury (mTBI) and	Mean age for mTBI and controls: 43.3 (12.2) / and 41.1 (12.3). 45	mTBI	mTBI, using the Mental Fatigue Scale (MFS) questionnaire and WAIS-III measuring information processing speed, and Digit Span, and	The TBI group significantly slower vs control on the complex sub-test ($F = 17.116$, $p < 0.001$,	"The results indicate a less efficient performance over time in complex and demanding	Data suggest mental fatigue post TBI correlates with diminished

			Gothenburg and Sodra Bohuslan, The Health & Medical Care Committee of the Vastra Gotaland Region, The Swedish Stroke Association and the Swedish Association For Survivors of Accident and Injury (RTP). No COI.	45 healthy controls.	males and 76 females.		WAIS-III, measuring attention and working memory (N = 76) vs Control (N = 45).	$\eta p^2 = 0.099$), and there was a significant interaction effect over time (F = 2.797, p = 0.044, $\eta p^2 = 0.023$), controls faster at the end of the test, vs TBI subjects remained on a similar level. TBI with a lower MFS rating (between 10.5 – 19.5, N = 29) and one with a higher MFS rating (>20, N = 46) showed an interaction trend with those with a higher MFS rating becoming slower at the end of the complex computer test, (p = 0.091).	cognitive tasks for individuals experiencing from mental fatigue after brain injury."	performance for complex cognitive tasks.
Maki-Marttunen 2015 (NA)	Attention Test	Prognostic	Sponsored by the Academy of Finland and the Competitive Research Fund of Pirkanmaa Hospital District. No COI.	N = 27 mTBI and N = 17 ankle injury.	mTBI mean age 41 years, and ankle injury: 12 females and 15 males	mTBI	MTBI, biomechanical force applied to the head resulting in loss or alteration of consciousness, confusion, and/or post-traumatic amnesia or PTA (N = 27) vs Controls with previous ankle injury (N = 17). Questionnaires, including BRIEF-A, Rivermead Post Concussion	mTBI patients were faster vs controls in the emotion relevant condition, mTBI vs controls: T = 2.13, p = 0.039, effect size = 0.58). N2 peak amplitude was significantly enhanced by emotional Go signals in the mTBI group, (N2, interaction effect emotion by group: F = 8.13, P = 0.007;	"mTBI may be associated with enhanced allocation of attentional and executive resources to threat-related stimuli."	Data suggest mild TBI patients had reported more emotional symptoms than controls when threat stimuli were evoked, the mTBI group responded quicker than controls suggesting

							Symptoms and Beck's Depression Inventory (BDI). Executive reaction time (RT) test computer-based Go-NoGo visual discrimination alterations in emotion–attention interaction.	post-hoc t test in mTBI, threat vs. neutral: T = 7.3, P < 0.001, effect size = 0.45).		TBI patients have enhanced threat related attention functions.
Zimmermann 2015 (NA)	Attention Test	Prognostic	Sponsored by Conselho Nacional de Desenvolvimento Cientıfico e Tecnologico (CNPq) for the first author studentship. No COI.	N = 84 with mild and moderate/ severe TBI.	Aged 18–72 years. 62 males and 22 females.	Mild and moderate/ severe TBI	Cluster 1, focused attention (Time A Composite score), cognitive flexibility, inhibition, speed for focused attention (N = 35) vs Cluster 2, focused attention (Time A Composite score, cognitive flexibility, inhibition, speed for focused attention, and working memory (N = 15) vs Cluster 3, no significant deficits (N = 34). All participants underwent the following tests: Hayling test, Trail Making Test, Modified Wisconsin Card Sorting Test (48 cards), Verbal fluency tasks-Montreal Communication Assessment Battery, and Auditory oral word span in sentences-Brief Neuropsychological Assessment Battery NEUPSILIN	No difference in clinical or demographical variables for the 3 clusters.	"The first cluster replicated findings of previous studies on TBI EF profiles."	Data suggest EF profiles in TBI adults is more important for rehab outcomes than demographic or clinical variables.

Cicerone 2002 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 64 with cognitive impairments after mild traumatic brain injury (mTBI) and subgroup persistent post-concussion syndrome (PCS).	Mean age 39.4 (9.6) for PCS and 37.2 (9.7) for controls.	mTBI	Post-concussion syndrome or PCS (N = 32) vs Controls (N = 32). Attention tests; Digit Span, Trail Making Test, Part A and Part B, Stroop Color-Word Test, Continuous Performance Test of Attention (CPTA), aced Auditory Serial Addition Test (PASAT), and Ruff 2 & 7 Selective Attention Test.	The greatest overall efficiency was apparent for the CPTA at a criterion level of -1.5 z. The CPTA exhibited acceptable levels of sensitivity and specificity and exhibited a moderately positive association with PCS, (LR = 4.5). Positive associations were also apparent for the Stroop Color (LR = 7.4) and Stroop Color - Word trials (LR = 3.4).	"Examination of the Odds Ratios indicated that measures assessing processing speed had a reliable, positive association with PCS, while measures without a processing speed component did not."	Data suggest those measures with high specificity such as stroop color and processing speed were shown to have strong positive predictive power. Those measures with high sensitivity such as CPTA reflect strong negative predictive power for diagnosing PCS.
Kurča 2006 (NA)	Attention Test	Prognostic	No mention of sponsorship. No COI.	N = 60 with mTBI.	Mean age for; MRI traumatic / MRI nontraumatic and MRI traumatic and non-traumatic controls: 33.71 ± 14.24 / 31.57 ± 11.30 / and 32 ± 13.47 / 29.39 ± 11.82, 42 males and 19 females.	mTBI	Mild traumatic brain injury MTBI, Concentration underwent the Concentration and Attention Test (CAT), Disjunctive Reaction Time test (DRT) (N = 30) vs Control group consisted of sex- and age-matched healthy volunteers (N = 30).	The MRI nontraumatic group significantly differed vs control in scores of recall after first reading (TS1R), working memory and quantity score in the CAT, Mann-Whitney U-test MRI traumatic vs non-traumatic, QS / SEr / and QualS: 0.71 / 0.02 / and 0.19. MRI nontraumatic vs controls and	"There is evidence that MTBI patients with true traumatic MRI lesions are neuropsychological different from MTBI patients with nonspecific MRI lesions or normal brain MRI."	Data suggest that these may be MRI visible traumatic lesions associated with mild TBI causing associated signs and symptoms and there lesions are distinctly different from non special

								traumatic vs control: 0.01 vs 0.14 / 0.59 vs 0.07 / 0.84 vs 0.03.		MRI lesions or normal MRI images.
Nolin 2006 (NA)	Attention Test	Prognostic Experimental	No mention of sponsorship or COI.	N = 85 with mTBI examined 12 to 36 months post-injury.	Aged 16 to 65 years.	mTBI	Those with mTBI who had returned to work (n = 67) vs. those with mTBI who had not returned to work (n = 18). All participant participated in these tests or questionnaires: MTBI Consultation Questionnaire / Paced Auditory Serial Addition Task / Stroop ColorWord Test / California Verbal Learning Test	PASAT, Stroop, and CVLT were related to return to work, beta coefficients were nonsignificant.	"Patient characteristics, injury severity indicators, and cognitive functions were not associated with vocational status."	Quasi-experimental design. Data suggest severity of injury and cognitive functions not associated with vocational status. Patients not returning to work had reported a higher number of symptoms.
Pastorek 2004 (NA)	Attention Test	Prognostic	Sponsored in part by National Institutes of Health Grants as well as National Institute of Disability and Rehabilitation Research Grant. No mention of COI.	N = 105 with head injury.	Mean age 31.5 (12.7), 92 males and 13 females.	Head injury	All participants underwent the following comparisons: Best Day 1 GCS of 3–8, an abnormal neurological evaluation, and abnormal CT findings Best Day 1 GCS of 9–12 Complicated mild traumatic brain injury associated with Best Day 1 GCS of 13–15 and abnormalities on CT	At 1 month, post injury increased the odds of a favorable GOS outcome at 6 months post injury by a factor or 28.2 for VNS, 26.7 for ANS, 17.1 for CIM, and 12.9 for MTT. At 1-month post injury accounted for substantially less variance in DRS scores (7.7–8.4%).	"Neuropsychological data, including the testability of patients, collected uniformly at 1 month following injury can contribute to the prediction of global outcome."	Data suggest that the neuropsychological data derived from closed head injury 1 month after the injury may predict ultimate global outcomes.

							Best Day 1 GCS was uniformly defined as the highest GCS score obtained during the first 24 hours post injury Attention tests: Auditory Number Search Test (ANS) and Visual Number Search Test (VNS)			
Willmott 2009 (NA)	Attention Test	Prognostic	Sponsored by the Victorian Neurotrauma Initiative and the Wenkart Foundation. No mention of COI.	N = 40 with traumatic brain injury (TBI) and 40 healthy controls.	Aged 16 to 60 years, 55 males and 25 females.	TBI	Traumatic brain injury (N = 40) vs Healthy controls (N = 40). Symbol Digit Modalities Test (SDMT), 2&7 Selective Attention Test (2&7), Selective Attention (SAT), Sustained Attention to Response Task (SART), Four Choice Reaction Time (4CRT) tasks, Letter Number Sequencing Task (LNS), and Wechsler Test of Adult Reading (WTAR)	The TBI participants were significantly slower vs control $F(1, 76) = 19.28$, $p < 0.001$, and performance was slower on the complex vs simple condition $F(1, 76) = 448.92$, $p < 0.001$.	"The present study provides evidence for a significant contribution of slowed processing speed to impaired performance on attentional tasks after TBI."	Data suggests significant attentional impairments post TBI and decreased informational processing results in poor task performance.
Withaar 2003 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 26 with subacute closed head injury (CHI) and 25 orthopedic controls.	Aged 15 to 55 years, 39 males and 12 females.	Closed head injury	subacute closed head injury or CHI (N = 26) vs Orthopedic controls (N = 25). Reaction time (RT) task, Trail Making Test and Continuous Tracking and Arrow identification task	CHI needed longer than controls to finish the Trail Making B task; longer time needed to finish the Trail Making test for patients and Trail making B version; $F = 5.71$, $p = 0.021$ and $F = 60.46$, $p < 0.001$.	"Additional impairments in complex divided attention tasks only emerged in the most complex tasks (that is the strategy driven flexibility task)."	Data suggest that divided attention impairments are related to a decreased rate of the processing of information.

								Single and dual task performance between two groups, F = 6.89, p = 0.011.		
King 1996 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 50 with mild or moderate head injury had a range of measures administered at 7-10 days after injury.	Aged 17 to 65, 23 males and 27 females.	Head injury	All participants underwent the same testing. Information processing subtest of the adult memory and information processing battery (AMIPB), Stroop test, and PASAT.	5 scores accounted for 68% of the variance in RPQ scores; including, HADS anxiety, post-traumatic amnesia, SOMC, PASAT 2.4, and PASAT 1.6. At 7-10 days not significantly correlated with any of the neuropsychological tests of divided attention (Stroop, PASAT, and AMIPB subtests).	"A combination of measures may significantly aid the prediction of persistent PCS."	Data suggest combination of measures, specifically HADS, post-traumatic amnesia, SOMC, PASAT and RPQ enhance the prediction of persistent PCS.
Chan 2005 (NA)	Attention Test	Prognostic	Sponsored by the 100-Scholar Plan of the Sun Yat-Sen University, and Erik Kvan Fellowship from the University of Hong Kong. No mention of COI.	N = 51 with TBI and 51 matched controls.	Mean age for TBI / and controls; 42.9 (6.35) / and 41.7 (5.74), 42 males and 9 females.	TBI	Mild to moderate TBI (N = 51) vs Matched controls (N = 51). The Sustained Attention Response to Task (SART), Monotone Counting Test, The Glasgow Coma Scale	For Monotone Counting Test and SART performance, the corresponding effect sizes ranged from modest to very large (0.25 1). A cut-off of less than 1 SD gives optimal diagnostic information in terms of sensitivity in the present sample. The SART was also associated with loss of consciousness in patients with TBI (r = 0.247, p = 0.05).	"These findings suggest that the SART and Monotone Counting Test are sensitive to patients with mild TBI."	Data suggest SART and MCT are sensitive in mild TBI patients and SART detected attention impairment. Patients with mild TBI performed significantly worse than did controls on both SART and MCT.

French 2014 (NA)	Attention Test	Prognostic	No sponsorship and no COI.	N = 109 military with mild-severe TBI.	Aged 19-56 years, 109 males.	mTBI	Mild TBI (N = 50) vs Moderate to severe TBI (N = 59). All participants underwent these tests: WAIS-III Letter Number Sequencing; Trail Making Test Part A and B; Auditory Consonant Trigrams (ACT) 36" Interval Delay, Conner's Continuous Performance Test-Second Edition (CPT-II) Omissions, Commissions, and Hit Rate, California Verbal Learning Test-Second Edition (CVLT-II) Total 1–5 and Long Delayed Recall, Rey Complex Figure Test (RCFT) Immediate Recall and Delayed Recall, WAIS-III Digit Symbol Coding and Block Design, RCFT Copy; Tower of London (TOL) Total Correct, Moves, and Initiation Time	83.4% had a valid PAI profile, 71.9% had been administrated WMT and 88.6% passed the WMT, 80.6% completed PCL-C, 58.5% completed Neurobehavioral Symptom Inventory (NSI) (of sample), and 74.3% completed a core set of neurocognitive measures. Self-reported cognitive complaints significantly correlated with psychological distress (PCL-C total: r = 0.50–0.58; half the PAI clinical scales: r = 0.40–0.58).	"In sum, self-reported cognitive complaints were not associated with neurocognitive test performance, but rather were associated with psychological distress."	Data suggest self-reported cognitive complaints seem not to be associated with test performance but likely associated with psychological distress.
Tramontana 2014 (3.5)	Attention Test	RCT	Sponsored by Shire Pharmaceuticals, Michael G. Tramontana, PhD, Principal Investigator. No mention of COI.	N = 22 with TBI, newly acquired attention deficits persisting for 6–34 months post-injury.	Aged 16–45, 9 males and 4 females.	TBI	Lisdexamfetamine dimesylate or LDX 30 mg po on study day 1 for 1 week, 50 mg at week 2 and 70 mg at week 3 (N = 13) vs Placebo repackaged to appear identical to treatment (N = 13). All participants underwent these attention tests: Wisconsin Cart Sorting Test, Trail	15% reported having a history of pre-injury attention problems. Better performance on vs. off LDX on WAIS-IV Digit Span-Backward, (p = 0.003). Lower self-ratings of Inattentive symptoms on the CAARS-Long Form, (p = 0.040).	"Positive treatment effects were found involving selective measures of sustained attention, working memory, response speed stability and endurance and in aspects of executive functioning."	Small number of patients completed the trail. Data suggest LDX may have some benefit for improiving selected measures of memory, attention, response

							Making Test-Part A and B, Conners Continuous Performance Test, Digit Span – Forward and Backward, Stroop Colour/Word Test, Digit Symbol-Coding, Paced Auditory Serial Addition Test (PASAT), Verbal Paired-Associate Learning, Benton Visual Retention Test, Conners Adult ADHD Rating Scale (CAARS)-Long Form Follow-up for 12 weeks.			speed and endurance.
Niemann 1990 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 29 outpatients suffering from moderate to severe traumatic brain injury.	Mean age for experiment and control groups; 28.9 and 34.3.	Severe TBI	Experimental group or measures of attention + memory, 9 weeks for 2-hour sessions per week (N = 13) vs Control group or measures or attention, 9 weeks for 2-hour sessions per week (N = 13). Measures of attention: d2 test, Paced Auditory Serial-addition task revision (PASAT-R), Divided Attention Test and Trail Making Test Part B test. Memory tests: Rey Auditory Verbal Learning Test-modified (RAVLT-M), and Learning Block span learning test (BSLT).	The attention group improved vs memory group on four measures of attention, Wilks's lambda = 64, approximated: F (4, 21) = 2.93, $p < 0.02$, one-tailed.	"The experimental design evaluated outcome by juxtaposing a multiple baseline procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on 2nd set of neuropsychological tests."	Data suggest significant improvement in experimental groups vs. controls when attention retraining occurred prior to memory retraining.

Evidence for the Use of Executive Function Tests

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Adjorlolo, 2016 (NA)	Executive Function Test	Prognostic	No Industry sponsorship or COI	N=100- 50 patients with TBI, 50 controls	Mean age was 32.0 years. 63 males, 37 females	Moderate Traumatic Brain Injury	Stroop test - This test measures selective attention and interference control vs. Trail Making Test - The TMT is a test of speed processing, sequence alternation, cognitive flexibility, visual search, motor performance, and complex attention. vs. Controlled Oral Word Association - This test required the participants to produce as many words as they can, beginning with the letters F, A, and S. vs. Revised Quick Cognitive Screening Test (RQCST) - This test screen for deficits in several neurocognitive domains	The sensitivity and specificity were given for the following tests respectively; Stroop Word (80%, 78%), Stroop Color (76%, 90%), Stroop Color-Word (80%, 84%), Stroop Interference (74%, 63%), Controlled Oral Word Association Test (97%, 57%), Trail Making Test (94%, 84%), RQCST (90%, 92%).	"In general, this study has shown that commonly used EF tests in Western countries have diagnostic accuracy, sensitivity, and specificity when administered in Ghanaian samples."	Data suggest EF tests which are typically used in Western countries may be administered in Ghana and maintain diagnostic accuracy sensitivity & specificity.
Cossette, 2014 (NA)	Executive Function Test	Prognostic	No mention of Sponsorship or COI	N= 14 – 7 patients with Traumatic Brain Injury, 7 controls	Mean age was 20±1.6 years in TBI group, 22.4±1.4 years in control	Mild Traumatic Brain Injury	Cognitive Conditions –Stroop, Verbal Fluency, Arithmetic. vs.	The Mild Traumatic Brain Injury Group indicated significantly lower	"These preliminary results suggest that both absolute gait	Small sample (N=14). Data suggest in mild TBI patients, dual

					group. 2 males, 12 females		Gait Condition - walking 6m unobstructed, walking 6m and stepping over a 15-cm obstacle placed 4m from the start position, and walking 6m and stepping down from a 15-cm step 4m in front of the start position.	gait speed for the obstacle avoidance task paired with the various cognitive conditions when compared to the control group. The P values for each cognitive condition goes as follows: verbal fluency, .021; Stroop, .037; arithmetic, .039.	speed and calculated dual-task costs during the combination of stepping over an obstacle with a simultaneous cognitive task are sensitive to revealing executive dysfunction in persons with MTBI. Gait speed can be easily measured in the clinic to provide important information to make diagnoses and decide about return to play or function."	task costs (DTCs) in gait speed during obstacle avoidance may be sensitive to executive function differentiation.
Clarke, 2012 (NA)	Executive Function Test	Prognostic	No Industry Sponsorship or COI	N= 60 – 21 patients with Mild Traumatic Brain injury, 19 with spinal injury, 20 neurological-normal controls	Mean age was 35.6 years in the Mild Traumatic Brain Injury group, 34.1 years in the spinal injury group, 19 years in the control group. The gender in the MTBI, Spinal	Mild Traumatic Brain Injury	Attention Index – Working Memory Index of Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Vs. Memory Index – Rey Auditory Verbal Learning Test and the Rey-Osterrieth Complex Figure Test Vs.	The mean values in terms of z-scores for the Attention index, Memory Index, Executive Function Index, and Speed of Processing Index in the Mild Traumatic Brain Injury group are 0.86, 0.37, -0.04, and 0.15	"It was concluded that long-term post-concussive symptoms are largely representative of psychological symptoms and not brain damage, but	Data suggest PCS related to psychological symptoms and cognitive deficits may persist post mild TBI for long periods of time.

					injury, and control were given respectively; 14 males and 7 females, 14 males and 5 females, and 12 males and 8 females.		Executive Function Index – Trail Making Test and Controlled Oral Word Association Test Vs. Speed of Processing Index - Symbol Digit Modalities Test and Trail Making Test	respectively. The Mild Traumatic Brain Injury group depicts R-values under the Affective Factors Index as Neuropsychological index - -0.48 with p<0.05, PACCQ total – 0.55 with p<0.01, RPQ total – 0.57 with p<0.01. Under Neurophysiological Index -0.66 PACCQ total with p<0.01 and -0.57 RPQ total with p<0.01. Under cognitive complaint 0.79 RPQ total with p<0.001.	that genuine, albeit subtle, cognitive deficits also may be present for long-term periods following mild traumatic brain injury."	
Morton, 2010 (NA)	Executive Function Test	Prognostic	No Industry Sponsorship or COI	N= 34 – 11 patients with Moderate Traumatic Brain Injury, 23 patients with Severe Traumatic Brain Injury	Mean age was 35 years. 31.6 years in the moderate traumatic brain injury group, 36.6 in the severe traumatic brain injury group. The sex within the moderate group is 10 males and 1 female. In the severe traumatic brain injury group the sex is 22	Moderate Traumatic Brain Injury Vs. Severe Traumatic Brain Injury	Self-ordered Pointing Test (SOPT) - measure of response monitoring Vs. The Sorting Test (ST) -measure of concept formation Vs. The Brixton - measure of strategy initiation and response inhibition Vs. Verbal Fluency task – FAS, modality specific distractor task	The total group mean scores for executive function measures for the moderate TBI group were 14.2 – SOPT, 9.2 – ST, 6.2 – Brixton, and 37.7 – FAS. For the severe group they were 24.1 with $p <$ .05 SOPT, 6.6 with $p <$ .05 ST, 5.4 Brixton, and 27.8 with $p <$ .05 FAS. The severe group showed lower scores on Sorting test U=62.5, p=.02;	"Severe injuries resulted in greater impairments across most awareness, executive and implicit measures compared with moderate injuries, although deficits were still seen in the moderate group."	Data suggests increasing injury severity correlated with greater dysfunction in most awareness, executive and implicit measures when compared to moderate injuries but deficits were observed in both groups.

					males, 1 female.			FAS verbal fluency U=70, p=.04, and SOPT U=65.5, p=0.2 than the moderate group.		
Paxton, 2014 (NA)	Executive Function Test	Prognostic	Sponsored by the National Institute on Disability and Rehabilitation Research (N.D.C., H133A070037 & H133P090009). No COI.	N= 45 patients with moderate or severe traumatic brain injury.	Mean age was 39.29 years. 33 males, 12 females.	Moderate or severe traumatic brain injury	Prospective memory measures from Rivermead Behavioral Memory Test – test belonging, appointment, and message. Vs. Neuropsychological evaluation – with subcategories: Retrospective Memory – tested with California Verbal Learning Test, Open Trial Selective Reminding Test, and Prose Memory from the Memory Assessment Scales. Executive Functioning – tested with the Trail Making, Color-Word Interference, Tower, and Verbal Fluency subtests from the Delis-Kaplan Executive Function System. Working Memory – tested with Digit Span subtest from the Wechsler Adult Intelligence Scale – Third Edition and	The correlation values for the Total PM compared to Immediate memory is 0.49, p<0.01, delayed memory is 0.56, p<0.01, learning is 0.22, executive achievement 0.44, p<0.01, rule monitoring is 0.43 p<0.01, processing speed is 0.24, and working memory is 0.32, p<0.5. Immediate memory compared to the same factors listed above respectively are DM 0.70, p<.01; L 0.44, p<.01; EA 0.53, p<.01; RM 0.28; PS 0.42, p<.01; and WM 0.34, p<.05. Delayed memory compared to L 0.31, p=.05; EA 0.43, p<.01; RM 0.31, p=.05; PS 0.29; WM 0.25. Learning compared to EA 0.26, RM 0.18, PS -	"Results suggest that PM performance is dependent upon rule monitoring abilities only when RM is impaired following TBI."	Data suggest TBI patients with impaired RM show a dependent relationship between PM performance and rule monitoring.

							Letter Number Sequencing subtest from the Wechsler Memory Scale – Third Edition.	0.12, WM 0.01. Executive Achievement with RM 0.44, p<.05; PS 0.54, p<.01; WM 0.29. Rule monitoring with PS 0.26 and WM 0.36, p<.05. Processing Speed with WM 0.32, p<.05.		
Ponsford, 2008 (NA)	Executive Function Test	Prognostic	Sponsored by Monash University and the Transport Accident Commission. No COI	N=103, 60 patients with TBI, 43 patients in control group.	Mean age for the TBI group was 31.37 years. 33 males, 27 females. Mean age for control group was 42.30 years. 24 males, 19 females.	Traumatic Brain Injury, Not specified	The Extended Glasgow Outcome Scale (GOSE) Vs. Current cognitive abilities - Digit Span Forwards Test and Digit Span Backwards Test, Trail Making Test Part A, Sustained Attention to Response Task, Symbol Digit Modalities Test, and Digit Symbol Coding (DSC) Test. Vs. Memory - Rey Auditory Verbal Learning Test and Doors and People Test Vs. Executive function were total error scores from the TMT Part B, SART, Hayling and Brixton Tests, Porteus Maze Test–Vineland Revision,	The patient GOSE groups (Upper/lower good outcome, disability/poor outcome) with TMT A mean value is (26.2, 40.1), p<.001; with SDMT (56.5, 44.0), p<0.001; DSC (77.6, 54.5), p<.001; Digit Span Forward (10.8, 9.4), p=.046; Digit Span Backward (7.8, 5.6), p<.001; RAVLT (51.8, 42.9), p=.002; Doors (18.7, 16.2), p=.02; People (27.5, 20.5), p<.001; Shapes (33.3, 26.5), p=.001; Names (20.4, 17.3), p<.001; Porteus Mazes errors (2, 4.8), p=.01; COWAT (42.1, 31.6), p<.001; and HADS	"Participants showing poorer outcome on the GOSE had significantly longer posttraumatic amnesia duration; less education; performed more poorly on cognitive measures of information processing speed, attention, memory, and executive function; and showed higher levels of anxiety on the HADS."	At 10 years, patients performed more poorly on cognitive measures and showed higher levels of anxiety on HADS.

							Controlled Oral Word Association Tests. Vs. Hospital Anxiety and Depression Scale (HADS)	anxiety (3.6, 6.5), p=.01.		
Jelcic, 2013 (NA)	Executive Function Test	Prognostic	Sponsored by Department of Neuroscienc e: Sciences NPSRR. No COI.	N=5	Median Age was 37±12.9 years. 5 males, 0 females.	Traumatic Brain Injury	MRI scan Vs. Neurophysical Evaluation – compromised of: Global Cognitive performance – Mini-Mental State Examination (MMSE) Attention – Digit Cancellation Test and Trail Making Test (TMT) Working Memory – Immediate Brief Story Recall, Immediate Rey Auditory Verbal Learning Test, and Digit Span Forward and Backward tests, Verbal and Visual spatial memory – Delayed Brief Story Recall, Delayed RAVLT, Delayed Rey–Osterrieth Complex Figure (ROCF) Visual-Constructive Abilities - ROCF Copy and the Clock Drawing Test (CDT) Language- Phonemic and Semantic Fluency tests	The Pre-cranioplasty and Post-cranioplasty neuropsychologica l test respectively report mean scores for MMSE (26.2±3.7, 27.4±3.1, p=0.36), Digit Cancellation (41.9±8.5, 42.7±10, p= 0.6), TMT-A (55.6±22.5, 60±38.7, p=0.73), TMT-B (208.6±110, 140.8±55, p=0.04), CDT (8.1±3.8, 8.8±3, p=0.18), RAVLT Immediate (32.1±16.7, 39.1±15.4, p=0.04), Story Recall Immediate (11.6±8.1, 15.4±5.2, p=0.03), Digit Span Forward (4.6±1.1, 5.3±0.8, p=0.07), Digit Span Backward (3.1±0.7, 3.6±1, p=0.11), Letter Fluency (23.6±16.9, 29.6±17.6, p=0.02), RAVLT Recall Delayed (6.1±4.9, 7.3±4.6,	"The cognitive improvement induced by cranioplasty, even when performed after a long interval from craniectomy, may be due to the restoration of physiological cerebrospinal fluid circulation which, in turn, allows an efficient brain volume transmission signal circulation. The restoration of this essential way of signal communicatio n seems to affect large-scale neuronal networks responsible for the executive functions."	Sample size too small for conclusions.

								p=0.14), Story Recall Delayed (14±8.4, 18±4.2, p=0.09), ROCF Recall Delayed (14.8±9.8, 19.2±7.7, p=0.05), ROCF copy (30.4±5.2, 33±5.1, p=0.17), and Semantic Fluency (33.6±13.2, 37.4±16.6, p=0.25).		
Muller, 2010 (NA)	Executive Function Test	Prognostic	No mention of industry sponsorship or COI	N= 30, 15 Severe Traumatic Brain Injury Patients, 15 normal control group	Mean age of STBI group was 37.2 years. 13 males, 2 females. Mean age of Control Group was 37 years. 13 males, 2 females.	Severe Traumatic Brain Injury	Neurophysical Assessment: Wechsler Adult Intelligence Scale-Revised (WAIS-R), Stroop Color Word Test Trail Making Test A and B, Verbal fluency, and California Verbal Learning Test (CVLT) Vs. Theory of Mind (ToM) Test: Faux Pas Test First Order False Belief Task (FOFBT) Second Order False Belief Task (SOFBT) Character Intention Task (CIT) Reading the Mind in the Eyes Test (RMET)	The correlation between the Theory of Mind tests with TMT-B, Stroop Test, semantic verbal fluency, and formal fluency respectively are: Faux Pas Test (r= -.40, p=.20), (r=-.25, p=.40), (r=.47, p=.10), (r=.22, p=.47); FOFBT (r=-.19, p=.55), (r=-.42, p=.15), (r=.47, p=.10), and (r=.19, p=.53); SOFBT (r=-.63, p=.02), (r=-.33, p=.27), (r=.50, p=.08), and (r=.03, p=.91); CIT (r=-.34, p=.27), (r=.07, p=.83), (r=.33, p=.27), and (r=.15, p=.63); RMET (r=-.13, p=.68), (r=-.22, p=.46), (r=.23,	"In conclusion, the present findings have implications for the evaluation of ToM impairment after TBI. They confirm an impairment in the ability to make inferences about others' mental states following TBI."	Data suggest ToM deficit is most likely independent from other types of social cognition like empathy & comunnicatio n.

								p=.45), and (r=.24, p=.42).		
Simmons, 2014 (NA)	Executive Function Test	Prognostic	No industry sponsorship or COI	N=12, 4 patients with Traumatic Brain Injury and 8 patients who underwent a Cerebrovascular accident	Mean age for patients was 53.9 years. 8 males, 4 females.	Traumatic Brain Injury and Acquired Brain Injury	Executive Function Performance Test (EFPT) – independent living tasks: simple cooking, telephone use, medication management, and bill payment. Vs. EFPT skills - Initiation of task, organization, sequencing, and safety and judgment. Vs. PreMotor Exercise Game [487]	Changes in EFPT in overall task completion report a mean difference of -0.3 from baseline 1 to baseline 2 and -1.1 from baseline 2 to post intervention. Changes in overall performance report a mean difference of +0.2 from baseline 1 to baseline 2 and -9.4, $p<0.05$ from baseline 2 to post intervention.	"Using PEGs as a modality for both motor and cognitive intervention is a potentially beneficial adjunct to rehabilitation and warrants further study."	Small sample (N=12). Data suggest improvement in chronic TBI patients (both motor & cognitive) using PEGs.

Evidence for the Use of Audiometry

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Munjal 2011 (4.0)	Audiometry	Diagnostic	No mention of Sponsorship or COI.	N=290 w/ TBI. N=50 Control	No mention of sex; No mean age, Age Range from 18-45.	Traumatic Brian injury using Glascow Coma Score. TBI split into Mild, Moderate, and Severe.	Audiological tests including: pure tone audiometry (PTA), speech audiometry, tympanometry, auditory brain stem response (ABR) audiometry, and middle latency response (MLR) audiometry.	PTA 1 (500, 1000, 2000 Hz) mean scores of mild, moderate, and severe closed head injury (CHI), vs Control: 23.97 dB, 19.66 dB, 23.75 dB vs 10.70 dB ($p<0.001$). PTA 2 (4000, 8000, 12000 Hz) CHI groups vs control: 23.4 dB, 28.17 dB, 29.9 dB vs 9.23 dB ($p<0.001$). Speech Reception Threshold difference between Chi groups and control ($p<0.01$). ABR wave 1 significant difference for right ear ($p<0.01$), left ear ($p<0.05$). MLR Na wave CHI groups vs control: 19.62 msec, 19.47 msec, 19.75 msec vs 18.23 msec ($p<0.05$). No significant differences in Tympanometry.	"To conclude, there is a high incidence of audiological deficits in head injured subjects. Peripheral and central auditory areas are affected as revealed by the subjective as well as electrophysiologic auditory investigation."	Data suggests hearing loss is prevalent post closed head injury with MLR abnormalities occurring more frequently than ABR.

Evidence for the Use of Specific Vestibular Function Test

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Gottshall 2010 (4.0)	Specific Vestibular Function Tests	Diagnostic	No mention of COI or sponsorship.	N = 82	3 female, 79 male Mean age overall 24 years	Soldiers, blast injuries including secondary mTBI, diagnosed with 1 out of 4 vestibular disorders – benign paroxysmal positional vertigo, exertion-induced dizziness, blast-induced disequilibrium, and blast-induced disequilibrium with vertigo	Series of vestibular-visual-cognitive tests: Static visual acuity, perception time, target acquisition, target following (TF), dynamic visual acuity (DVA), gaze stabilization tests All participants underwent all tests	Mean pre-VPT measures for perception time and target acquisition similar to normative values, no significant changes. TF and DVA scores below normative at time 0 but elevated to normative at week 8. Gaze stabilization also below normative but improved at week 8.	"A battery of vestibular-visual-cognitive tests is valuable for establishing initial functional levels and can be used to document improvement. These outcome measures may also be useful to determine return to duty/work status as well as return to physical activity status for military personnel."	Data suggest use of vestibular-visual-cognitive tests useful for baseline determination of balance dysfunction through recovery.
Hoffer 2016 (3.5)	Specific Vestibular Function Tests	Diagnostic	Supported by Head Health Challenge II grant from the National Football League, Underarmor, and General Electric, and a grant from the Department of	N = 150	43 female, 107 male Mean age for mTBI group 26.6 years, mena age for control group	100 controls, 50 mTBI	Series of vestibular function tests including the following areas: Post-Traumatic Headache/Migraine, Nausea, Emotional/ Affective, Fatigue/Malaise, and Dizziness/Mild Cognitive Impairment	mTBI group had higher prevalence of headache, dizziness, and cognitive dysfunction compared to controls. Sleep disorders and emotional issues also	"A fairly simple set of questions inquiring about dizziness, headache, and cognitive issues may provide diagnostic accuracy but it remains unclear if other symptoms are more important	Data derived from questionnaire. Data suggest a simple question set may provide useful diagnostic and prognosis information in mild TBI patients

			Defense grant. No COI.		29.4 years			were more prevalent	for prognostic information or treatment planning.”	

Evidence for the Use of Computerized Dynamic Platform Posturography

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Kaufman 2006 (3.0)	Computerized Dynamic Platform Posturography	RCT	No mention of sponsorship or COI.	N=10 w/ TBI N=10 Control	12 males, 8 females; Mean age 41 (11)	Traumatic brain Injury based on medical history and clinician evaluation.	Sensory Organization Test [493] between TBI patients and controls.	Controls scored higher for all SOT conditions. Mean Composite SOT score, TBI vs Control, 70±12 vs 80±8 (0.04). Correlation between Dizziness and Posturography test 6, however not statistically significant.	"Moreover, this study has also demonstrated that gait analysis can be used to objectively quantify the subjective complaints of unsteadiness reported by patients with TBI."	Small sample (n=10). Date suggest objective measurement are useful for quantification of functional deficits post TBI.

Evidence for the Use of Rotary Chair Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Akin 2016 (4.0)	Rotary Chair Testing	Diagnostic	No mention of Sponsorship or COI	N = 31 Veterans with history of blast exposures and/or mTBI.	Mean Age: 37 years, No mention of sex	Dizziness and/or imbalance	Vestibular and Balance assessment tests including : rotary chair, videonystagmography, Cervical vestibular evoked myogenic potential (cVEMP), Subjective Visual Vertical (SVV), Dux-Hallpike and roll test, ocular motor fixation test, sensory organization test [493], and Dizziness Handicap Inventory (DHI)	Horizontal semicircular canal dysfunction (caloric weakness and/or abnormal rotational testing) was found in 29% of patients. In comparison, Otolith dysfunction (abnormal cVEMP and/or SVV) was found in 84% of patients.	"Preliminary results in the authors' laboratory suggest that otolith testing may be an important component of the vestibular test battery in patients with mTBI and/or blast exposure."	Data suggest otolith testing may be beneficial in the vestibular testing battery in m TBI patents and/or blast exposed patients

Evidence for the Use of Burr Holes, External Ventricular Drains, and Ventriculostomy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Liu 2015 (4.0)	Ventriculostomy	Prospective observational study Randomized controlled	No mention of sponsorship and no COI.	N = 122 with TBI ≥ 13 years old.	Mean age 43.37 ± 14.40 years, 101 male and 21 female.	External ventricular drain or EVD (N = 62) vs Intraparenchymal fiberoptic monitor or IPM (N = 60).	6 mo	AT 1-month survival rate 90.3% in the EVD group vs 76.7% in the IPM group (log-rank test, p = 0.04), 6-month postinjury survival rate vs with those treated with IPMs (88.7% vs. 68.3%, log-rank test, P [0.006), and patients managed with EVDs had a significantly higher.	"Device selection for ICP monitoring provides prognostic discrimination, and use of EVDs may have a bigger advantage in controlling refractory intracranial hypertension."	Not an RCT, an observational study. Data suggest ICP device selection may benefit prognostic outcome.

Evidence for the Use of Craniectomy

There is 1 high- and 2 moderate-quality RCTs incorporated into this analysis. There are 15 systematic reviews.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cooper J 2011 (8.5)	Decompressive craniectomy	RCT	(Funded by the National Health and Medical Research Council of Australia and others; DECRA Australian Clinical Trials Registry number, ACTRN012605000009617.) No mention of COI	N= 152 patients with a severe, nonpenetrating traumatic brain injury	120 males, 32 females Mean age: 24 years	Decompressive Craniectomy (n=73) Vs. Standard Care (n=82)	6 months	Mean intracranial pressure after randomization: craniectomy 14.4±6.8 mm Hg v. standard care 19.1±8.9 mm Hg, p<0.001. Median intracranial hypertension index after randomization: craniectomy 11.5 v. standard care 19.9, p<0.001. Median cerebral hypoperfusion index after randomization: craniectomy 5.7 v. standard 8.6, p=0.03. Median days of mechanical ventilation: craniectomy 11 v. 15, p<0.001. Median days in ICU stay: craniectomy 13 v. 18, p<0.001. Median days of hospitalization: NS. Extended Glasgow Outcome Scale median score 6 months after injury: craniectomy 3 v.	"[I]n patients with severe diffuse traumatic brain injury and increased intracranial pressure that was refractory to first-tier therapies, the use of craniectomy…decreased the mean intracranial pressure and the duration of both ventilatory support and the ICU stay but was associated with a significantly worse outcome at 6 months, as measured by the score on the Extended Glasgow Outcome Scale."	Data suggest short-term benefits of craniectomy including 28% shorter ICU stays. However, long term worse outcomes (70% vs. 51%, OR=2.2).

								standard 4, p=0.03; unfavorable score of 1 to 4 (no.) craniectomy 51 v. standard 42, p=0.02.		
Jiang J 2005 (7.5)	Decompressive craniectomy	RCT	No mention of industry sponsorship or COI.	N= 486 with severe TBI	Mean age: 44.5 years, 347 males, 139 females	Standard trauma Craniectomy - a unilateral frontotemporoparietal bone flap (N=245) Vs Learning Craniectomy with a routine temporoparietal bone flap (N=241)	6- month follow-up	Glasgow Outcome Scale (GOS) at 6 months: STC good recovery/moderate deficit 39.8%, severe deficit/persistent vegetative status 34%, death 26.2% v. LC good recovery/moderate deficit 28.6%, severe deficit/persistent vegetative status 36.3%, death 35.1%, p<0.05. Intracranial pressure before and after craniectomy: NS. Post-operative complications: delayed hematoma STC 26 v. LC 43, p<0.05; incision CSF fistula STC 6 v. LC 18, p<0.05; encephalomyelocele, NS; traumatic epilepsy, NS; intracranial infection, NS.	"Our multicenter prospective, randomized, controlled clinical study confirms that unilateral STC significantly improves the outcome in severe TBI with refractory intracranial hypertension and unilateral cerebral contusion."	Data indicate higher survival in the limited craniectomy group.

Qiu W 2009 (score 7.0)	Decompressive craniectomy	RCT	This study was supported by the Scientific Research Fund of Zhejiang Health Department, the Scientific Research Fund of Hangzhou Health Department and the Scientific Research Fund of Science and Technology Department of Zhejiang, China. No COI.	N= 74 patients with acute post-traumatic brain swelling (BS) with midline shifting > 5 mm from TBI with Glasgow Coma Scale (GCS) of 8 or less.	Mean age: 40.1 years 51 males, 23 females	Unilateral Decompressive Craniectomy (DC) (n=37) Vs. Control group (n=37)	Six months	Mean ICP at 24, 48, 72, and 96 hours: unilateral DC (15.19±2.18 mmHg, 16.53±1.53, 15.98±2.24, and 13.518±2.33) v. control (19.95±2.24 mmHg, 18.32±1.77, 21.05±2.23 and 17.68±1.40), no p-value presented but authors noted a significant difference. Mortality rates 1 mo. after craniotomy: unilateral DC 27% v. control 57% (p=0.010). Glasgow Outcome Score (GOS) 1 year after injury for good neurological recovery: unilateral DC 56.8% v. control 32.4%, no p-val but authors stated significance.	"Although the application of DC in severe TBI is controversial and the population in the present study is small, our study demonstrated that unilateral DC had superiority in lowering ICP, reducing the mortality rate and improving neurological outcomes over routine temporoparietal craniectomy."	Data suggest lower mortality and better neurological outcomes in the decompressive craniectomy group vs. unilateral routine temporoparietal craniectomy. However, higher delayed intracranial hematoma and subural effusion in DC group.

Moein 2012 (4.5)	Decompressive Craniectomy	Pilot RCT	No mention of sponsorship. No COI.	N = 20 with head injury	Aged 18 - 60 years, gender not specified.	Group A, received surgical and conservative treatment (N = 10) vs Group B, underwent conservative treatment (N = 10).	Unknown	GCS improved after surgery in group A, difference between the 2 groups not statistically significant, (p = 0.087). Death rate higher is group B 30% vs 10% in group A, (p = 0.28).	"Decompressive craniectomy seems to be helpful and may lead to a better GOS achievement and improve the mortality rate among traumatic brain injury patients…"	Data suggest decompressive craniotomy may reduce mortality and improve Glascow outcomes scale.

Bhat 2013 (4.0)	Craniectomy	RCT	No mention of sponsorship or COI.	N = 225 with severe brain trauma.	Aged 21-40 years, 180 males and 45 females.	Glasgow coma scale or GCS (N = 119) vs Controls or open-dural flap (N = 106).	Unknown	Survival of multi-dural stab group vs open dural flap; 77.31% (92/119) /and with good recovery 42.02% (50/119) and / mortality 22.69% (27/119) vs 46.23% (49/106) / 15.09% (16/106) and good recovery and mortality of 53.77% (57/106).	"This new approach, known as SKIMS-Technique or Combined Technique i.e., "decompressive craniectomy with multi-dural stabs", proved much effective in increasing survival of low GCS and severe traumatic brain edema patients with acute subdural hematoma."	Data suggest the SKIMS(combined technique) is more than 2x as effective as conventional decompressive craniectomy re. survival for severe TBI (22.7 v. 46.2% mortality).
Xu 2014 (4.0)	Decompressive Craniectomy	RCT	No mention of sponsorship or COI.	N = 169 with severe traumatic brain injury (STBI).	80 years or older, 119 males and 50 females.	pressure dressing (N = 82) vs Control group (N = 87)	Hospital stay of 30 days or less	No significant difference in age, sex, GCS score, or GOS score between groups, ($p > 0.05$). Significant differences were found in the subdural effusion incidence rate $W^2 = 5.449$, ($p = 0.021$) and hospitalization time $W^2 = 5.245$, ($p = 0.027$).	"The results of this study suggest that early pressure dressing 7 to 10 days after DC, which is a noninvasive, simple procedure, reduces the incidence rate of subdural effusion and shortens hospitalization time in patients with STBI."	Data suggest application of an early pressure dressing 7-10 days post discharge decreased subdural effusion rate and rate of rehospitalization post-DC.

Wang 2014 (4.0)	Decompressive craniectomy	RCT: Quasi-randomized (every other)	No mention of COI. Supported by the Nanjing Military Region.	N = 128 with severe head injury, GCS 3-8	20 female, 108 male. Mean age decompressive craniectomy 41.8±13.9 years, controlled decompression 44.2±14.2 years	Decompressive craniectomy (DC) (n = 64) vs controlled decompression (CD) (n = 64)	6 months	Clinical outcome measures: Intracranial pressure – DC 45.6±9.8 mmHg, CD 45.0±9.9 mmHg, (P=0.741). Glasgow Outcome Scale (Good Recovery, Moderate Disability, Severe Disability, Vegetative State, Dead): DC – 23, 8, 5, 5, 23, CD – 34, 7, 4, 4, 15, (P=0.417).	"Controlled decompression may reduce or delay intraoperative acute brain swelling by delaying hematoma formation in patients with severe head injury."	Data suggest controlled decompressive craniectomy may be better than conventional decompressive craniectomy in controlling acute brain swelling in TBI patients.

Evidence for the Use of Robotics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Esquenazi 2012 (4.5)	Body Weight Support Treadmill Training	RCT	No COI. Study was supported by grants from MossRehab Research Fund Disclosure and Departmen t of Defense, CDC.	N = 16 with TBI and baseline over group walking self-selected velocity of ≥ 0.2 m/s to 0.6 m/s	Mean age for RATT 37.1 ± 10.6 (5 female, 3 male). Mean age for MATT 41.9 ± 16.8 (4 female, 4 male)	Robotic-assisted treadmill training (RATT), 45 minutes 3 times a week Vs. Manually assisted treadmill training, 45 minutes 3 times a week	6 to 8 weeks	All parameters produced no significant between-group differences. The average SSV increased in RATT by 49.8% (p=0.01) and by 31% (p=0.06) for MATT. RATT group average maximal velocity increased by 14.9% (p=0.06) and MATT group increased by 30.8% (p=0.01). RATT group step-length asymmetry ratio improved by 33.1% (p=0.01) and by 9.1% (p=0.73) for MATT group. RATT group distance walked increased by 11.7% (p=0.21) and MATT group increased by 19.3% (p=0.03). Mobility improvement was present for both groups (p=0.03).	"The results of this study demonstrate greater improvement in symmetry of gait (step length) for RATT and no significant differences between RATT and MATT with regard to improvement in gait velocity, endurance, and SIS. Our study provides evidence that participants with a chronic TBI can experience improvements in gait parameters with gait training with either MATT or RATT."	Small Sample. Data suggest comparable results for both RATT and MATT on all outcome measures except greater improvement of step length, **gait velocity, endurance stroke impact scale [545].**
Freivogel 2009 (4.0)	Robotics	RCT	No mention of sponsorship and no COI.	N = 16 with stroke, severe brain or spinal injury.	Mean age for Group AB / BA: 22.4 (6.0) / 25.8 (6.1); 11 males	Study intervention sequence AB: 20 treatments of locomotor training with an electromechanical gait device (N = 8) vs Study	6-weeks	Between group significance after Intervention A: mean 0.9 (SD 1.4), median 0 (IQR 2.0); after intervention B:	"Locomotor training with or without an electromechanical gait trainer leads to improved gait ability; however,	Crossover RCT. Mixed pop. Of spinal cord injury, TBI or stroke. Duration of illness dissimilar between groups.

					and 5 females.	intervention sequence BA: 20 treatments of locomotor training with treadmill or task-oriented gait training (N = 8).		mean 0.5 (SD 1.0), median 0 (IQR 1.0); p = 0.155). The distance walked during training sessions was significantly higher during intervention A, mean 553 m (SD 116) vs intervention B, mean: 400 m (SD 245), p = 0.009.	using the electromechanical gait trainer requires less therapeutic assistance, and therapist discomfort is reduced."	Conclusions derived from patient reports and not objective measures.

Evidence for the Use of Intracranial Pressure Monitoring and Thresholds

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Kirkness, 2005 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=157 patients	Mean age 37.1±18.1 Years. 124 males, 33 females.	Traumatic Brain Injury	CPP Vs. TBI outcome	Post-resuscitation GCS scores showed moderate to severe TBI, with 73% having a score of 8 or less. The mean ISS score was 29.1. The percent time that CPP was below threshold levels over the first 4 days of monitoring ranging from 5% for 55 mmHg threshold to 29% for the 70 mmHg threshold. Patients with less percent time below fixed CPP thresholds ranging from 55-70 mmHg were more likely to have better outcomes by higher GOSE scores.	"Although differences in GOSE scores at six months were not significant, those with less time below CPP thresholds were more likely to survive. Accumulated episodes of low CPP had a stronger negative relationship with outcome in patients with more severe primary brain injury."	Data suggest increased episodes of low CPP have a stronger negative outcome in severe TBI patients.
Kahraman, 2011 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=60	Mean age: 33.9±14 Years. 51 Males, 9 Females.	Traumatic Brain Injury	ICP: intracranial pressure monitoring Vs. CPP: cerebral perfusion pressure monitoring	Thirty-five of 60 patients had a good outcome. Injury severity was similar for both good and poor outcomes ($p<0.1$-0.7). Eight patients died and 14 patients had craniectomy. BTI<2 was better than CPP<60 mm Hg in	"Calculation of a BTI from continuous digital data predicts outcome in severe TBI and has potential for the design of real-time bedside early warning systems."	Data suggest the BTI can predict outcome in severe TBI patients.

								predicting unfavorable Extended Glasgow Outcome Scale at 6 months (p <0.05). BTI, CPP, and ICP graphs were provided.		
Kuo, 2006 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=30 patients	Mean age: 36.8±14.9 years. 20 males, 10 females.	Traumatic Brain Injury	ICP: Intracranial pressure monitoring Vs. CPP: Cerebral perfusion monitoring	Initial ICP for unfavorable outcomes was 47.4 ± 21.4 mmHg, resulting in a CPP of 22.8 ± 12.83 mmHg. The initial ICP for favorable outcomes were 26.4 ± 10.1 mmHg, resulting in a CPP of 48.8 ± 13.4 mmHg. The CPP thresholds of 37 mmHg, 51.8 mmHg (intraoperative) and 52 mmHg (after scalp closure). The ROC curve analysis showed that CPP was a better predictor of outcome than ICP.	"We conclude that the initial ICP may be higher than suspected and CPP very low in patients with severe head injury, particularly those with unfavorable outcomes. Based on ROC curve analyses, CPP is a better predictor of outcome than ICP."	Data suggests CPP predicts outcomes better than ICP.
Narayan, 1981 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=133 severely head-injured patients	Mean age: 27 years. No mention of gender.	Traumatic Brain Injury	ICP: Intracranial Pressure Vs CT: Computerized Tomography Vs MEP: Multimodality Evoked Potential	Glasgow Coma Scale score, pupillary response, presence of surgical mass lesions, extraocular motility, and motor posturing were used to predict outcome of severe head injury with 82% accuracy, 43% with over 90% confidence. The GCS score was accurate in 80% of predictions, but a	"The clinical examination remains the strongest basis for prognosticating outcome in severe head injury, but additional studies enhance the reliability of	Data suggest reliable outcome predictors utilize a combination of clinical data and CT and ICP can add to the predictive value but alone, CT and ICP are poor prognostic indicators.

								lower CI level (25% at over 90% level). CT and ICP proved to be poor prognostic indicators; however, increased number of predictions made with over 90% to 52-55%. Data from MEP was the most accurate with 91% correct, 25% at over 90% confidence level. MEP data showed 89% accuracy rate, with 64% over 90% confidence level.	such predictions."	

Evidence for the Use of Brain Oxygen Monitoring and Thresholds

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Eriksson 2012 (NA)	Brain Oxygen Monitoring	Prognostic	No COI. No mention of sponsorship.	N= 32	9 females, 22 males Mean age 39 years ± 16.5 years	Severe TBI	$pBtO_2$ levels: monitor (Licox) 2-3 cm below dura vs Intracranial pressure (ICP) levels and cerebral perfusion pressure (CPP): ICP monitor/ventriculostomy All participants underwent both monitoring	The mean injury severity score was 27.78 ± 10.7 and the mean GCS score was 6.6 ± 3.4. 68% of participants survived. Those who died showed lower pBtO2 levels, taking into account age (F = 12.898, p<0.001). pBtO2 levels were higher at 8 hours, 12 hours, 20-44 hours, 52-60 hours, and 72 hours during monitoring (p<0.05). ICP and CPP levels were not significantly different (F=1.690, p=0.204 and F=0.764, p=0.389, respectively) between nonsurvivors and survivors. The threshold that pBtO2 was more predictive for mortality was 29 mm Hg.	"The first 72 hours of pBtO2 neurologic monitoring predicts mortality. When the pBtO2 monitor remains below 29 mm Hg in the first 72 hours of monitoring, mortality is increased. This study challenges the brain oxygenation threshold of 20 mm Hg that has been used conventionally and delineates a time for monitoring pBtO2 that is predictive of outcome."	Data suggests that brain tissue oxygenation in the first 72 hours post TBI predicts mortality such that if levels remain below 29 mmHg mortality increases.
Leal-Noval 2010 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. Supported by Spanish Government funds (Fondo de Investigaci´on Sanitaria–	N= 22	No gender distribution described Mean age 33 ± 13 years	Severe TBI (GCS ≤ 9), intraparenchymal ICP/PbrO2 catheter previously inserted, passing initial resuscitation phase,	ICP and PbrO2 levels: Monitor LICOX IMC system Vs Regional transcranial oxygen saturation (rSO2): monitored by	PbrO2 and rSO2 displayed direct and independent correlation in an adjusted regression (β = 0.36, 95% CI (0.35-0.37) as well as logistic regression analyses (adjusted odds ratio = 1.11, 95% CI (1.10-1.12)) with PbrO2 C15 mmHg being the dependent variable. rSO2 had lower accuracy for identifying moderate	"In patients with severe TBI, PbrO2 and rSO2 were directly and significantly related. Severe intracerebral hypoxia was better detected by rSO2 than was moderate intracerebral hypoxia. However, the diagnostic accuracy of rSO2 was limited, and this	Regional oxygen saturates measured by NIRS cannot precisely predict PhrO2.

			FIS–Proyecto de Investigaci o´n) and by Consejerı´ a de Salud de la Junta de Andalucı´a .			under controlled mechanical ventilation	near-infrared spectroscopy (INVOS 5100 Cerebral Oximeter) All participants underwent both monitoring	intracerebral hypoxia (PbrO2 B15 mmHg) on a receiver-operating characteristic curve (area under curve = 0.62). This ROC displayed a likelihood ratio of a positive test being 1.2 and an optimal cutoff of rSO2 ≤ 70%. rSO2 was moderately accurate for detecting severe intracerebral hypoxia (area under curve = 0.82, likelihood ratio = 5.3) with an optimal cutoff of rSO2 ≤ 60%.	measure should not be considered a substitute for routine PbrO2 monitoring."	
Santbrin k 2003 (NA)	Brain Oxygen Monitoring	Progn ostic	No mention of COI or sponsorsh ip.	N= 41	6 females, 35 males Mean age 33 ± 16	Severe TIB, GSC ≤ 8	Intracranial pressure (ICP): monitored by fiberoptic device (Camino lab) vs Local brain tissue partial pressure of oxygen All participants underwent both monitoring	PbrO2 ranged from 4 to 50 mmHg at baseline. PaO2 values ranged from 73-237 mmHg. When Fi02 was at 1, PrbO2 ranged from 9.1-200 mmHg and PaO2 ranged from 196-499 mmHg. A stable plateau pattern of PbrO2 was more prevalent 48 hours post injury. This pattern was related to a positive outcome (p=0.06) if seen within the first 24 hours post injury. TOR mean level for all test was 0.73 ± 0.59. Those who had negative outcomes presented higher TOR (1.03 ± 0.60) compared to those with positive outcomes (0.61 ± 0.51) within the first 24 hours. Using tissue oxygen response as a predictive value for negative outcomes was verified and	"Evaluation of TOR affords insight in (disturbances in) oxygen regulation after traumatic brain injury, is of prognostic value and may aid in identifying patients at (increased) risk for ischemia."	The evaluation of tissue oxygen response (TOR) leads information in oxygen disruptions post TBI.

								supported through a multiple logistic regression analysis (OR = 4.8). Mean TOR dropped significantly from 0.75 ± 0.54 to 0.65 ± 0.45 (Wilcoxon test, p = 0.06) during increased hyperventilation. A decrease in TOR after hyperventilation was significantly related to more negative outcomes (p=0.01) within the first 24 hours post injury.		
Adamides 2009 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by a Victorian Trauma Foundation best practice grant.	N= 30	8 females, 22 males Mean age overall 36.57 years	Severe TBI, post-resuscitation GCS < 9	Brain tissue oxygen (PbrO2): not treated, monitored through Licox probes within uninjured frontal white matter (n=10) vs Same measurements and probes, treated according to brain tissue oxygen-guided algorithms (to improve cerebral oxygen availability) (n=20)	Group 1 (control) presented mean duration times of brain hypoxic episodes (PbrO2<15 mmHg) of 106 minutes where group 2 presented a significantly different mean time of 34 minutes (p=0.01). Group 1 has brain tissue oxygen levels <15 mmHg for 10% of the time while group 2 only presented the same levels 2.8% of the time (p=0.12). Mean Injury Severity Score (ISS) was statistically higher for those undergoing cerebral hypoxia compared to those not suffering those events (33.7 vs 24.2, p=0.04). Neurological outcomes between the two groups were not statistically significant.	"The introduction of a brain oxygen-guided algorithm into the management of patients with severe TBI was associated with decreased duration of episodes of cerebral hypoxia and a trend towards better neurological outcome. Episodes of inadvertent hyperventilation and systemic hypoxia significantly decreased, and brain tissue oxygen monitoring enabled selective optimisation of CPP in individual patients. Cerebral hypoxia was more likely to occur in patients with multiple systemic injuries and higher ISS. The peak incidence of episodes of cerebral hypoxia occurred during post-injury day 5	No difference in outcome between patients treated with or without oxygen guided therapy.

									suggesting that brain oxygen monitoring and mechanical ventilation may optimally be	
Stiefel 2005 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI or sponsorship.	N= 53	11 females, 42 males Mean age of ICP/CPP group 44 ± 14 years. Mean age of brain tissue PO2 group 38 ± 18 years	Severe TBI, between January 2000 and July 2002, GCS score < 8, ISS ≥ 16	Group A: ICP and CPP treatment, ICP monitor (Camino) inserted via frontal burr hole (n=25) vs Group B: brain tissue PO2-directed management, ICP and brain tissue PO2 and temperature probes inserted through triple-lumen bolt (Licox CMP Triple Lumen Monitoring System) (n=28)	Mean ICP monitoring time, mean daily ICP, and mean daily CPP were not statistically different as well as mean maximal daily ICP, mean minimal daily CPP, mean number of episodes of elevated ICP (> 20 mmHg), and reduced CPP (< 60 mmHg). Group B presented a mean daily brain tissue PO2 of 34.7 ± 12.3 mmHg. During monitoring periods this group presented 142 episodes of compromised brain tissue PO2 levels (PO2 < 25 mmHg) and 35 episodes of ischemic PO2 levels (< 15 mmHg). In group A 44% of participants died whereas a statistically smaller amount of 25% died in group B (p=0.05). 14 participants (17%) of the survivors in group A underwent additional hospitalization or nursing home placement, whereas zero from group B experienced either result. Of those in group B, those who died displayed more frequent cerebral hypoxia episodes (< 15 mmHg) than those who survived (1.23 ± 1,	"The concept of multimodality monitoring is not new. As brain tissue PO2 monitoring gains increasing acceptance at head-injury centers and in neurointensive care units, it is critical to compare its use to ICP monitoring alone. In addition, as new information about current CPP management compels questions, we must identify better resuscitation end points. Brain tissue PO2 monitoring may help in this process. Our results, although preliminary, are compelling and provide the first evidence that the use of multimodality monitoring with both an ICP and a brain tissue PO2 monitor as well as therapy directed at brain O2 can be associated with a reduced patient mortality rate after severe TBI."	Data suggest decreased mortality associated with use of ICP and brain tissue PO2 monitors and therapy.

								0.34 ± 8, respectively, p=0.007). Survivors presented shorter cumulative periods of compromised cerebral oxygenation (< 25 mmHg) than those who died (164.9 ± 362.9, 364.1 ± 422.7 minutes, respectively, p=0.04).		
Valadka 1998 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by grant from the National Institutes of Health. No mention of COI.	N= 43	9 females, 34 males Mean age 32 ± 14 years	Severe head-injured, GCS ≤ 8	PbtO2 monitored using Licox or Paratrend probes containing miniaturized Clark electrodes All participants underwent continuous PbtO2 monitoring	PO2 readings at room temperature = 141 ± 20 torr (18.8 ± 2.7 kPA, range 82-187 torr or 10.9-24.9 kPa) for Licox probes, 138 ± 1.3 torr (18.4 ± 1.3 kPA, range 131-145 torr or 17.4 ± 19.3 kPa) for Paratrend probes In blood gas standard calibration solution (Level I arterial blood gas control) PO2 readings were 70 ± 8 torr (9.3 ± 1.0 kPA, range 49-80 torr or 6.5-10.6 kPa) for Licox probes and 68 ± 32 torr (9.0 ± 4.3 torr, range 45-90 torr or 6.0-12.0 kPA) for Paratrend probes. Licox probes stabilized within 15 minutes at 0.3 ± 0.3 torr (0.04 ± 0.04 kPA) in zerooxygen solution. Paratrend probes showed higher PO2 values of 7.0 ± 1.4 torr (0.9 ± 0.2 kPa) after 30 minutes.	"Analysis of the PbtO2 monitoring data suggested that the likellhood of death increased with increasing duration of time at or below a PbtO (2) of 15 torr (2.0 kPa) or with the occurrence of any PbtO2 values of <or=to6 torr (<or=to0.8 kPa)."	Data suggest increased mortality associated with increased duration of time at or below 15 torr.

Bardt 1998 (NA)	Brain Oxygen Monitoring	Prognostic	No COI or sponsorship mentioned.	N= 35	7 females, 28 males Mean age 33.2 ± 11.3 years	Severe head injury, GCS ≤ 8	Continuous brain tissue (PtiO2) via Licox microcatheter, placed into non-injured frontal white matter in 8-125h post-injury All participants underwent the same monitoring	Mean PtiO2 was 22.7 ± 9.1 mmHg. Cerebral hypoxia incidence was 15.0 ± 23.2 hours when indicated by PtiO2 levels < 10 mmHg. 12 participants underwent <30 minutes of PtiO2 < 10 mmHg. PtiO2 was <15 mmHg for 7.8 ± 2.6 hours for this group. 11 participants died, 22 were in a severely disabled or vegetative state, and 2 had more positive outcomes. After six months after injury 13 participants had died, 6 were still disabled, and 16 had more positive outcomes. More frequent periods of hypoxic PtiO2 < 10 mmHg was correlated with poor neurological outcomes. Of those who underwent <30 minutes of hypoxic PtiO2 80% were in a vegetative state at discharge, 20% had a positive outcome, and 0% died in the acute phase. After six month post injury over 72.8% of participants had a positive outcome, 18.2% had a negative outcome, and 9% died. Of those who underwent >30 minutes of hypoxic PtiO2 48% died in the acute phase and 52% had negative outcomes at discharge. 55.6% died, 22.2% were disabled, and	"These result underscore the associated of cerebral hypoxia with poor neurological outcome and stress the meaning of monitoring PtiO2 as an independent parameter in patients following TBI."	Data support correlation between cerebral hypoxia post TBI and poor neurological outcomes.

								22.2% had a positive outcome at six month. Intracranial hypertention (ICP > 20 mmHg) was associated with cerebral hypoxia in 11.5% of patients. In 16.8% of patients CPP was compromised <60 mmHg. Hypocarbia was present in 48.0% of the time during hypoxic PtiO2 episodes.		
Cormio 1999 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. Supported by a grant from the National Institutes of Health.	N= 450	63 females, 387 males Median age of 30 years (range 23-41 years)	Severe head injury, between 1986 and 1997	Intracranial pressure (ICP): ventriculostomy, a parenchymal microtransducer, or a fiberoptic monitor vs SjvO2: via oximeter (IL-284 CO-Oximeter), blood samples drawn through indwelling catheter in jugular bulb All participants underwent all monitoring	Group classification: Group 1 had high SjvO2 (75% of higher), Group 2 had normal SjvO2 (56-74%), and Group 3 had low SjvO2 (55% or lower). 19.1% of participants underwent a high SjvO2 measurement. SjvO2 and simultaneous cerebral blood flow had no consistent relationship. There was also no relationship between SjvO2 and cerebral perfusion pressure. Those in group 1 had significantly greater CBF and lower cerebral metabolic rate of oxygen (CMRO2). Group 1 had 48.8% of participants either died or were in a vegetative state and 25.6% were severely disabled. These percentages were significantly higher	"Posttraumatic elevation of SjvO2 is common but cannot be automatically equated with hyperemia. Instead, elevated SjvO2 is a heterogeneous condition that is associated with poor outcome after head injury and may carry important implications for the management of comatose patients."	Data suggest post-traumatic elevation of jugular venous oxygen saturations correlates with poorer outcomes.

								compared to groups 2 and 3. Those who had poor outcomes in group 1 were older and more likely to suffer from a focal head injury. These individuals had lower CMRO2 levels and higher rates of cerebral lactate production.		
Cruz 1998 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. The Rotary Foundation of Rotary International supported a PostGraduate Fellowship for this study.	N= 353	No gender distribution described Mean age of cerebral extraction of oxygen group 30 ± 9 years. Mean age of initial cerebral perfusion pressure group 29 ± 8 years.	Severe acute closed brain trauma, in a coma, GCS score from 3-8	(CEO2) Continuous fiberoptic monitoring and management of jugular bulb oxyhemoglobin saturation and cerebral extraction of oxygen with cerebral perfusion pressure (n=178) vs (CPP) Continuous monitoring and management of cerebral perfusion pressure only (control group) (n=175)	16 participants in the CEO2 group died (9%) while 53 participants in the CPP group died (30%) post-injury. Overall figures in outcome were significantly better in CEO2 group compared to the control group. Categories of the Glasgow Outcome Scale were compared between the two groups and resulted in the following: good recovery of moderate disability (G-M) – 132 participants in CEO2 group, 98 in CPP group, and severe disability (S) – 25 CEO2, 21 CPP, vegetative state or death (V-D) – 21 CEO2, 56 CPP. These differed significantly ($p < 0.00005$). In the CEO2 group cerebral perfusion pressure monitoring occurred over 6.5 ± 1.5 days, while in the control group it occurred over 10.5 ± 2 days ($p < 0.001$).	"In patients with severe acute brain trauma and intracranial hypertension associated with compromised cerebrospinal fluid spaces, monitoring and managing cerebral extraction of oxygen in conjunction with cerebral perfusion pressure result in better outcome than when cerebral perfusion pressure is managed alone."	Data suggest in severe brain trauma patients with intracranial hypertension the management of cerebral perfusion pressure in tandem with cerebral extraction of oxygen leads to better patient outcomes.

								Participants were matched for the following variables: age, postresuscitation Glasgow Coma Scale scores, and initial levels of intracranial pressure and cerebral perfusion pressure, between-group rates of early arterial hypotensive episodes (before intensive care monitoring), pupillary abnormalities, small lateral ventricles, compromised basilar cisterns, and acute surgical intracranial hematomas. There were no significant differences between the two groups in these variables.		
Robertson 1995 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by a grant from the National Health Institute. No mention of COI.	N= 177	19 females, 158 males Mean age 32.9 ± 14.7 years	Severe head injury, GCS ≤ 8	Jugular venous oxygen saturation (SJVO2), catheter placed on dominant side All participants underwent this monitoring	In the participants monitored, jugular venous desaturation (SJVO2 < 50%) occurred within 39% at least during monitoring. Episodes of this desaturation were due to intracranial hypertension and systemic causes. Oxygen depletion was associated with a negative outcome. 6 out of 8 participants monitored during emergency evacuation of a traumatic intracranial hematoma displayed jugular venous desaturation. 28% was the lowest level of SJVO2. SJVO2 levels increased	"Despite these limitations, the present data suggest that Sjv02 monitoring is useful in detecting episodes of cerebral hypoperfusion in patients with severe head injury. The incidence of observing jugular venous desaturation is frequent enough to justify the small risk of the catheter. The occurrence of jugular venous desaturation is strongly associated with a poor neurological outcome. The causes of the hypoperfusion are often	Data suggest jugular venous oxygen monitoring is critical in detection of cerebral hypoperfusion in head injured patients.

								from 47 ± 10% to 63 ± 5% after evacuation of hematoma. Lactate concentration increased from 0.9 ± 0.3 to 2.4 ± 0.5 µmol/L and glutamate elevated from 11.5 ± 8.5 to 55.0 ± 10.4 µmol/L within 8 episodes of jugular venous desaturation in 7 of 22 patients monitored with microdialysis.	treatable systemic insults."	
Stocchetti 2004 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI or sponsorship.	N= 229	39 females, 190 males Mean age was 36 years.	Severe head injury, comatose, GCS ≤ 8	Intracranial pressure (ICP) vs Mean arterial blood pressure (MAP) vs Cerebral perfusion pressure (CPP) vs Samples from artery and internal jugular samples, via catheter inserted into internal jugular vein, tip positioned at superior bulb, analyzed with cooximeter and	Mean SJO2 (jugular hemoglobin oxygen saturation) level was 68%. Mean AJDO2 difference was 4.24 vol% (sd = 1.3 vol%). 304 measurements (17.6%) had SJO2 levels >75% and 80 (4.6%) with levels <55%. 8 calculations (0.4%) of AJDO2 resulted in higher than 8.7 vol% and 718 calculations (42%) resulted in lower than 3.9 vol%. AJDO2 results were higher during the first measurements and over the course of a few days decreased steadily. Those who were severely disabled or in a vegetative state at six months post injury had mean AJDO2 of 3.8 vol% (sd = 1.3 vol%) and those who died had	"We conclude that low levels of AJDo2 are correlated with a poor prognosis, whereas normal or high levels of AJDo2 are predictive of better results"	Data suggest low levels of arterio-jugular difference of oxygen content correlate to poor prognoses.

							gas analyzer (IL 481 Co-oxymeter) vs Arterio-jugular difference of oxygen content (AJDO2), calculated as the following: AJDO2 = (art Sat % - j Sat %) x 1.34 x Hb x [(art PO2 – j PO2) x 0.003] All participants underwent all monitoring	mean AJDO2 measures of 3.6% (sd = 1.0 vol%). Those with a more positive outcome had a significantly higher AJDO2 measure of 4.3 vol% (sd = 0.3 vol%) compared to those who were severely disabled, in a vegetative state, or those who had died combined ($p < 0.001$).		
van den Brink 2000 (NA)	Brain Oxygen Monitoring	Prognostic	No COI. No mention of sponsorship.	N= 101	18 females, 83 males Mean age 34 ± 16 years	Comatose, severe head injury, GCS ≤ 8	All participants were monitored for the following: heart rate, respiratory rate, mean arterial blood pressure via a pressure transducer calibrated at level of heart, peripheral oxygen saturation, ICP via Camino fiberoptic device, CPP, PbrO2 via Clark-type microcatheter and Licox partial pressure of oxygen	PbrO2 monitoring started 7.0 ± 3.5 hours post-injury. 83 participants were monitored for over 24 hours with average monitoring time being 86 hours (range 4-180 hours). When monitoring PbrO2, post-measurement calibration resulted in average zero display error of 0.42 ± 0.85 mm Hg. PO2 display error (calibrated at mean room air PO2 of 157.6 ± 1.5 mm Hg) was 0 ± 6%. In first 12-24 hours low initial values occurred in over 50% of participants. 57 cases had values lower	"Monitoring the partial oxygen pressure of local brain tissue is a safe and reliable method for regulating cerebral oxygenation. Because brain tissue hypoxia occurs frequently and is significantly related to poor outcome, future efforts should be aimed at the treatment of brain tissue hypoxia. The effects of such brain hypoxiatargeted treatment need to be established in a multicenter study."	Data suggest ability to monitor brain partial oxygen pressure to detect hypoxia which leads to poor outcomes in severe head injury.

							measuring computer Local brain oxygen tension probes, inserted in undamaged part of frontal region vs CT scanning using the Marshall classification	than 15 mm Hg, 42 had values lower than 10 mm Hg, and 22 had values lower than 5 mm Hg. Of those with initial low values, 30 displayed an overshoot in mean high value of PbrO2 (46 mm Hg in 36-48 hours post-injury). Occurrence of overshoot not related to outcome. After using the Spearman rank coefficient, no significant correlations were found for between low initial values and clinical variables. Compression of cisterns was the only significantly correlated variable in CT scans with initial low PbrO2. Survivors presented higher PbrO2 values. 24 out of 43 participants with low initial values died. Only 14 out of 66 participants with higher values died. When outcomes were dichotomized into negative versus positive outcomes the odds ratio of death was 3.8 (p = 0.002). The odds ratio for unfavorable outcome was 2.8 (p = 0.015). Low values within 24 hours post-injury were broken		

								into <5, <10, and <15 mm Hg. Lower PbrO2 values related to higher risk of death. There was no increase in risk of death after several hours. The odds ratio for death was 3.8 (95% CI = 1.6-8.9) at 30 minutes. Low initial PbrO2 remained an independent prognostic factor when analyzed in a logistic regression model. Status of perimesencephalic cisterns were related to PbrO2 and reduced the prognostic value.		

Evidence for the Use of Mannitol

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Cottenceau 2011 (score = 5.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship. No COI.	N = 47 TBI patients with increased intracranial pressure (ICP) Ages 36.1±16.8 for Mannitol group and 42.7±19.9 for Hypertonic saline group		Mannitol (MTL) group. Received 20% (4 ml/kg) (N =25) vs. Hypertonic saline [567] group. Received 7.5% (2ml/kg) (N =22). Baseline assessment was followed by additional tests performed at 30 and 120 min.	Neurological outcome was assessed at 6 months during follow-up examinations.	As a correlate for Intracranial pressure decrease, there was a noticeable and significant increase in cerebral perfusion pressure (CPP) at 30 min in both groups (Main effect of measurement time p = 0.0001). Although cerebral blood flow (CBF) increased in both groups at 30 min, it was more pronounced in the HTS group, p=0.0087. There was a significant elevation of hematocrit at 30 min following MTL infusion.	"MTL was as effective as HTS in decreasing ICP in TBI patients although both solutions failed to improved cerebral metabolism. HTS showed an additional and stronger effect on cerebral perfusion of potential benefit in the presence of cerebral ischemia. Treatment selection should therefore be individually based on sodium level and cerebral hemodynamics".	Data suggest similar efficacy but HTS showed a benefit on cerebral perfusion in the presence of cerebral ischemia.
Francony 2008 (score = 5.0)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 20 with severe brain injury (n=17 TBI) and (n=3 stroke) with intracranial pressure (ICP) greater than 20 mmHg for more than 10 minutes. Mean age		Mannitol 20% 231 mL (N = 10) vs. Hypertonic saline solution 7.45% (HSS) 100mL (N = 10). Osmolar dose was 255	Follow-up for 120 minutes.	At every time point both mannitol and HSS significantly reduced ICP in the two groups. Mannitol reduced ICP by 45% +/- 19% from baseline to 60 minutes (-14	"[2]0% mannitol is as effective as 7.45% HSS in treating stable patients with sustained elevated ICP…Both osmotic agents exerted a clear and comparable effect on ICP, lasting >120	Data suggest comparable reductions in ICP including better cerebral blood flow with mannitol.

				mannitol 43±11 years, HSS 37±16 years.		mOsm for each treatment.		+/- 8 mmHg). HSS reduced ICP by 35% +/- 14% from baseline to 60 minutes (-10 +/- 5 mmHg). Mean arterial blood pressure remained unchanged and was significantly different between groups (p=0.32). HSS blood flow velocities after treatment was significantly reduced compared to mannitol at every time point (p<0.01).	mins, whereas CPP and cerebral blood flow velocities rose significantly in the mannitol group only."	
Schwartz 1984 (score = 4.5)	Mannitol vs Pentobarbitol	RCT	Sponsored by the Sunnybrook Medical Center grant. No mention of COI.	N = 59 with elevated intracranial pressure from severe head injury. Glasgow Coma Scale scores <8. Mean age mannitol 30.1 years, pentobarbital 28.9 years.		Mannitol 20% 1g/kg with a serum osmolality of 320mOs/L (N = 31) vs. Pentobarbital IV bolus of 10mg/kg and continuous infusion at 0.5-3mg/kg/hr. (N = 28). All patients given CT scan.	Follow-up at 3 months and one year.	Scores on the GCS correlated with survival rates at 3 months 16/28 patients had dies in the pentobarbital group and at 1-year 6/12 remained hospitalized. For mannitol 13/31 had died and at 1-year 8/16 were hospitalized. Twice as many patients starting with pentobarbital had to use mannitol as	"There is no evidence that pentobarbital is 25 percent better than mannitol, either for the control of raised intracranial pressure or for improving survival in patients with intracranial hypertension due to head injury."	For patients experiencing elevated episodes of ICP they were given rescue medicine, making the study a cross-over, unblinded study. Severe TBI. Data suggest mannitol superior for mortality (77 % vs. 41%).

								rescue medicine, making pentobarbital not 25% better (p=0.04) than mannitol.		
Sayre 1996 (score = 4.5)	Mannitol vs Normal Saline	RCT	Supported by grants from the Aeromedical Research Foundation and The Department of Emergency Medicine, University of Cincinnati. No mention of COI.	N=44 with head injuries, a Glasgow Coma Scale<12, IV access, airway control with an endotracheal tube, and were being hyperventilated. Mean±SD age: Mannitol: 29±12 years. Placebo: 27±8 years.		Control group: 5mL/kg of 0.9% saline solution (308 mOsmoVL) (n=21) Vs. Treatment group: 5mL/kg of 20% mannitol (1,098 mOsmoVL) (n=20).	Follow-up 120 minutes.	Systolic BP 2 hours after treatment: Mannitol vs. placebo: 116±24mmHg vs. 142±25mmHg, p<0.003.	"Out-of-hospital administration of mannitol did not significantly change systolic BP in this group of head-injured multiple-trauma patients."	Out of hospital administration of mannitol did not significantly change systolic BP.
Ichai 2009 (score = 4.0)	Mannitol vs Lactate	RCT	Sponsored by Innogene Kalbiotech Pte. Ltd. 24 Raffles Place 27-06 Clifford Center, Singapore. No mention of sponsorship. No mention of COI.	N = 34 with isolated severe traumatic brain injury with a Glasgow Coma Scale greater than 8. Mean age MAN 33.8±3.2 years, LAC 37.6±4.0 years.		Lactate solution contained Na 504 mmol/L, K 4 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L and lactate 504.1 mmol/L (n=17) vs. Acute infusion of 1.5 ml/kg of either mannitol (20%, i.e., 0.3 g/ kg) vs. Lactate over 15 min (n=17).	Follow-up 240 minutes.	Intracranial pressure: LAC was lower than MAN (group effect p=0.016). Lactate infusion increased arterial pH (+0.5±0.1%, p<0.001).	"Acute infusion of a sodium lactate-based hyperosmolar solution is effective in treating intracranial hypertension following traumatic brain injury. This effect is significantly more pronounced than that of an equivalent osmotic load of mannitol. Additionally, in this specific group of patients, long-term outcome was better in terms of GOS in those receiving as compared to mannitol. Larger	Severe TBI. Data suggest greater reductions with lactate and more treatment failures with mannitol measured by ICP. Better outcomes with lactate at 1 year.

									trials are warranted to confirm our findings."	
Biestro 1997 (score = 4.0)	Mannitol vs Glycerol & Saline	RCT	No mention of sponsorship or COI.	N=17 with severe head injury including two craniocerebral gunshot wounds (GSW), 31% with a Glasgow Coma Scale score (GCSs) of 6 or less, 50% with a GCSs of 7. Mean age: mannitol 34 years (range: 15-69) group. Glycerol was 39.5 years (range: 15-68).		15% mannitol, 100 ml given in ten minutes [860 mOsm170] Vs. 10% glycerol in 0.5 normal saline at rate of 250 ml per 1 hour [1.300 mOsm170].	2 hour follow up.	ICP decrease Mannitol: At two hours: 36.8±2.9 (SE) to 18.6±1.8 (SE) mmHg, p<0.0005. Glycerol group: 41.8±3.0 (SE) to 26.8±2.9 (SE) mmHg, p<0.0005.	"[M]annitol would be most indicated as a bolus to control sudden rises in ICP whereas glycerol would be most indicated." as a basal treatment.	Small sample. Data suggest similar efficacy between mannitol and glycerol for decreasing ICP and increasing CPP.
Smith 1986 (score = 4.0)	Mannitol (ICP) vs. Mannitol (empirical)	RCT	No mention of sponsorship or COI.	N = 77 with head injury with a Glasgow Coma Scale rating of 8 or less. Average age of 27 years) range 8 months to 78 years).		Group I mannitol therapy based on intracranial pressure (ICP) levels (N = 37) vs. Group II mannitol empirical therapy (N = 40).	Follow-up at 1 year.	Death occurred in 13/37 (35%) of group I and 17/40 (42.5%) group II. All patients that died had abnormal CT scan. The outcomes from both group I and group II did not differ significantly for good recovery, moderate disability, severe disability, or vegetative state. There were no other statistically significant differences between groups in outcomes.	"The finding that empirically treated patients had lower mean ICP curve overall than patients given mannitol only when ICP rose above 25 mmHg suggests that the regular and frequent administration provides a smoother ICP curve overall and prevents ICP from rising above 25 mmHg…"	Data suggest no differences.

Vialet 2003 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 20 with severe head trauma and persistent coma. Mean age mannitol 30.8±19 years, saline 35.0±18 years.		Mannitol 2mL/kg 20% (N = 10) vs hypertonic saline solution 2mL/kg 7.5% (N = 10).	Follow-up for mortality or 9-day neurologic status.	Episodes of intracranial pressure (ICP) were elevated in the mannitol group (p<0.02) and length of ICP was significantly longer (p<0.04) compared to HSS. Episodes of cerebral perfusion pressure were not significantly different between the groups. Treatment failure was significantly higher in the mannitol (7/10) group compared to HSS (1/10; p<0.01). Plasma osmolality was also significantly higher in the HSS group (p<0.01).	"[I]ncreasing the osmotic load during osmotic therapy (from 175 +/- 12 mOsm of 20% mannitol to 361 +/- 13 mOsm of HHS) was followed by a better efficacy on the number and the duration of established ICH episodes…"	Severe TBI. Lower initial Glasgow in hypertonic saline solution (4.7 vs. 6.0). Data suggest hypertonic saline solution lowered ICP better. No differences in outcomes.
Mir 2012 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT	No sponsorship. COI, this paper is the outcome of the first author thesis study and was supported by TUMS. Since the third author is the Editor-in-Chief of the	N=33 patients, Ages not reported		Received mannitol 20% as a bolus of 1g/kg. Repeated dosing was given at 0.25 to 0.5 g/kg as needed (Group A n=10) Vs. Received 125 cc Hypertonic Saline [567] 5% as bolus in 1 hour every 6	Follow-up at baseline, 7 days and 60 days.	There was a correlation between mean APACHE II, SOFA and GCS scores in treatment groups, (p=0). There was a difference between expired and alive patients in mean APACHE II (p=0.005), SOFA (p=0.006) and GCS scores (p=0.000) after 60 days.	"Heart rate can be a prognostic factor for estimating mortality rate in brain injury patients along with APACHE II and SOFA scores in patients with brain injury".	Open label trial suggesting heart rate can be used as a prognostic measurement. Similar efficacy between groups. Small sample.

			journal; all review process and decisions on the submission were managed by one of the section Editors.			hours (Group B, n=11) Vs. Received 500 cc HTS 5% as infusion during 24 hours (Group C, n=12) In all groups, Acute Physiology and Chronic Health Evaluation (APACHE II), the sequential organ failure assessment (SOFA) and Glasgow coma scales (GCS) scores and heart rate were collected				
Scalfani 2012 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT Pilot Study	Sponsored by NIH grant members. No COI.	N=8 patients with acute TBI. Ages, 37.4±17.4 years old.		Received 1.0 g/kg of 20% mannitol Vs. 0.686 mL/kg of 23.4% saline In both groups, treatments were infused for 15 min, and 1 hour after initiation of infusion.	Follow-up for 3 days	There were no differences in results from patients who received HS and mannitol were and combined for all analyses. Serum sodium concentration rose 4 hours after osmotic therapy (p=0.05) After intervention, CBF increased by 20% (p=0.001), and OEF decreased (both p<0.05) The number of regions with CBF less than	"Osmotic agents, in addition to lowering ICP, improve CBF to hypo perfused brain regions in patients with intracranial hypertension after TBI".	Small sample (n=8). Data suggest similar efficacy between mannitol vs. hypertonic saline in TBI patients with intracranial hypertension.

								25 mL per 100 g/min decreased by 40% from a mean of 13 per patient 8 per patient(P<0.001)		
Sakellaridis 2011 (score = 2.5)	Mannitol vs Hypertonic Saline	RCT	No COI. No mention of sponsorship.	N=29 (199 hypertensive events) with severe head injury (GCS score ≤ 8) during the time period 2006–2008. Age range: 14 to 82 years (mean 36 years).		Mannitol 20% at a dosage of 2 ml/kg administered over 20 minutes (N=NA) vs. Hypertonic saline 15% at 0.42 ml/kg administered as a bolus via a central venous catheter (n=NA).	Follow-up for 3 months.	Mean duration of effect: Mannitol: 3 hours 33 minutes (SEM 31 minutes) vs. Saline: 4 hours 17 minutes (SEM 50 minutes), p=0.40.	"No difference between the 2 medications could be found with respect to the extent of reduction of ICP or duration of action."	Crossover design. Data suggest comparable efficacy. Sparse methods.
Hendoui 2013 (score = 1.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 39 with moderate to severe TBI. Aged between 18 to 65 years		Group A, 1 g/kg mannitol of 20% as a bolus, repeated with a dose of 0.25-0.5 g/kg every 6 hours based on patient's response for 3 days (N = 10) vs. Group B, 125 cc of hypertonic saline or HTS 5% every 6 hours as bolus (N = 11) vs. Group C, 500 cc of HTS 5% as infusion for 24 hours (N = 12).	Follow-up for 3 days of treatment and 60 days of survival.	No significant difference in 60 days survival of patients in different groups, (p = 0.1). Concentration of S100B was 0.01 ± 0.004 µg/l for control group vs the healthy control group, TBI patients had significantly higher initial serum levels of S100B at ICU admission, (p < 0.0001). Increased GCS levels, (p = 0.047) and	"S100B is closely related to the pathophysiological mechanism in TBI and may be useful as a therapeutic tool for treatment monitoring in TBI patients HTS is a safe and effective osmotic agent in TBI setting."	Moderate and severe TBI. Small sample size. Open label. Baseline differences that appear to favor bolus HTS and concerning for randomization failure.

								reduced SOFA scores, (p = 0.002). MAP was significantly increased in bolus of HTS (p = 0.002) and infusion of HTS groups (p < 0.0001).		
Mojtahedzadeh 2014 (score = 1.5)	Mannitol vs Hypertonic Saline	RCT	Sponsored by Tehran University of Medical Sciences. No COI.	N = 39 with Glasgow coma scale (GCS) ≤12, closed head trauma and evidence of brain edema on head computed tomography (CT) scan. Aged between 18 and 65 years.		Group A, mannitol 20%, 1 g/kg administered over 20 min via central venous catheter and repeated with a dose of 0.25-0.5 g/kg every 6 h based on patient response (N = 10) vs. Group B, received 125 cc HTS 5%, over an hour via central venous catheter every 6 h for 3 days. And in the third group (C) 500 cc HTS 5%was continuously infused over 24 h for 3 days (N = 11) vs. Group C, as a continuous infusion of HTC (N = 12). Both groups of healthy	Follow-up at baseline and 3 days.	Serum concentration of ROS was 1.57 ± 0.5 picoM for the control group vs healthy group. TBI group had higher serum level of ROS at ICU admission, (p = 0.01), this reduction was significant for infusion part of HTS and mannitol, (p = 0.001 and 0.003). Serum TAP significantly decreased in mannitol group, (p = 0.004).	"HTS 5% has significant effects on the oxidant responses compared with mannitol following TBI that makes HTS as a prefect therapeutic intervention for reducing unfavorable outcomes in TBI patients."	Second report of Hendoui 2013

						volunteers (N = 30) assessed for establishment of normal serum levels of ROS.				
Battison 2005 (score = 1.0)	Mannitol vs Hypertonic Saline plus Dextran	RCT Crossover Pilot Study	No mention of sponsorship or COI.	N = 9 with traumatic brain injury patients with intracranial pressure (ICP) >20mmHg.		Mannitol 20% 200mL 1245 mOsm/kg (N = 9) vs. Saline 7.5% and dextran-70 solution 6% (HSD) 100 mL (N = 9). Each patient received two treatments of mannitol and two HSD in a random order.	210 minutes	HSD reduced the minimum ICP more than mannitol (mean difference -5 mmHg; 95% CI -10.8 to -3.0; (p=0.014)). HSD reduced ICP to ≤16 mmHg in 2/18 treatments. Mannitol reduced ICP to ≤18 mmHg in 14/18 treatments. HSD significantly lowered mean arterial pressure (mean difference 7.0 mmHg; 95% CI 0.5 to 22.3; (p=0.044)). There was no significant difference between groups for cerebral perfusion pressure.	"It is the first trial to show that HSD reduced ICP more effectively than mannitol. This has implications for management of ICP. HSD may be a useful alternative in the treatment of increased ICP, but it remains to be seen if there is a clear fluid balance advantage of HSD over mannitol.	Pilot. Crossover trial. Sample size = 9. Deaths unclear.

Evidence for the Use of Hypertonic Saline

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ichai 2013 (score = 5.5)	Treatment Evidence for Hypertonic Saline: vs Lactate	RCT	No mention of sponsorship. No COI.	N= 60 with severe non-penetrating TBI with an initial Glasgow Coma Scale (GCS) score of \9, and required measurement of ICP as part of their management within the first 12 h following injury.	Mean±SD age: Control group 33±15 years. SL group 40±18 years.	NaCl 0.9% (n=30) Vs. Half-molar sodium lactate (n=30).	Follow-up for 48 hours.	ICP episodes at 48 hours: SL vs. control group: 23 vs. 53 episodes, p<0.05).	"[S] L solution could be considered as an alternative treatment to prevent raised ICP following severe TBI."	Data suggest SL decreased ICP episodes in severe TBI patients compared with NS.
Hui 2014 (score = 4.0)	Treatment Evidence for Hypertonic Saline vs Ulinastatin	RCT	No mention of sponsorship or COI.	N=92 with a diagnosis of sTBI by computed tomography or magnetic resonance imaging; Glasgow Coma Scale (GCS) score of <8; and admittance to ICU within 8 h after injury.	Age range: 28-63 years.	Control group (n=46): Conventional therapy plus a placebo (0.9% sodium chloride) vs. observation group (n=46): conventional therapy plus 200,000 units ulinastatin via intravenous injection	Days 1, 3, 5 and 7.	Mean±SD jugular venous blood lactate at day 7: Observation group 1.32±0.39 vs. Control group 2.85±0.36, p<0.05. Cerebral extraction of oxygen at day 7: Observation 40.18±5.47 vs. Control 32.43±4.15, p<0.05.	"[U]linastatin effectively improved cerebral oxygen metabolism and reduced the CRP level in patients with sTBI."	Sparse methods. Data suggest ulinastatin "may" be beneficial in TBI patients by improving cerebral oxygen metabolism and decreasing CRP levels (at one week).

						twice a day for seven days.				
Shackford 1998 (score = 3.5)	Treatment Evidence for Hypertonic Saline vs Saline	RCT	Sponsorship, supported by Grant NINDS P20 NS 30324 from the National Institute of Health. No mention of COI.	N=34 With blunt mechanism of injury, GSC score ≤13 requiring monitoring of ICP or operative therapy and postoperative monitoring of ICP.		Hypertonic patients received 1.6% hypertonic saline [567] given at a rate of 15 mL/kg/day. Vs. Hypotonic patients received lactated Ringer's solution (LRS).	Follow-up for 5 days.	Mean maximum ICP with therapy was negative in the HTS group (-9.1±-3.6 mm Hg) and positive in the LRS group (2.5± 3.3, p<0.05).	"As a group, HTS patients had more severe head injuries. HTS and LRS used with other therapies effectively controlled the ICP. The widely held conviction that sodium administration will lead to a sustained increase in ICP is not supported by this work."	Baseline comparability differences between groups (HTS group with more severe head injuries). Suggests randomization failure.
Schatzmann 1998 (score = 3.5)	Treatment Evidence for Hypertonic Saline vs Saline	Experimental	No mention of sponsorship or COI.	N=6 with trauma and severe head injury.	Mean (range) age: 40 (16-73) years.	Hypertonic saline (100ml 10% NaCl)	Follow-up at 6 hours.	The ICP decrease was 43% (28%-58%). The corresponding pressure drop was 18mmHg [570]. Relaxations lasted for 93 min [171] and a relative ICP min was reached 26min [234] after infusion.	"[T]he infusion of hypertonic saline reduces ICP in patients suffering from SHI. The pressure drop, duration and dynamic behavior are suspected to depend on the pressure level to reduce and concomitant medications."	Small sample (n=6). Data suggest administration of hypertonic saline reduces ICP in severe head trauma patients.

Evidence for the Use of Sodium Lactate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ichai 2013 (score = 5.5)	Treatment Evidence for Sodium Lactate vs Saline	RCT	No mention of sponsorship. No COI.	N= 60 with severe non-penetrating TBI with an initial Glasgow Coma Scale (GCS) score of \9, and required measurement of ICP as part of their management within the first 12 h following injury.	Mean±SD age: Control group 33±15 years. SL group 40±18 years.	NaCl 0.9% (n=30) Vs. Half-molar sodium lactate (n=30).	Follow-up for 48 hours.	ICP episodes at 48 hours: SL vs. control group: 23 vs. 53 episodes, p<0.05).	"[S] L solution could be considered as an alternative treatment to prevent raised ICP following severe TBI."	Data suggest SL decreased ICP episodes in severe TBI patients compared with NS.
Ichai 2009 (score = 4.0)	Treatment Evidence for Sodium Lactate vs Mannitol	RCT	Sponsored by Innogene Kalbiotech Pte. Ltd. 24 Raffles Place 27-06 Clifford Center, Singapore. No mention of sponsorship. No mention of COI.	N = 34 with isolated severe traumatic brain injury with a Glasgow Coma Scale greater than 8.	Mean age MAN 33.8±3.2 years, LAC 37.6±4.0 years.	Mannitol 20% (MAN) 1160 mOsm/L (N = 17) vs. Lactate solution (LAC) 1100 mOsm/L (N = 17).	Follow-up 1 year after treatment.	The LAC treatment group shad a significant decrease in ICP (p=0.016) compared to MAN. For the interaction between time and group effects there was a significant difference (p=0.0049), which indicates a longer and pronounced change. At the fourth hour the ICP was decreased by -5.9 +/- 1 mmHg compared to MAN -3.2 +/- 0.9 mmHg (p=0.009). The LAC group had a significant increase in glucose (p=0.04), lactate (p<0.00001), and plasma osmolality (p=0.04) compared to MAN. Mean	"[H]yperosmolar sodium0lactate solution appears to be an interesting alternative in the treatment of episodes of cranial hypertension in TBI patients. This solution is more effective on ICP than the reference treatment mannitol."	Severe TBI. Data suggest greater reductions with lactate and more treatment failures with mannitol measured by ICP. Better outcomes with lactate at 1 year.

								arterial pressure (p=0.96) and cerebral perfusion pressure (p=0.51) were not statistically significant between the two treatments.		

Evidence for Resuscitation of Hypertonic Saline vs. Ringer's Lactate

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cooper 2004 (score = 8.5)	Resuscitation Evidence for Hypertonic Saline vs Ringer's Lactate	RCT	No COI. Sponsorship, grant 124330 from the National Health and Medical Research Council, Australia, and grants from the Australian and New Zealand Intensive Care Research Foundation, the Victorian Trauma Foundation, the Neurosurgical Research Foundation, and the Alfred Hospital, Melbourne, Australia	N=229 with TBI who were comatose (Glasgow Coma Scale score, <9) and hypotensive (systolic blood pressure, <100 mm Hg).	Mean±SD age: Hypertonic saline 38±19 years. Control group: 37±19 years.	250-mL Infusion of Hypertonic Saline (n=114) Vs. 250-mL Infusion of Ringer's Lactate Solution (Control) (n=115).	Follow up for 6 months.	No differences between the groups with respect to ICP (p=0.08), CPP (p=0.40), duration of CPP of less than 70 mm Hg (p=0.06), gas exchange (PaO2/FIO2 ratio), or duration of mechanical ventilation. Median (IQR) GOSE score at 6 months: Hypertonic vs control: 5 (3-6) vs. 5 (5-6), p=0.45.	"[P]atients with hypotension and severe TBI who received prehospital resuscitation with HTS had almost identical neurological function 6 months after injury as patients who received conventional fluid."	Data suggest administration of prehospital hypertonic saline [567] to patients with hypotension and severe TBI not superior to conventional (LR) solution at 6 months.

Vassar 1991 (score = 6.0)	Resuscitation Evidence for Hypertonic Saline with Dextran vs Ringer's Lactate	RCT	Supported in part by grant 1-ROM1-GM38508 from the National Institutes of Health and by Pharmacia Inc. COI, George C. Kramer, PhD, and Dr.Holcroft, hold rights to a patent that describes the use of hypertonic saline/hyperoncotic solutions for the resuscitation of patients in shock.	N= 166 trauma patients undergoing transport, systolic blood pressure of ≤100 mm Hg, palpable peripheral pulse or a sinus complex on electrocardiography, age≥18 years.	Median (IQR) age: HSD 29 (21-42) years. LR 33 (21-42) years.	Solution of 7.5% sodium chloride in 4.2% dextran 70 solution (HSD) (n=83) vs. 250 mL of lactated Ringer's (LR) solution (n=83).	Follow-up through day 8.	Rate of survival: 32% HSD vs. 16% LR group, p=0.044. Median (IQR) Serum osmolality (mOsm/kg): HSD 333 (319-354) vs. LR 308 (296-333), p=0.0001.	"Administration of small volumes of sodium chloride/dextran 70 before hospitalization increased the blood pressure of severely injured patients more effectively than did lactated Ringer's solution and showed tendencies toward improving survival in the patients with severe head injuries.	Data suggest 7.5% NaCl with Dextran before hospitalization trended towards increased blood pressure in severe TBI injured patients vs. LR.
Ponsford 2008 (score = 4.5)	Resuscitation Evidence for Hypertonic Saline vs Ringer's Lactate with Crystalloid or Colloid or Combination	RCT	No sponsorship or COI.	N=229 with severe blunt head trauma, initial GCS<9 and hypotension.	Mean±SD age: Male 33.8±16.3 years, Female 43.3±23.1 years.	Saline resuscitation: 250 ml intravenous infusion of 7.5% saline [567] vs. conventional fluid management: 250ml intravenous infusion of Ringer's lactate solution. Following infusion, a 10-ml/kg crystalloid, Ringer's	Follow up for 6 months.	Median (IQR) Glasgow outcome scale extended at 6 months male vs. female: 3 (1-5) vs. 1 (1-5), p=0.006). No gender differences in GCS score or injury severity scores.	"The study provides no evidence that females fare better than males following severe TBI, suggesting rather that females may fare worse."	Data suggest females do not do better post TBI when compared to males.

						lactate solution, or a colloid solution, or both was administered.					

Resuscitation Evidence for Hypertonic Saline vs. Saline

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*

Rhind 2010 (score = 5.5)	Resuscitation Evidence for Hypertonic Saline vs Saline	RCT	No COI. No mention of sponsorship.	N=65 who experience loss of consciousness due to isolated blunt head trauma and/or had a Glasgow Coma Scale (GCS) score <8.	Mean±SD age: HSD 41.8±17.4 years. NS 42.8±18.8 years.	A single prehospital bolus infusion of 250-mL of 7.5% hypertonic saline in combination with 6% dextran-70 (HSD) (n=30) vs. 250-mL of the standard 0.9% normal saline (NS) (n=35).	Follow-up for 48 hours.	Mean±SEM Leukocytes count at 48 hours: HSD: 11.4±0.6, p<0.05 vs. age-matched healthy controls. NS: 11.4±0.5, p<0.05 vs. age-matched healthy controls.	"These findings support an important modulatory role of HSD resuscitation in attenuating the upregulation of leukocyte/endothelial cell proinflammatory/prothrombotic mediators, which may help ameliorate secondary brain injury after TBI."	Small sample of a larger RCT (Morrison 2011). Data suggest HSD resuscitation may help reduce secondary brain injury post TBI when compared to NS by causing functional changes to inflammatory cells.

Resuscitation Evidence for Albumin vs. Saline

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Myburgh 2007 (score = 8.5)	Resuscitation Evidence for Albumin vs Saline	Saline versus Albumin Fluid Evaluation (SAFE Study), Post-hoc RCT	Sponsored by the Victorian Trauma Foundation. Main SAFE study was supported by the Auckland District Health Board and the Australian Commonwealth Department of Health and Aged Care (CSL). COI, Dr. Davies and Dr. Stephens own shares in CSL.	N=515 with traumatic brain injury, score ≤13 on the Glasgow Coma Scale.	Median (IQR) age: Albumin group: 37 (23-55) years, Saline 35 (23-50) years.	4% albumin group (N=255) Vs. Normal saline group (0.9%) (N=260).	Follow up for 24 months.	Death rate at 24 month albumin vs. saline group: 33.2% (RR, 95%CI: 1.63, 1.17-2.26) vs. 20.4%, p=0.003.	"[F]luid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline."	Posthoc study of critical TBI patients. Data suggest fluid resuscitation with albumin associated with higher mortality (41.8% vs. 22.2%).

Cooper 2013 (score = 5.0)	Resuscitation Evidence for Albumin vs Saline	Post hoc analyses of the SAFE study	Sponsored by CSL Limited. COI, authors received travel refund to present study findings from CSL Limited.	N=321 with TBI, score ≤13 on the Glasgow Coma Scale.		Mean±SD age: Albumin 37.8±17.4 years, Saline 36.0±15.8 years. 4% albumin group (N=164) Vs. Normal saline group (0.9%) (N=157).	Follow up: 14 days post-randomization.	Mean±SD ICP values comparing albumin vs. saline: Day 7: 19.2±1.07 vs. 15.4±1.06mm, p=0.01. No differences at day 3 or 14.	"The use of albumin for resuscitation in patients with severe TBI is associated with increased ICP during the first week."	A post-hoc analysis subset of a previous RCT. Data suggest TBI patients treated with albumin have an increased ICP during the first week post injury compared with saline likely associated with the significant increased mortality rate in these patients.

Resuscitation Evidence for Dextran-Saline vs. Saline

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Baker 2009 (score = 7.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	No sponsorship or COI.	N= 64 blunt trauma patients with severe head injuries. Coma or loss of consciousness due to isolated blunt head trauma and/or a Glasgow Coma Scale (GCS) score of ≤8.	Mean (range) age: 41.4 (18.8) years.	Single 250-mL intravenous infusion of 7.5% hypertonic saline in 6% dextran 70 (HSD; RescueFlow Bio-Phausia AB, Stockholm, Sweden) (n=31) vs. 250mL of 0.9% isotonic normal saline (n=33) (NS).	Follow up 48 hours.	Overall mortality rate was 16%. No significant differences between both groups. GOS score HSD vs. NS: 3.3±1.4 vs. 3.3±1.4, p=0.87. DRS score: 3.0±4.3 3.9±4.6, p=0.26.	"Pre-hospital resuscitation with HSD is associated with a reduction in serum S100B, NSE, and MBP concentrations, which are correlated with better outcome after severe TBI."	Data suggest the lowest biomarker levels were seen in survivors resuscitated with HSD and patients with high biomarker levels were seen in NS resuscitated patients with fatal outcomes.

Bulger 2010 (score = 7.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	Sponsored by the National Heart, Lung, and Blood institute. No COI.	N=1331 with blunt trauma, Glasgow Coma Scale score≤8.	Mean±SD age Saline/dextran: 38.5±18.6 years, hypertonic saline: 38.6±17.3 years, Normal saline: 39.5±19.2 years.	A single 250ml bolus of: 7.5% saline/6% dextran 70 (hypertonic saline/dextran) (N=373) vs. 7.5% saline (hypertonic saline) (N=355), vs. 0.9% normal saline (N=603).	Follow up: 6 months.	No differences between groups for initial ICP or decreased cerebral perfusion pressure over first 12 hours. Survival at 28 days: 74.3% saline/dextran vs. 75.7% hypertonic saline vs. 75.1% normal saline, p=0.88.	"Among patients with severe TBI not in hypovolemic shock, initial resuscitation with either hypertonic saline or hypertonic saline/dextran, compared with normal saline, did not result in superior 6-month neurological outcome or survival."	Data suggest hypertonic resuscitation with either hypertonic saline or hypertonic saline/dextran not superior to normal saline for neurological outcomes or survival at 6 months.

Morrison 2011 (score = 6.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	Sponsorship, in part from the DRDC grant no. w7711-027801/001/TOR (Government of Canada). No mention of COI.	N=107 with head injured, blunt trauma adult patients with a Glasgow Coma Scale of <9.	Mean±SD age: HSD 46±21years vs. 43±21 years.	A single dose of 250mL of hypertonic saline and dextran (HSD) (n=50) Vs. Control group receiving 250 mL normal saline (NS) intravenously (n=57).	Follow up for 12 months.	Median disability rating scale (IQR): HSD vs. NS: 0.5 (0, 2.9) vs. 1.5 (0, 7).	"It is feasible to conduct a prehospital randomized controlled trial with HSD for treatment of blunt trauma patients with head injuries; however, consent for neurofunctional outcomes in this cohort is problematic and threatens the feasibility of definitive trials using these potentially meaningful end points."	High dropout rate (48% completed trial). Data suggest HSD not superior to NS in blunt head injury patients for survival or better neurological outcomes at 30 days.

Vassar 1993 (score = 6.5)	Resuscitation Evidence for Dextran-Saline vs Hypertonic Saline-Dextran vs Lactated Ringers	RCT	Sponsorship, supported in part by a grant from Kabi-Pharmacia, Piscattaway, Nf. COI, George C. Kramer, PhD, and Dr.Holcroft, through the University of California-Davis, Sacramento, hold rights to a patent that describes the use of combined 7.5% sodium chloride and dextran solutions for the resuscitation of patients in shock.	N=194 trauma patients undergoing transport, systolic blood pressure of ≤90 mm Hg.	Mean±SD age: LR 37±18, HS 31±13, HSD 6% 30±12, HSD 12% 34±15 years.	250 mL of: lactated Ringer's (LR) solution Vs. 7.5% sodium chloride (hypertonic saline solution [HS]) vs. 7.5% sodium chloride combined with 6% dextran 70 (HSD-6%) vs. 7.5% sodium chloride combined with 12% dextran 70 (HSD-12%).	Follow-up for 7 days.	Mean±SD change in systolic blood pressure: HSD vs. lactated Ringer's solution group (34±46 vs. 11±49 mmHg, p<0.03).	"Prehospital infusion of 250 mL of 7.5% sodium chloride is associated with an increase in blood pressure and an increase in survival to hospital discharge compared with survival predicted by the MTOS norms. Patients with low baseline Glasgow Coma Scale scores seem to benefit the most from 7.5% sodium chloride resuscitation. Hypertonic saline solution without added dextran 70 is as effective as the more expensive solutions that contain dextran 70."	Data suggest addition of dextran to hypertonic saline solutions is not superior to hypertonic saline alone for resuscitation of trauma patients with SBP <90 resuscitated either in the field or during helicopter transport.

Vassar 1993 (score = 6.0)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	Sponsorship, supported in part by a grant from Kabi-Pharmacia, Piscattaway, Nf. No mention of COI.	N=258 trauma patients transported by ambulance to the hospital, systolic blood pressure of ≤90 mm Hg.	Mean±SD age: NS 31±12, HS 32±15, HSD 31±14 years.	250 mL of: normal saline (NS) (n=84) Vs. 7.5% NaCl (HS, for hypertonic saline) (n=85) vs. 7.5% NaCl in 6% dextran 70 (HSD) (n=89).	32 month trial.	Indicators of survival: ISS ($p<0.0005$), RTS ($p<0.004$) and age ($p<0.01$).	"The addition of a colloid, in the form of 6% dextran 70, did not offer any additional benefit, at least in this setting of rapid urban transport."	Data suggest addition of dextran to hypertonic solution did not add benefit in prehospital resuscitation.

Resuscitation Evidence for Saline

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Roquilly 2008 (score = 7.5)	Resuscitation Evidence for Saline	RCT	COI, Karim Asehnoune and Yvonnick Blanloeil have received honoraria from Braun Medical for public speaking. No mention of sponsorship.	N=42 with severe traumatic brain injury (TBI) (Glasgow Coma Scale score ≤8) on mechanical ventilation within the first 12 hours after brain injury.	Mean (IQR) age: Saline 47 (28-57) years. Balanced 49 (27-77) years	Balanced group (allocated solutions, crystalloids: Isofundine/HES: Tetraspan; B Braun Medical, Melsungen, Germany) (n=21) vs. Saline group (allocated solutions, crystalloids: 0.9% saline solution/HES: HEAfusine, B Braun Medical) (n=21).	Follow-up for 48 hours.	Hyperchloraemic acidosis: 19 (95%) in the saline group vs. 13 (65%) in the balanced group presented with within the first 48 hours (hazard ratio = 0.28, 95% CI: 0.11-0.70; p=0.006.	"[B]alanced solutions reduce the incidence of hyperchloraemic acidosis in brain-injured patients compared to saline solutions. Even if the study was not powered sufficiently for this endpoint, intracranial pressure did not appear different between groups."	Pilot study (small sample). Data suggest balanced fluid resuscitation solutions reduce hyperchloraemic acidosis in brain injured patients compared to saline solution.

Ponsford 2008 (score = 4.5)	Resuscitation Evidence for Hypertonic Saline vs Ringers Lactate with Crystalloid or Colloid or Combination	RCT	No sponsorship or COI.	N=229 with severe blunt head trauma, initial GCS<9 and hypotension.	Mean±SD age: Male 33.8±16.3 years, Female 43.3±23.1 years.	Saline resuscitation: 250 ml intravenous infusion of 7.5% saline [567] vs. conventional fluid management: 250ml intravenous infusion of Ringer's lactate solution. Following infusion, a 10-ml/kg crystalloid, Ringer's lactate solution, or a colloid solution, or both was administered.	Follow up for 6 months.	Median (IQR) Glasgow outcome scale extended at 6 months male vs. female: 3 (1-5) vs. 1 (1-5), p=0.006). No gender differences in GCS score or injury severity scores.	"The study provides no evidence that females fare better than males following severe TBI, suggesting rather that females may fare worse."	Data suggest females do not do better post TBI when compared to males.

Evidence for the Use of Hyperbaric Oxygen Therapy (HBO or HBOT)

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age / Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Miller 2015 (6.5)	Hyperbaric Oxygen Therapy	Case Control	Sponsored by US Army Medical Materiel Development Activity, Naval Health Research Center, Army Contracting Command and US Army Office of the Surgeon General. No mention of COI.	N = 72 with TBI, military personnel. Mild TBI, symptoms at least 4mo. after TBI.	Mean age of 31.4 years. 3 females, 69 males.	Standard Care group, no-chamber sessions (N = 23) vs HBO group plus TBI care, assigned intervention (N = 24) vs Sham group plus TBI care, assigned intervention (N = 25).	Follow up time not mentioned	The group randomized to no supplemental chamber intervention showed no improvement during the 3-month observation period. The HBO group improved symptomatically with a mean change score of 1.2 (p = 0.04) on the RPQ-3 scale and 0.5 (p = 0.008) on the total RPQ. The sham group also improved with a score of 1.5 (p = 0.04) on the RPQ-3 scale and 5.4 (p = 0.008) on the total RPQ.	"Among service members with PCS, HBO showed no benefits over an air sham compression procedure, but symptoms in both groups improved compared with mTBI care without supplemental chamber interventions."	Outcome measures derived from questionnaire. Data suggest lack of efficacy of hyperbaric oxygen on post-concussion symptoms when compared to sham suggesting any observed improvements were not oxygen medicated.
Walker 2014 (6.0)	Hyperbaric Oxygen Therapy	RCT	Sponsored by a Defense Advanced Research Projects Agency grant, US Navy Bureau of Medicine and Surgery for contract funding temporary duty requirements, and the US Army Medical Material Development Activity for	N=60 Marine patients with combat-related mild TBI and PCS persisting for 3 to 36 months	Mean age: 23.2±2.9 5 years; 60 males, 0 females	2.0 ATA Group: (n=21) breathed 10.5% oxygen (balance 89.5% nitrogen) at 2.0 ATA vs 1.5 ATA Group: (n=18) the 1.5-ATA oxygen group breathed 75% oxygen (balance 25% nitrogen) at	Follow up at baseline and 10 weeks	No differences between groups were observed in WAIS-III Working memory index, Stroop, BVMT-R Delayed Recall total, or BVMT-R Recognition discrimination index. Post hoc t-test showed that 1.5 ATA group recognition total hits compared to 2.0 ATA group was p=0.006 and p=.035 compared to Sham group.	"These results do not support the use of HBO2 to treat cognitive, balance, or fine motor deficits associated with mTBI and PCS."	Data suggest lack of efficacy. No benefit on either cognitive or psychomotor performance measures compard to sham.

			end-of-study contract funding. Drs Franke's and Walker's efforts were additionally supported, in part, through contracts from the Defense and Veterans Brain Injury Center. No COI.			2.0 ATA vs Sham Group: (n=21) the 2.0-ATA oxygen group breathed pure oxygen (0% nitrogen) at 2.0 ATA				
Rockswold 2013 (score=5.5)	Hyperbaric (HBO2) & Normobaric Hyperoxia (NBH)	RCT	Sponsored by the National Institute of Neurological Disorders and Stroke Hyperbaric and Normobaric Oxygen in Severe Brain Injury Grant.	N=42 patients with severe TBI with GCS at or less 8 after resuscitation. Randomized within 24 hrs of injury.	Mean age 65; 33 males, 9 females.	Group 1 (N=20) received HBO2/NBH treatment which consisted of 100% FiO2 for 60 min at 1.5 atmospheres absolute (ATA) followed by 3 hours of 1.0 ATA vs. Group 2 (N=22) received standard care (not detailed)	Follow up at baseline, and 6 months.	Mortality rate group 1 vs group 2 at 6 months: 16% vs 42% (p=0.0482). Number with Favorable outcome on Glascow Outcome Scale (GOS), group 1 vs 2: 14-19 (74% vs 8/21 (38%) (p=0.0239).	"The combined HBO2/NBH treatment significantly improved markers of oxidative cerebral metabolism in relatively uninjured brain tissue but, importantly, also in pericontusional tissue. The combined HBO2/NBH treatment reduced intracranial hypertension and thereby decreased the therapeutic intensity of treatment of intracranial hypertension."	Data suggest that combination therapy of HBO2/NBH is superior to either HBO2 or NBH alone for improving markers of oxidative metabolism, reducing intracranial hypertension and cerebral toxicity.
Rockswold 1992 (5.5)	Hyperbaric Oxygen Therapy	RCT	Sponsored by the Minneapolis	N = 168 with acute severe head injury	Mean age of 31.5	Hyperbaric oxygen – compression	2 weeks	Mean ± SD peak ICP in each treatment group: hyperbaric oxygen and	"Hyperbaric oxygen treatment dramatically reduced	Data suggest HBO did not increase numbers of

			Medical Research Foundation. No mention of COI.	(Glasgow Coma Scale score of 9 or less) admitted to a Level I trauma center.	years; 125 males and 43 females.	, 100% oxygen to 1.5 atm absolute (ATA) at a rate of 1 psi/min for 60 minutes every 8 hours for 2 weeks or until brain dead or could consistently respond to commands intracranial pressure (ICP), collected every 15 minutes during the 60-minute treatment and after hourly for 7 hours (N = 84) vs Controls ICP collected every hour (N = 84).		myringotomy (22.1±11.7) v. only hyperbaric oxygen (33.0±20.6), p<0.05) v. control (30.3±24.3), p < 0.05. Patient mortality data at 12 months: hyperbaric oxygen 17% v. control 32%, (p = 0.04). Favorable outcome at 12 months: NS.	the mortality rate among the severely head-injured patients assigned to receive it."	patients with favorable outcome defined by these authors as good recovery and moderate disability and there was no significant difference between groups. However the HBO treated groups had increased survival (mortality was 17% in HBO group vs. 34% in control group).
Rockswold 2010 (4.5)	Hyperbaric Oxygen Therapy	RCT	Sponsored by Minneapolis Medical Research Foundation Bridging Fund,	N = 74 with severe traumatic brain injury (TBI), GCS score ≤ 8 after	Mean age of 35 years; 58 males and 11 females.	HBO_2, 100% Fi02 (fraction of inspired oxygen) delivered for 60 minutes at 1.5 ATA	24 -hours	Cerebral blood flow (CBF): for 6 hours after HBO2 - elevated by 26% vs controls, (p = 0.0061) At 6 hours after treatment, cerebral metabolic rate of oxygen	"Hyperbaric O2 has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to	Data suggest HBO had a significantly better posttreatment effect compared to normobaric hyperoxia (NBH).

			National Institute of Neurological Disorders and Stroke, and the Western Family Foundation. No mention of COI.	resuscitation at a Level I trauma center.		for 3 treatments (N = 26) vs Controls or normobaric hyperoxia or (NBH), 100% Fi02 given for 3 hours at 1.0 ATA for 3 treatments (N = 21) vs Standard care (N = 22).		(CMRO2): increased by 32% for HBO2 vs controls (p = 0.0103). After 6 hours ventricular CSF lactate levels, decreased in the NBH vs controls, (p < 0.05). At 5 hours; dialysate lactate levels: significantly decreased by 13% in HBO2 vs controls, (p = 0.0170). NBH levels decreased by 7% vs controls, NS. Microdialysate lactate/pyruvate (L/P) ratios: post treatment decreased by 10% for HBO2 (p < 0.0001) and by 3% for NBH, (p = 0.0037) vs controls. Intracranial pressure (ICP): HBO2 was lower than control after treatment until the next treatment (p = 0.0010). TIL score: decreased from pre to post treatment for HBO2 compared to control, (p = 0.0006).	procude a brain tissue PO2 ≥ 200 mm Hg."	ICP was not reduced in NBH group but was treated less rigorously in HBO group.
Ren 2001 (4.0)	Hyperbaric Oxygen Therapy	RCT	No mention of sponsorship or COI.	N = 55 with severe brain injury (SBI), Glasgow Coma Scale (GCS) ≤ 8.	Mean age of 35.3 years; 42 males and 13 females.	HBO for 40-60 minutes with 10 minute breaks each time, 10 times of the treatment equaled 1 therapy course; total 3-4 courses of treatment (N = 35)	6 - months	GCS score after 3 courses: treatment group was higher than control group, p<0.01. Glasgow Outcome Scale (GOS) prognosis evaluated 6 months after injury: good recovery or mild disability (29 treatment patients v. 6 controls), p<0.01; middle-severe disability (6 treatment patients v. 13 controls), p < 0.001.	"[H]BO treatment benefits recovery of brain function, improves prognosis, GCS, BEAM and GOS and reduces the mortality rates of SBI patients."	Data suggest HBO improved GCS, BEAM and GOS in severely brain injured patients.

						vs Control receiving dehydrating, cortical steroid and antibiotic therapy (N = 20).				
Rockswold 2001	Hyperbaric Oxygen Therapy	RCT	Sponsored by Grant to Dr. Rockswold from the National Institute for Neurological Disorders and Stroke. No mention of COI.	N = 37 with closed head brain injuries.	Mean age of 36 years. 10 females, 27 males	HBO group, 100% oxygen, 1 psi/minute for 15 minutes (N = 32) vs Class A group (N = 5).	24 hours up to 5 more days.	AVDO2 measurements were compared by both groups. There was significant difference between values for Session 1 and the rest of the sessions. Both before and after treatment values for session 1 were higher when compared to other sessions (p = 0.042). Intracranial pressure values higher than 15 mmHg were decreased 1 hour and 6 hours after HBO.	"The increased CMRO2 and decreased CSF lactate levels after treatment indicate that HBO may improve aerobic metabolism in severely brain injured patients."	Not an RCT. Data suggest improved aerobic metabolism in severely brain injured patients may be the result of shorter but more pregnant HBO treatments which may successfully decrease CSF lactate and increase CMRO2.

Evidence for the Use of TPN in TBI Patients

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Acosta-Escribano 2009 (score=4.0)	Gastrointestinal Complications	RCT	No mention of sponsorship or COI.	N=104 patients with Closed Head Injury.	Mean age: 38.4±19.5 years. 90 males, 14 females.	TPF: Transpyloric feeding (N=50) given diet of 25 kcal kg^{-1} day^{-1} for 30 days. GF: gastric feeding (N=54) given diet of diet of 25 kcal kg^{-1} day^{-1} for 30 days.	30 days	Mean efficacious volume of diet for TPF vs GF, (92±7 vs. 84±15% $p < 0.01$)TF patients had a (14%) rate of Gastrointestinal complications. GF group had a (27%) rate. (OR: 0.2, 95% CI 0.06–0.4; $p = 0.001$). TPF patients had a (7%) rate of increased gastric residuals. GF group had a (28%) rate. (OR 0.2, 95% CI 0.04–0.6; $p = 0.003$).	"Enteral nutrition delivered through the transpyloric route reduces the incidence of overall and late pneumonia and improves nutritional efficacy in severe TBI patients."	Data suggest that the TPF-TBI group experienced improved nutritional efficacy and less overall as well as late onset pneumonia compared to the GF-TBI group

Evidence for Enteral Nutrition in TBI Patients

Taylor 1999 (score=4.0)	Enteral Nutrition	RCT	Sponsored, in part, by the South and West Research and Development Directorate, Bristol, UK. No	N=82 patients suffering with head injury and requiring mechanical ventilation.	Median age group 1, 34, group 2, 28; no mention of sex.	Group 1 (N=4) patients received standard enteral nutrition (EN) initially at estimated metabolic rate vs Group 2 (N=41) patients received	Follow-up at baseline, 1 week, 3 months, and 6 months.	Percentage of energy & nitrogen, at 1 week, group1 vs group 2: 59.2% vs 36.8% (p=0.008) & 68.7% vs 37.9% (p<0.001). Good neurological outcome at 3 months post injury, group 1 vs group 2: 61% vs 39% (p=0.08), risk ratio 1.6 (0.99-2.5).	"In conclusion, enhanced EN increased the percentage of estimated energy and nitrogen requirements delivered during the first week after head injury. This improvement in EN appears to speed up	Data suggest a trends toward early EN accelerating recovery in head injured patients.

			mention of COI.			EN at 15 mL/hr initially and increase by 15 mL/hr until estimated energy and nitrogen needs met.			neurologic recovery but does not change the ultimate outcome. In addition, enhanced EN reduces the number of patients suffering infective and total complications."	

Evidence for the Use of Hyperventilation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Muizelaar 1991 (7.0)	Hyperventilation	RCT	Sponsored by grant from the National Institutes of Health. Additional support provided by the Richard Roland Reynolds Neurosurgical Research Laboratories and the Lind Lawrence Fund. No mention of COI.	N = 113 with TBI.	Median age 27 / 26 / and 25 for Control / HV + THAM / and Controls; 78 males and 35 females.	Hyperventilation or HV group (N = 36) vs Hyperventilation or HV + Buffer Tromethamine or THAM group (N = 36) vs Control group or normoventilation (N = 42)	3, 6, and 12 months	At 12 months, fewer patients with favorable outcome in HV group vs control, ($p < 0.05$). At 12-months, 34% of the controls died vs 25% in the HV groups. HV group fared worse than the corresponding control group, ($p < 0.03$). Hourly ICP average was below the treatment threshold of 25 mm Hg for all groups during the 5-day period of observation. Those treated with HV + THAM exhibited the most stable ICP course with minimal variability vs control and HV groups.	"When sustained hyperventilation becomes necessary for ICP control, its deleterious effect may be overcome by the addition of THAM."	Data suggest that in severely head injured patients, sustained, hyperventilation may become deleterious and be decreased by addition of THAM.
Bourgoin 2003 (7.0)	Hyperventilation	RCT	No mention of sponsorship or COI.	N = 25 with severe head injury.	Aged 16-75 years, 19 males and 6 females.	Sedation with a continuous infusion of ketamine-midazolam (N = 12) vs Continuous infusion of sufentanil-midazolam (N = 13).	4-days	The average infusion rates during 4-days of sedation: 82 ± 25 mg-kg $^{-1}$ min $^{-1}$ ketamine and 1.64 ± 0.5 mg-kg $^{-1}$ min $^{-1}$ midazolam in the ketamine group and 0.008 ± 0.002 mg-kg $^{-1}$ - min $^{-1}$ sufentanil and 1.63 ± 0.37 mg-kg $^{-1}$- min $^{-1}$ midazolam	"The results of this study suggest that ketamine in combination with midazolam is comparable with a combination of midazolam-sufentanil in maintaining intracranial pressure and cerebral perfusion	Data suggest comparable efficacy.

								in the sufentanil group. The number of the intracranial pressure elevations similar in both groups. Heart rate values were significantly higher in the ketamine group on therapy days 3 and 4, ($p < 0.05$).	pressure of severe head injury patients placed under controlled mechanical ventilation."	
Wolf 1993 (4.5)	Hyperventilation	RCT	Sponsored by grant from the National Institutes of Health. Mo mention of COI.	N = 149 with acute head injury.	Aged 16-75 years, 123 males and 26 females.	Tromethamine or THAM group, 0.3-M solution (N = 73) vs Control group received intravenous electrolyte solution (N = 76).	3, 6 and 12 months	Day 4, pCO_2 lower vs those in THM group, ($p < 0.005$). At 3 months, 47.4% and 35.6% THAM-treated patients had good outcomes, and only 40% of the posturing patients had good results vs 66% of those with a best motor response score of 4 or 5, ($p < 0.05$). First 48 hours – 18.2% were above 20 mm Hg in the THAM group vs 34.2% in control, ($p < 0.05$).	"[T]HAM ameliorates the deleterious effect of prolonged hyperventilation, may be beneficial in ICP control, and warrants further study as to the dose and timing of administration".	Data suggest addition of THAM in severely head injured patients may be of benefit in the control of ICP thus reducing the deleterious effect of prolonged hyperventilation.

Evidence for the Use of Induced Hypothermia

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Harris 2009 (7.0)	Induced hypothermia	Prospective RCT	No COI. No mention of sponsorship.	N = 25 adults with severe traumatic brain injury.	3 female, 22 male Mean age 35.4 ± 17.3 years	Treatment group patients received a cooling cap and were treated with selective crebral hypothermia for 24 hrs. then rewarmed over 24 hrs (N = 12) vs. Control group patients who did not receive a cooling cap. (N = 13).	Data collected every 15 mins for the first 2 hrs of treatment and then every hour for 70 more hrs 28 days	After hour 3, the treatment group had a significantly lower temperature than the control group (P < 0.05) at all time points except for hours 4 (P = 0.08) and 6 (P = 0.08). Only 2/11 patients in the treatment group achieved the target temperature of 33°C. There was no significant intergroup difference in mortality rate or in time to death.	"[T]he Discrete Cerebral Hypothermia System cooling cap is not beneficial for the management of TBI."	Small sample. Data suggest groups equal (in) efficacy.
Andrews 2015 (7.0)	Induced Hypothermia	RCT	Supported by the National Institute for Health Research Health Technology Assessment Program, the European Society of Intensive Care	N = 387 with TBI, intracranial-pressure > 20 mm HG for at least 5 minutes within 10 days post-injury	No gender distribution described Mean age for control group 36.7 ± 14.9 years, mean age for hypothermi	Control group – mannitol, hypertonic saline, inotropes (keep cerebral perfusion pressure ≥ 60 mm Hg) (n = 192) Vs. Hypothermia	28 days post-admission, 6 months	Adjusted OR for GOS-E score = 1.53, (95% CI 1.02-2.30, P=0.04), pointing towards a more negative outcome in hypothermia group compared to control.	“In patients with an intracranial pressure of more than 20 mm Hg after traumatic brain injury, therapeutic hypothermia plus standard care to reduce intracranial	Open label study. Enrollment stopped due to safety concerns in 2014. Some data suggest lack of efficacy.

			Medicine, the University of Edinburgh and NHS Lothian. Andrews and Rhodes received lecture fees from C. R. Bard and Integra LifeSciences.		a group 37.4 ± 15.4 years	group – same treatment options as control group along with induced hypothermia therapy (n = 195)		Favorable outcome (GOS-E score 5-8) in 26% of hypothermia group, 37% of control group (P=0.03).	pressure did not result in outcomes better than those with standard care alone."	
Clifton 2011 (6.5)	Induced hypothermia	RCT	Funded by grant from the National Institute of Neurological Disorders and Stroke. No COI.	N = 97 with severe brain injury	No gender distribution described Mean age hypothermia group 26 ± 9 years, mean age normothermia group 31 ± 11	Normothermia group patients were maintained at 37°C (N = 45) vs. Hypothermia group patients were maintained at 35°C (N = 52)	2 weeks, 4 weeks, 3 month, and 6 months post-injury	Outcome was poor in 31 of 52 patients in the hypothermia group and 25 of 56 in the normothermia group (relative risk [RR] 1.08, 95% CI 0.75-1.53; P = 0.67). Twelve patients died in the hypothermia group and 8 died in the normothermia group (RR 1.30, 95% CI 0.58-2.52; P = 0.52). Patients in the normothermia group needed more interventions for raised intracranial pressure (P = 0.002) and had	"We found no significant difference in outcome in patients treated with hypothermia compared with those treated with normothermia; however, patients in the hypothermia group did have a signifi cantly higher number of episodes of increased intracranial pressure than those in the normothermia group."	High dropout rate for final 6 month analyses. Track terminated early for futility.

								more interventions in total (P = 0.0006). Patients in the hypothermia group seemed to have negative cumulative fluid balancs less often (P = 0.08) and had higher cumulutive fluid balances (P = 0.01).		
Maekawa 2015 (6.0)	Induced Hypotherm ia	RCT	No COI. Supported by grants from the Japanese Ministry of Health, Labour and Welfare and the Japanese Human Science Association 2002-2004.	N = 148 with severe TBI, GCS 4-8	45 female, 103 male Mean age for hypothermi a group 39±19 years, fever control group 39±18 years	Therapeutic hypothermia (32-34°C) (n=98) Vs. Fever control (35.5-37°C) (n=50)	6 months	53% of those in therapeutic group and 48% of those in fever control group had poor neurological outcomes at six months. Likelihood of poor neurological outcome (relative risk RR = 1.24, 95% CI 0.62-2.48) and likelihood of mortality (RR 1.82, 95% CI 0.82-4.03) were not statistically significant between the groups.	"Prolonged TH (≥72 h) for patients with severe TBI together with tight hemodynamic management and slow rewarming (<1.0°C/day) did not improve neurological outcomes or mortality compared with strict fever control. However, the CIs for the primary outcome were wide, and do not exclude either benefit or harm for MTH.	Data suggest that tight hemodynamic control and gradual rewarming with prolonged hypothermia did not increase outcomes or decrease mortality vs strict temperature control.

Marion 1993 (5.5)	Induced hypothermia	Preliminary RCT	No mention of COI. Funded by grants from the Brain Trauma Foundation and the National Institute of Neurological Disorders and Stroke	N = 40 with a severe closed head injury.	6 female, 34 male Mean age for normothermia group 32.1 years, hypothermia group 31.9 years	The hypothermia group was cooled to a brain temperature of 32 to 33°C using cooling blankets and cold saline gastric lavage maintained for 24 hrs and rewarmed to 37 to 38°C over 12 hrs. (N = 20) vs. the normothermia group was maintained at 37 to 38°C (N = 20).	The last follow-up was at 3 months.	During the cooling period, the hypothermia group had a significantly lower mean ICP ($P < 0.004$). In the first 36 hrs. after injury revealed that the incidence of hourly ICP measurements over 20 mm Hg was significantly lower in the hypothermia group (13% of time) vs. normothermia group (25% of time, $P < 0.001$). In both groups the cerebral metabolic rate for oxygen declined in the first 5 days after injury, but the decline was greater in the normothermia gorup ($p < 0.001$). During hypothermia, the global cerebral blood flow values in the hypothermia group were	"[H]ypothermia significantly reduces ICP and CBF during the period of cooling and that no rebound increase occurs in these parameters after rewarming."	Data suggest a trend towards better outcomes with hypothermia.

								significantly lower vs normothermia (P < 0.001).		
Marion 1997 (5.5)	Induced hypothermia	RCT	No mention of COI. Funded by grant from the National Institute of Neurological Disorders and Stroke.	N = 82 with sever closed head injuries.	13 female, 69 male Mean age for hypothermia group 31 ± 12 years, normothermia group 35 ± 15 years	Moderate hypothermia group was cooled using cooling blankets to a rectal temperature of 33°C and was kept between 32-33°C for 24 hrs. Then was rewarmed passively for the 12 hrs. to 37-38.5°C at a rate no greater than 1°C per hr. (N = 80) vs. Normothermia group was kept above 37°C (N = 42). All patients were given continuous infusions of vecruonium bromide, 10 mg/hr and fentanyl citrate, 50-100 µg/hr.	Follow-ups were at 3, 6, and 12 months.	Three months after injury 15 (38%) in the hypothermia group had a score on the Glasgow Outcome Scale of 4 or 5 as compared with 7 (17%) in the normothermia group (P = 0.03). Patients with more sever coma scores benefited from hypothermia more than did patients with coma scores of 3 or 4 in the Glasgow coma, whereas those with scores of 5-7 did. Among the patients with the higher scores, 16 (73%) in the hypothermia group and 9 (35%) in the normothermia group had a good outcome at 6 months (P = 0.008).	"[T]reatment with moderate hypothermia (a temperature of 32 or 33°C) for 24 hours, initiated soon after severe traumatic brain injury, significantly improved the outcomes at three and six months in patients without flaccidity or decerebrate rigidity (those with Glasgow coma scores of 5 to 7) on initial evaluation."	Data suggest there may be improved GCS and neurological outcomes from the use of moderate hypothermia for 24 hours post injury.

Mayer 2004 (5.5)	Induced hypothermia	RCT	Funded by grant from Medivance Inc. (SAM). Mayer received speaking honoraria from Medivance, Inc.	N = 53 admitted to the Columbia-Presbyterian Medical Center Neurologic Intensive Care Unit.	30 female, 17 male Mean age for Arctic Sun group 54 ± 15 years, SubZero group 51 ± 16 years	Group 1 treated with an artic sun termperature management system keeping the core body temp at 37°C (N = 26). Vs. Group 2 treated with a conventional water-circulating cooling blanket placed over the patient with the blanket set at 4°C (N = 27).	The last follow-up was at discharge of the patient.	The artic sun resulted in a 75% reduction in fever burden compared with the sub-zero blanket, from 16.1 to 4.1°C-hrs (P = 0.001). The artic sun also reduced the time febrile by 81%, which resulted in a 20 times increase in normothermic, a 36% increase in the likelihood of attaining normothermia, and a 73% reduction in time to attain normothermia. Minute to minute measurement of body temperature averaged over 15-min intervals were lower in the artic sun group (P = 0.008).	"The Arctic Sun Temperature Management System is superior to conventional cooling-blanket therapy for controlling fever in critically ill neurologic patients."	Data suggest Artic sun temp Mgt system may be superior to conventional cooling blanket therapy.
Qiu 2007 (5.0)	Induced hypothermia	RCT	Funded by the Health Bureau of Hangzhou, Zhejiang Province. No	N = 80 with severe traumatic brain injury.	28 female, 52 male Mean age hypothermia group	Mild hypothermia group (N = 40) vs.	The last follow-up was at 1 year after treatment.	The ICPs of the hypothermia group at 24, 48, and 72 hrs were significantly lower (about	"[T]herapeutic mild hypothermia not only could reduce the ICP and increase the	Data suggest mild therapeutic hypothermia in severe TBI post craniectomy

			mention of COI.		41.3 years, control group 40.2 years	Control group treated with normothermia (N = 40).		10%) than those of the normothermia control group at the same time point (mild hypothermia: 23.49 ± 2.38, 24.68 ± 1.71, and 22.51 ± 2.44 mm Hg; control; 25.87 ± 2.18, 25.90 ± 1.86, and 24.57 ± 3.95 mm Hg, respectively (P = 0.000 and P = 0.006, respectively). No differences were found between the groups for overall neurologic outcomes at 1 yr. There was a difference found favoring the hypothermia group at in favorable neurologic outcome (70.0% vs. 47.5%, P = 0.041: odds ratio, 2.58; 95% confidence interval, 1.03-2.46). The mortality rate was 22.5% in	serum SOD levels, but also improve the neurologic outcome in patients with severe TBI after craniotomy."	may be beneficial.

								the hypothermia group and 32.5% in the control group (odds ratio, 1.66; 95% confidence interval, 0.61-4.48).		
Liu 2006 (5.0)	Induced hypothermia	Preliminary RCT	No COI. No mention of sponsorship.	N = 66 with severe traumatic brain injury.	24 female, 42 male Mean age for SBC group 40.2 years, MSH group 39.6 years, and Control group 42.3 years	Selective brain cooling (SBC) group was treated using a cooling cap around the head in which 4°C water was circulating keeping the brain temperature at 33-35°C (N = 22) vs. Mild systemic hypothermia (MSH) group was treated using a cooling blanket and refrigerated ice bags maintaining the rectal temperature at 33-35°C (N = 21) vs. Normothermia group was treated with the same conventional	The last follow-up was at 2 years.	The ICP values of the groups receiving hypothermia were significantly lower 24, 48, and 72 h after injury than those of the control group (P < 0.05), no differences were seen between the hypothermia groups. The serum SOD level increase of the two hypothermia groups on days 3 and 7 were 45% and 76% in the SBC group and 60% and 86% in the MSH group on the respective days (Day 3 r = 0.948 in the SBC group and 0.965 in the	"[S]BC, as applied in this preliminary study – an easy and noninvasive method of producing hypothermia – cannot only reduce elevated ICP and increase serum SOD levels, but can also improve the prognosis without severe complications in patients with severe TBI."	Data suggest SBC may reduce ICP and increase SOD levels and may improve prognostic outcomes in severe TBI patients.

						treatment as the other groups without hypothermia (N = 23)		MSH group and day 7 r = 0.968 in the SBC group and 0.906 in the MSH group, respectively). The frequency of mild or no disability was significantly higher in the normothermia group (P < 0.05).		
Clifton 2012 (4.5)	Induced hypothermia	Post hoc/RCT	Funded by grants from the National Institute of Neurological Disorders and Stroke. No mention of COI.	N1 = 392 with severe brain injury and N2 = 97 with severe brain injury	No gender distribution described for either trial Age distribution for trials: N1 - Mean age of five centers of recruitment: 31 ± 12, 32 ± 13, 32 ± 14, 30 ± 12, 33 ± 11 N2 - Mean age hypothermia group 26 ± 9 years, mean age normothermia group 31 ± 11	Patients treated with standard management and normothermia (N = 264) vs. Patients treated with standard management and hypothermia (N = 128)	Physiological variables were recorded hourly for the first 96 hours 6 months	The first 24 hrs had significantly fewer poor outcomes than those treated with normothermia (hypothermia, 5/15 (33%) vs normothermia 9/13 (69%) relative risk 0.44, 95% CI 0.22-0.88; P = 0.02). Outcome was poor in 14/31 (45%) of patients reaching 35°C within 1.5 hrs of surgery, in 14/23 (61%) reaching 35°C more than 1.5 hrs of surgery, and in 35/58 (60%) of patients in the normothermia	"Induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 hours thereafter may improve outcome of patients with hematomas and sever traumatic brain injury."	Data suggest use of hypothermia (35 °C) before or immediately after craniotomy may improve outcomes.

								group (relative risk 0.74, 95%, CI 0.49-1.13; P = 0.16		
Clifton 2001 (4.5)	Induced hypothermia	RCT	Funded by grant from the National Institutes of Health (For Clifton and Choi). No mention of COI.	N = 392 with severe brain injury	No gender distribution described. Mean age of five centers of recruitment: 31 ± 12, 32 ± 13, 32 ± 14, 30 ± 12, 33 ± 11	Patients treated with standard management and normothermia (N = 264) vs. Patients treated with standard management and hypothermia (N = 128)	6 months	No relation was seen between the time to reach the target temperature and the outcome. No differences were seen in mean intracranial pressure for between the groups. In the first 96 hours, the percentage of patients with an intracranial pressure of more than 30 mmHg was lower in the hypothermia group (P = 0.02). More patients in the hypothermia group had serum creatinine concentrations greater than 2.5 mg per deciliter (P = 0.05). Ten percent of the hypothermia patients had critical	"Treatment with hypothermia, with the body temperature reaching 33°C within eight hours after injury, is not effective in improving outcomes in patients with severe brain injury."	Data suggest treatment of TBI patients with hypothermia (temps reaching 33° within 8 hours post injury) does not improve outcomes.

								hypotensionn, while only 3% had it in the normothermia group. (P = 0.01). Mortality was 28% in the hypothermia group and 27% in the normothermia group. Death in both groups was greater in patients over 45 years old (P = 0.001). There were more poor outcomes in those over 45 in the hypothermia group than the normothermia group (88% vs. 69%, P = 0.08).		
Shiozaki 2001 (4.5)	Induced hypothermia	Prospective RCT	No mention of COI. Funded by grant from the Ministry of Health and Welfare in Japan.	N = 91 with severe head injury.	25 female, 66 male No mean age given. Majority of participants in HT group between ages 10-39 (27 total, 60%), in NT group between ages 40-69	Mild hypothermia group (HT group) kept at 34°C with cooling blankets above and below the patient and with nasogastric lavage with iced saline (N = 45) Vs. Normothermia group (NT group) kept at 36.5-	Follow-up was at 3 months after the injury.	Five patients died in the HT group and 2 died in the NT group due to uncontrollable intracranial hypertension. In 21/45 (47%) of the patients in the HT group and in 27/46 (59%) of the patients in the NT group a favorable	"Mild hypothermia should not be used for the treatment of severely head injured patients with low ICP because this therapy conveys no advantage over normothermia in such patients."	Poor replication. Data suggest mild hypothermia should not be used in severe TBI patients with low ICP.

					(25 total, 54%)	37.5°C by surface cooling for 5 days (N = 46).		outcome was achieved (P = 0.251). No overall effect was seen by the GOS scores at 3 months.		
Zhao 2011 (4.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 81 with traumatic brain injury.	22 female, 59 male Mean age for normothermia group 37.5 ± 15.2 years, for hypothermia group 36.9 ± 14.8 years	Normothermia group (N = 41) Vs. Mild hypothermia group kept at 32.7°C for 72 hrs. (N = 40).	Follow-up was at 3 months after the injury.	The intracranial pressure in the hypothermia group was lower than normothermia group at 72 hrs (P < 0.01). Glucose and lactate levels were lower in the hypothermia group (P < 0.05). More patients in the hypothermia group had a favorable recovery (GOS 4-5, 75.0% vs. 51.2%, P = 0.038). The hypothermia group also had a lower percentage of poor recovery (GOS 2-3, 25.0% vs 48.8%, P = 0.038). Glucose was inversely correlated with the GOS scores in hypothermia	"[H]yperglycemia after severe TBI was associated with a poor neurologic outcome, whereas the predictive value of blood lactate level requires further investigation. Mild hypothermia therapy for 72 hours improves functional recovery 3 months after the injury, and reduction in blood glucose may be partly responsible for the favorable outcomes of the hypothermia therapy."	Data suggest hypothermia may lower blood glucose thus improving TBI outcomes.

								group (r = -0.562, P < 0.01) and in normothermia group (r = -0.677, P < 0.01). The same was seen for lactate levels in the hypothermia group (r = -0.302, P < 0.05) and in normothermia group (r = -0.366, P < 0.05).		
Hifumi 2016 (4.5)	Induced Hypothermia	RCT [post-hoc of article upon]	See previous study.	N = 129 with severe TBI	42 female, 87 male Mean age for AIS 3-4 hypothermia group 30, AIS 3-4 fever control 42, AIS 5 hypothermia 24, AIS 5 fever control 11	See previous study. Also classified participants into AIS head score 3-4 (n=78) and AIS head score 5 (51)	See previous study.	TBI-related mortality was significantly reduced in the fever control group compared to the hypothermia group (9.7% vs. 34.0%, P=0.02). In patients with AIS 3-4, there was no significant difference in favorable neurological outcomes between the fever group and hypothermia group (64.5% vs. 51.1%, respectively, p=0.26). No difference in	"Fever control may be considered instead of MTH in patients with TBI (AIS 3-4)."	Post hoc study at 6 months (B-HYPO Study). Data suggest fever control management in MTH TBI patients with (AIS 3-4) may reduce mortality and increase good outcomes.

								mortality or favorable outcome among AIS 5 patients.		
Yan 2001 (4.5)	Induced Hypothermia	RCT	No mention of COI or sponsorship.	N = 44 with severe closed head injury (GCS 3-8)	14 female, 30 male Overall mean age 41.8 years	Groups classified by GCS value: Group A = GCS 3-5 (n=20), Group B = GCS 6-8 (n=24) Randomized into: Hypothermia treatment (32-34°C) (n=10 from A, 14 from B) Vs. Controls (n=10 from A, 10 from B)	4, 24, 48, 72, 96, 120 hours post-injury	Group B – N_{20} amplitude in SLSEP and I/V amplitude in BAEP differed significantly between those treated with mild hypothermia treatment and controls ($p<0.05$). Group A – no statistically significant difference in parameters discovered.	"These results demonstrate that mild hypothermia treatment (32-34°C) in the Group B has a significant neuroelectrophysiological effect on severe brain injury. Nevertheless, the effect of mild hypothermia in Group A is not apparent and needs further studying."	Data suggest group B was effected by mild hypothermia as compared to controls but group A did not show an effect.
Smrcka 2005 (4.0)	Induced Hypothermia	RCT	No mention of COI. Supported by grant from the Internal Grant Agency of the Czech Ministry of Health.	N = 72 with severe head injury	21 female, 51 male Mean age overall 41 years	Hypothermia treatment of 34° C for 72 hours (n=37) Vs. Controls (n = 35)	72 hours post-injury, 6 months	Normothermia and primary lesions (n=17): median GCS at admission = 5, mean ICP = 18.9, mean CPP = 73, median GOS = 4 Normothermia and extracerebral hematomas (n=20): GCS = 4, ICP = 16, CPP = 71, GOS = 3	"Hypothermia decreased ICP and increased CPP regardless of the type of brain injury. Hypothermia was not able to improve outcome in patients with primary brain lesions but this pilot study suggests that it significantly improves	Pilot study. Data suggest hypothermia did not improve brain injury outcomes but increased CPP and decreased ICP.

								Hypothermia and primary lesions (n=21): GCS = 4.62, ICP = 10.81, CPP = 78.1, GOS = 4 Hypothermia and extracerebral hematomas (n=14): GCS = 5, ICP = 13.2, CPP = 78, GOS = 5	outcome in patients with extracerebral hematomas."	
Sinz 1998 (4.0)	Induced hypothermia	RCT	No mention of COI. Partially funded by the Charles Schertz Fellowship Grant, Department of Anesthesiology and Critical Care medicine, and by the Laerdal Foundation, the National Institute of Neurological Disorders and Stroke, and the Center for Injury Research and Control, University of Pittsburgh.	N = 39 with a traumatic brain injury.	7 female, 32 male Mean age for normothermia group 39 ± 17 years, for hypothermia group 32 ± 14 years	Hypothermia group kept at 32°C using cooling blankets and nasogastric lavage with iced saline (N = 16) Vs. Normothermia group kept at 37-38.5°C (N = 23).	The last follow-up was at 120 hrs.	Patients who died had higher levels of quinolinic acid versus survivors (P = 0.003) after controlling for the effect of time. An association between time after TBI and increased CSF quinolinic acid was found (P < 0.0001).	"[T]he excitatory neurotoxin, quinolinic acid, markedly increases in eSF after severe TBI in humans and is strongly associated with mortality."	Data suggest quinolinic acid is elevated in the CSF of TBI patients which may be associated with increased mortality.

Aibiki 2000 (4.0)	Induced Hypothermia	Prospective RCT	No mention of COI or sponsorship.	N = 26 with traumatic brain injury (TBI) who have been ventilated.	6 female, 20 male Mean age normothermic group 38 ± 8 years, mean age hypothermic group 34 ± 6 years	Hypothermic group consisted of cooling the patients to 32 to 33°C after being giving vecuronium, midazolam, and buprenorphine. Hypothermia lasted for 3 to 4 days and afterwards the patients were rewarmed at 1°C per day (N = 15) vs. Normathermic group consisted of controlling the patients' body temperature at 36 to 37°C by cooling using the same treatment as the other group. Body temperature control was started 3 to 4 hrs after the injury (N = 11)	The last follow-up was at 6 months.	Arterial thrombaxane (TXB2) increased in both groups on admission, but 6-keto prostaglandin F1α did not increase, however, the hypothermia group eliminated prostanoid differences and permitted an improvement in the imbalance of TXB2 and 6-keto PGF1α. Patients in the hypothermic group showed a significant increase in 6-keto PGF1α levels on day 5 after injury. The arterial internal jugulary bulb differences in TXB2 were suppressed throughout the study only by hypothermia.	"The current results from a limited number of patients suggest that moderate hypothermia may reduce prostanoid production after TBI, thereby attenuating an imbalance of thromboxane A2 and prostaglandin I2."	Data suggest moderate hypothermia may decrease prostanoid production post TBI.
Clifton G 1993 (4.0)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 46 with severe nonpenetrating brain injury and a post	No gender distribution described No mean age listed.	Normothermia group patients were treated with standard management and were kept at 37°C	First 12 hours, 60 hours, 72 hours, 84 hours Three months GOS measured	Heart rate was significanlty lower in the hypothermia only in the second time	"Based on evidence of improved neurologic outcome with minimal toxicity,	Data suggest improved GCS in (GRIMD) groups as compared to (SDIVD) group.

				resuscitation GCS of 4 to 7.	A majority of participants were between ages 15-25 (50%)	with cooling blankets and were given acetaminophen for 80 h after injury (N = 22) vs. Hypthermia group patients treated with standard management and keeping the patients cooled by securely wrapping the patients in cooling blankets set at 5°C. Metocurine 10 mg/h and morphine-sulfate 10 mg/h were given continuously until the patient warmed to a temperature of 35°C (N = 24)		period ($p < 0.001$). Mean arterial pressure (MAP) was significantly different in the two groups only in the third time period with a 13 mmHg lower MAP in the hypothermia group. There was no differences seen in ICP. Cerebral perfusion pressure (CPP) was 16 mmHg lower in the hypothermia group in the third time period with a mean value in normothermia of 80.9 ± 3.42 and in hypothermia 64.96 ± 2.13 mmHg.	we believe that phase III testing of moderate systemic hypothermia in patients with severe head injury is warranted."	
Jiang 2000 (4.0)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 87 with severe traumatic brain injury.	15 female, 72 male Mean age hypothermia group 42.2, mean age for normothermia group 40.6 years	Long-term mild hypothermia group with temperatures at 33-35°C for 3-14 days (N = 43) vs. Normothermia group with	The last follow-up was at 1 year.	At 1 year, the hypothermia had 25.58% (11/43) mortalities and 46.51% (20/43) had a favorable outcome, the normothermia group had 45.45% (20/44)	"The data produced by this study demonstrate that long-term mild hypothermia therapy significantly improves outcomes in	Data suggest that at 1 year TBI patients receiving long term mild hypothermia had significantly better outcomes.

						temperatures at 37-38°C (N = 44).		mortalities and 27.27% (12/44, p < 0.05). On the 7th day the mean ICP for the hypothermia group was 18.9 ± 1.5 mm Hg and 28.13 ± 2.25 mm HG in the normothermia group (P < 0.01).	patients with severe TBI."	
Lee 2010 (4.0)	Induced hypothermia	RCT	No COI. Funded by grant from the China Medical University Hospital (Taichung, Taiwan, Republic of China)	N = 45 with severe traumatic brain injury.	18 female, 27 male Mean age for group A 43.5 ± 16.4 years, group B 44.0 ± 15.1 years, and group C 38.8 ± 18.0 years	Group A was treated with intracranial pressure/cerebral perfustion pressure (ICP/CPP) guided management only (N = 16) vs. Group B was treated with mild hypothermia and ICP/CPP guided management (N = 15) vs. Group C was treated with mild hypothermia and PtiO2 guided with ICP/CPP management (N = 14).	6 months	The highest ICP was observed 72 hrs after injury in Group A and 24-48 hrs in Groups B and C with the values in B and C much less than in Group A (P = 0.0459). The mean ICU stay was significantly longer in Groups B and C with Group A averaging 9 days, Group B 11.33 days and Group C averaging 11.6 days (P < 0.05). The total hospital costs were $5257 in Group A, $5915.35 in Group B, and $5815 in Group C.	"[T]he hypothermia groups reduce elevated ICP earlier than 24 hours after injury, and daily variations of ICP were significantly different among the three treatment groups after the third posttraumatic day."	Poor replication. Data suggest combining a strategy PO2 of hypothermia with guided CPP ICP is beneficial for treating TBI patients.

Idris 2014 (4.0)	Induced Hypothermia	RCT	No COI. Supported by the Short Term Grant of Universiti Sains Malaysia	N = 32 with severe TBI, GCS score 6-7	5 female, 27 male Mean ages of mild cooling group 28.9 years, deep cooling 26.7 years, and control group 45.5 years	Mild cooling (n = 10) Vs. Deep cooling (n = 9) Vs. No cooling (n = 13)	6 months	Patients in the cooling groups had no significantly different outcomes compared to controls. Good GOS scores at 6 months obtained by 63.2% of those in cooling group and by 15.4% of those in noncooling group (P=0.007). 70% of those in mild cooling group had good GOS compared to 15.4% of control (P=0.013) Those within the deep cooling group did not do significantly better compared to controls (P=0.074) and compared to mild cooling (P=0.650).	"This preliminary or pilot study found that direct regional brain hypothermia may have potential benefits in treating the severely head injured patients with initial GCS of 6 or 7. Other than a safe and practicable approach, this direct regional brain cooling therapy may serve as an added therapy for patients who require urgent decompressive craniectomy, irrespective of the underlying etiologies in the future.	Pilot study. Data suggest use of hypothermia in severe TBI patients may be useful.

Evidence for the Use of Family Visits

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Abbasi 2009 (5.5)	Family Visits	RCT	No mention of sponsorship or COI.	N = 50 comatose patients with a head injury. GCS score 6-8, age 18-45 years.	Mean age: Intervention 30.4 (6) VS control 30.4 (7). 172 males total 48 females, groups gender not specified.	Control group received	6 days	GCS of control group/Intervention group day 1: 6.9 (0.9)/7.0 (.08) (p = 0.7500). GCS On the 6th day control/Intervention: 6.8 (1.4)/ 8.8 (0.7) (p = 0.0001).	"The results of the present study provided evidence to support that a regular family visiting program could induce the stimulation of comatose patients."	Data suggest regular family visits may stimulate consciousness in comatose patients 6 days after admission.
Kalani 2016 (4.5)	TBI: Family Visits	RCT	No mention of sponsorship. No COI.	N 64 with GCS score 5-8 age 18-64.	Mean age 37.7. 51 males. 13 females.	Intervention family visits for45 minutes to an hour, patients received touch and auditory stimulations. (N= 32) vs The control group received the usual meeting in accordance with hospital and ICUs rules. Each group tested for level of consciousness 30 minutes before and after treatment (N =32).	2 weeks	GCS score on the 1st Day: intervention group 6.6 (0.9) vs control GCS 6.6 [170], (p = 1.0). GCS score on the 14th day: Intervention group 12.8 (1.6) vs control 7.6 (0.9), (p = 0.001). Difference of GCS scores: Intervention group 6.2 control group 1, (p = 0.001).	"Guided and targeted meetings by the patient's family is effective for improving the level of consciousness in comatose patients."	Cluster randomization. Inclusion criteria of GCS 6-8, but mean scores reported as 1.25-1.33. Data suggest sig. improved level of consciousness at 14 days.

Evidence for the Use of Multimodal Coma Stimulation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Pape 2015 (6.5)	TBI	RCT	Sponsored by the Department of Veterans Affairs, Office of Research and Development, Rehabilitation Research and Development Merit and career development transition award, and Northwestern University's Clinical and Translation Sciences Institute. No COI.	N = 15 in disordered consciousness (DOC).	Mean age 35.1 (11); 12 males and 3 females.	Familiar Auditory Sensory Training or FAST (N = 8) vs Placebo of silence (N = 7).	6-weeks	Mean DOCS; FAST = 13.5 (8.2) vs placebo = 18.9, (15.6). FAST had more CNC gains (p = 0.049, FAST = 1.01, (0.60) vs placebo = 0.25 (0.70). Mixed-effects models CNC findings, (p = 0.002). Treatment effect, based on CNC (d = 1.88, 95% CI = 0.77, 3.00).	"For persons with DOC 29 to 170 days after TBI, FAST resulted in CNC gains and increased neural responsivity to vocal stimuli in language regions."	Data suggest FAST participants had better neural responses to stimuli and CNC improvement compared with placebo.

Megha 2013 (6.0)	Multimodal Coma Stimulation	RCT	No sponsorship or COI.	N = 30 comatose patients with TBI.	Mean age:39.7 years. No mention of gender.	Group A, high frequency group, 5 sessions of multimodal coma stimulation a day, 20 minutes 2 weeks 5 days a week, 5 times a day with a 2 hours in between (N = 10) vs Group B, low frequency group, 2 sessions of multimodal coma stimulation a day for 50 minutes, 5 days a week, 5 cycles of stimulation 50 minutes, 2 times a day (N = 10) vs Group C, control or conventional physiotherapy, including positioning, stretching and passive movement, 2 times a day 5 days a week for 2 weeks, repeated passively 10 times a minute for 2 minutes (N = 10).	2 weeks	Pre Glasgow Coma Scale (GCS) scores between groups / post GCS: A vs B vs C, (p = 0.969) / (p = 0.009). Western Neuro Sensory Stimulation Profile (WNSSP) scores between groups / post WNSSP: A vs B vs C, (p = 0.801) / (p = 0.000). Post GCS comparison group A vs B (p = 0.579), A vs C (p = 0.005), B vs C (p = 0.019). Post WNSSP comparison: A vs B (p = 0.005), A vs C (p = 0.000), B vs C (p = 0.002).	"The data obtained replicates the effectiveness of multimodal coma stimulation in improving the consciousness levels of TBI comatose patients when compared to the control group."	Data suggest increased frequency short duration multimodal stimulation is better than longer duration stimulation or standard BID PT as measured by GCS and Western Neuro Sensory Stimulation Profile scores.
Parveen 2015 (4.5)	TBI	RCT	No mention of sponsorship or COI.	N = 80 comatose patients with TBI.	Age range 15-65; 67 males and 13 females.	Intervention group, auditory stimulation provided by a family member for 10 minutes, twice daily (N = 40) vs Control group monitored at admission (N = 40).	2-weeks	GCS Baseline scores / Day 7 / and Day 14: 5.10 ± 1.37 vs 5.12 ± 1.20 control, p-value not given / 7.26 ± 2.39 vs 5.54 ± 1.75, p = 0.001 / and 8.17 ± 2.06 vs 6.34 ± 2.36, p = 0.004.	"Auditory stimulation by family members appears to be effective in improving level of consciousness in comatose patients with TBI."	High dropout rate. Data suggest early auditory stimulation of comatose patients by family member improves LOC.

Lippert-Gruner (3.0)	Multimodal Coma Stimulation	Prospective Study	Supported by German Federal Government (BMBF-Projekt 01 KO 9517 Verbund Neuro-/Polytrauma Köln) No mention of COI.	N=24 patients	Mean age: 38 years. 19 males, 5 females.	All patients received multimodal coma stimulation and early onset rehabilitation.	12 months	Patients GCS score changed from 5.3 to 7.8 after rehabilitative treatment. Mean CRS score changed from 3.7 to 8.5. Spearman correlation analysis showed significance with GCS score with Barthel index (r=.54; p=.02), with duration of early onset rehabilitation (r=.72; p=.001), and with DRS score (r=.57; p=.01). Duration of coma was significant with Barthel index (r=.47; p=.049), FIM score (r=.50; p=.03), with GOS score (r=.51; p=.03), with duration of early-onset rehabilitation (r=.77, p<.001), and with DRS score (r=.52; p=.03).	"Despite intensive rehabilitation treatment, severe traumatic brain injury is still burdened with significant mortality and morbidity."	2-year follow-up of Gates 2004. Suggest Meniett device associated with reduction in vertiginous symptoms.
Gorji 2014 (1.5)	TBI	RCT	No mention of sponsorship. No COI.	N = 30 coma patients.	Aged 35-44 years and controls 15 – 24; gender not specified.	Intervention group, 10-minutes MP3 voice of a loved one twice a day (N = 15) vs Control group, GCS recorded in the same manner as intervention (N = 15).	About 6-months	Amount of time to reach GCS = 15 $x^2 = 12.96$, ($p < 0.0001$). Averages of consciousness before the 1st day 6.46 (1.53) vs 12.26 (5.53) in the controls.	"Results showed that a highest percentage of subjects in the intervention group were 35 to 44-year-old and in control group age range was 15 to 24."	Sparse methods. Data suggest interventional group (auditory stimulation) improved LOC.

Evidence for the Use of Occupational Therapy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cicerone 2008 (7.0)	Occupational therapy	RCT	Supported by the National Institute on Disability and Rehabilitation Research NO COI.	N = 68 with traumatic brain injury (TBI) recruited from clinical referrals and the community.	Standard Neurorehabilitation group 34.5 ± 12.4 Intensive cognitive rehabilitation group 38.7± 11.1 Gender (M:F) 46:22	Standard neurorehabilitation, includes physical, occupational and speech therapies (N = 34) vs. Intensive Cognitive Rehabilitation, includes communication group, cognitive group and life skills group (N = 34). Both groups received 15 hours of treatment for week for 16 weeks. Primary/ Secondary outcomes; Community integration (CIQ), Life satisfaction (PQOL) / NP functioning, Perceive self-efficacy, community based-employment.	6 months	There were no significant main effects for treatment or condition on the CIQ / PQOL / NP scores / Self – efficacy scores. 74% participant after completion of the study required follow – up treatment. Participants showed improvement on CIQ scores from post treatment to follow – up (p = 0.04).	"Improvements seen after intensive cognitive rehabilitation may be related to interventions directed at the self-regulation of cognitive and emotional processes and the integrated treatment of cognitive, interpersonal, and functional skills."	Data suggest a comprehensive NP rehab plan post TBI improves self perceived quality of life and community functions.as measured by CIQ and PQOL.
Andersson 2007 (5.5)	Occupational therapy	RCT	Supported by Swedish National Board of Health and Welfare, 95–170; The Vardal	N = 395 patients with Mild traumatic brain injuries	Intervention group: 32 years Control group: 34; Gender (M:F) 245:150	Intervention group: 264 patients were allocated to the intervention group, yet only 96	1 year	No statistical differences were found between the intervention	"In this particular MTBI sample, early Active rehabilitation did not change the outcome to a	Data suggest no significant differences between groups.

			foundation,V2000-263, V2002-027, Sweden; The Health and Medical Care Executive Board of the Västra Götaland Region, Sweden; The Trygg-Hansa Insurance Company, Sweden; The ForeningSparbanken Foundation for Scientific Research at Boras and Skene Hospital, Sweden; The Foundation Forenings Sparbanken Sjuhärad, Boräs, Sweden; The Axel Linders Foundation, Alingsäs, Sweden; The Alice Swenzons Foundation for Scientific Research, Boräs, Sweden. No mention of COI.			patients accepted intervention. Out of the 96, 78 patients received occupational therapy Control group: (N=131) received standard care		group and control group in primary effect variables defined by Post concussion symptoms and LiSat-II.	statistically-significant degree. Further studies should focus on patients with several complaints during the first 1–3 months and test various types of interventions."	patients who suffered few PCS 2-8 weeks post injury and refused rehab recovered at pre-injury level where those with multiple PCS and accepted the rehab were not recovered at one year.
Slade 2002 (5.5)	Occupational therapy	RCT	This work was funded by the Nuffield Institute and the NHS executive (Northern & Yorkshire), and the United Leeds Hospital Trust. No mention of COI	N=141 patients with TBI, stroke or multiple sclerosis	53 years old; chronic TBI as well as stroke, MS and other neurological deficit patients.	Experimental group (N=75) received 67% more therapy than control group, 62.5% of total therapy time Control group (N=66) received 37.5% of total therapy time. Therapy was a mix of physiotherapy and occupational therapy.	No long term follow-up mentioned	The experimental group received significantly more therapy hours than the control group (126.4 vs 81.7 (p=0.0001)) A second multiple regression	"In summary, enhanced levels of physiotherapy and occupational therapy (to a planned intensity of 67% above the standard) show results which vary according to the speciation of the model used in the analysis. Adjusting for confounders, a slight non-significant trend in favour of the	Data suggest intensive therapy group benefit from additional OT and PT as was demonstrated by a statistically significant shortened length of stay which also decreased hospital costs.

								showed that the experimental group had a significant reduction of 14 days in length of stay in a rehabilitation unit compared to the control group. (p<0.01)	experimental group was observed. Accounting for impairment/disability mix, and the consequent response of therapy, a significant benefit to the experimental group was demonstrated."	However, the duration of the study is not included in this article so conclusions are difficult to surmise.
Vanderploeg 2008 (4.5)	Occupational Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with mod-severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive33.2±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions vs Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All received 1.5-2.5hr/d TBI	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v.	"[N]o difference between cognitive-didactic and functional-experimental approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Data suggest both groups improved with similar long term global functional outcome. Data suggest more improvement in short term functional cognitive outcome for the cognitive treatment arm.

						protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until ready to discharge home or to community transitional rehabilitation program or completed 60 days specific protocol treatment.		functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).		
Ghaffar 2006 (4.0)	Occupational Therapy	RCT	Supported by the Physician Services Incorporated. No mention of COI	N = 191 patients with mild traumatic brain injuries	Treated group 30.7 ±10.9 Nontreated group: 33.3±12.4 Gender (M:F) 124:67	Treated Group (N=97) received assessment, education, and therapy by an occupational therapist. Control Group (N=94) did not receive any treatment.	6 months	The two groups didn't not differ in any outcome measure. In patients with preinjury psychiatric difficulties, subjects in the treated group did had significantly fewer symptoms in comparison to the control group.	"These findings suggest that routine treatment of all MTBI patients offers little benefit; rather, targeting individuals with preinjury psychiatric problems may prove a more rational and cost-effective approach."	Data suggest traditional treatment for MTBI patients may be of little benefit in treatment but assessing preinjury psychiatric issues may be useful in determining which individuals are likely to benefit the most from a multidisciplinar

								(F=6.8, (P=.01))		y treatment program.

Evidence for the Use of Physical Therapy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow -up:*	*Results:*	*Conclusion:*	*Comments:*
Schneider 2014 (7.0)	Physical Therapy	RCT	Sponsored by the Alberta Centre for Child, Family and Community Research. KJS is sponsored by the Alberta Heritage Foundation for Medical Research Studentship Award and the Alberta Children's Hospital Research Institute. CAE is sponsored by the Alberta Innovates Health Solutions Population Health Investigator Award and the Children's Hospital Foundation. No COI.	N = 31 patients with persistent symptoms of dizziness, neck pain and/or headaches following a sport-related concussion.	No mention of mean age. Median age of 15 yrs (12-30) 18 Males, 13 Females	Control Group (N=16) – Seen by physiotherapist once a week for 8 weeks or until medical clearance. Vs Intervention Group (N=15) – Same treatment as the control group, but with an addition of cervical spine physiotherapy and vestibular rehabilitation.	No follow up mentioned.	73% of the intervention group (11/15) were medically cleared within 8 weeks while only 7% (1/14) were in the control group. The intervention group was 3.91 (95% CI 1.31-11.34) times more likely to be medically cleared by 8 weeks.	"A combination of cervical and vestibular physiotherapy decreased time to medical clearance to return to sport in youth and young adults with persistent symptoms of dizziness, neck pain and/or headaches following a sport-related concussion."	Small sample. Data suggest the combination of cervical and vestibular PT significantly decreases the time to medical clearance in concussion patients
Zhu 2007 (7.0)	Physical Therapy	RCT	Sponsored by Hong Kong Health Service Researched Fund. No mention of COI.	N = 68 patients with moderate to severe TBI.	Control Group (N=36) Mean age of 36 ± 13. 28 Males, 8 Females Intensive Group (N=32) Meant age of 13 ± 13. 27 Males, 5 Females	Control Group (N=36) – 2 hrs of therapeutic training each day for 5 days a week. Vs Intensive Group (N=32) – 4 hrs of therapeutic training each day for 4 days a week.	6 months	The Functional Independence Measure (FIM) was significantly higher in the intensive group than the control group at the third month (47% vs 19%, p=0.015). The intensive Glasgow Outcome Scale (GOS) had higher scores than the	"Early intensive rehabilitation may improve the functional outcome of patients with TBI in the early months post-injury and hence increase the	Data suggest intensive rehab resulted in quicker return to work but did not affect functional outcomes as both groups were similar at one year.

						Up to 6 months of treatment for both groups.		control group on the second (28% vs 8%, p=0.34) and third (34% vs 14%, p=0.044) months. Overall, no significant differences in the FIM and Neurobehavioral Cognitive Status Examination (NSCE).	chance of their returning to work early"	
Krewer 2014 (6.5)	Physical Therapy	RCT	No mention of sponsorship or COI.	N = 66 patients with severe hemiparesis and mild to moderate spasticity resulting from a stroke or TBI.	rpMS Group (N=31) – Mean age of 55±13 19 Males, 12 Females Sham Group (N=32) – Mean age of 54±13 19 Males, 13 Females	rpMS Group (N=31) received rpMS stimulation Vs Sham Group (N=32) received sham stimulation 20 minute sessions of stimulation plus 20 minutes of OT, 2 times a day, 5 days a week, for 2 weeks.	2 Weeks	rpMS group showed significant effects on spasticity for wrist flexors (P=.048) and elbow extensors (P<.045) when compared to the sham group. Are motor function was not significantly different between the two groups. But rpMS had a positive effect on sensory stimulation.	"Therapy with rpMS increases sensory function in patients with severe limb paresis. The magnetic stimulation, however, has limited effect on spasticity and no effect on motor function."	Baseline comparability was unequal as time since injury differed between groups.(26 weeks vs 37 weeks).Data suggest use of rpMS therapy in severe limb paresis patient increasing sensory function but has no benefit for motor function and only a slight effect on spasticity.
Shiel 2001 (6.0)	Physical Therapy	Prospective Controlled	Sponsored by the NHS National Research and Development Porgramme for People with Physical and Complex Disabilities.	N = 56 with moderate to severe head injuries.	Mean age of 36.7 ± 15.2 years. No mention of sex.	Intervention group (N=24) – Received routine treatment with additional treatment Vs Routine Group (N=27) – Received routine treatment.	No follow up mentioned.	The results mostly compared the two centres were the study took place instead of the two groups. However, the study stated that subjects receiving more intensive therapy made more rapid	"Increasing the hours per week of therapy given adults recovering from brain injury in hospital can accelerate the	Data suggest brain injured patient with increasing hours of therapy make faster recoveries and acquire personal independence quicker and are discharged from

			No mention of COI.					progress and were discharged sooner.	rate of recovery of personal independence and result in their being discharged from hospital sooner."	hospitalization much sooner.
Vanderploeg 2008 (4.5)	Physical Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with mod-severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive33.2 ±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions vs Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All received 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until ready to discharge home or to	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).	"[N]o difference between cognitive-didactic and functional-experimental approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term functional cognitive outcomes for the cognitive treatment arm.

						community transitional rehabilitation program or completed 60 days specific protocol treatment.				
Wilson 2006 (4.0)	Physical Therapy	RCT Open label trial	Sponsored by the National Institute on Disability and Rehabilitation Research, United States Department of Education, under the Office of Special Education and Rehabilitation Services. No mention of COI.	N = 38 adults with a TBI diagnosis	Mean age of 29.6 ± 12.4 yrs. 35 Males, 3 Females	Experimental group receiving PWB gait training (N=19) Vs Control group receiving traditional physical therapy. (N=19)	No follow up mentioned.	Both groups showed significant improvements (P<0 .05) in both groups on the Functional Ambulation Category, Standing Balance Scale, Rivermead Mobility Index and FIM. However, there was no significant difference between the two groups.	"Results did not support the hypothesis that 8 wks of partial weight-bearing gait retraining improves functional ambulation to a greater extent than traditional physical therapy in individuals after traumatic brain injury based on common clinical measures."	Baseline comparability differences in months post injury (4.0 vs 2.8) and ages differences between groups. Data suggest similar efficacy between groups and that 8 weeks of partial weight bearing PT post TBI was not better than control group.

Evidence for the Use of Relaxation Exercises/Group Discussion

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow -up:*	*Results:*	*Conclusion:*	*Comments:*
Bateman 2001 (5.5)	Relaxation Exercises	RCT	No mention of COI.	175 patients that sustained a single-incident brain injury either traumatic or vascular	Control Group Mean age: 44.7±13.3 years. Training group Mean age: 41.7±14.3 years. 97 males, 60 females.	Ergometer Aerobic Training (Training Group) Vs Relaxation Training Control Group (Control Group)	12 weeks following end of training	Significant improvements in exercise capacity (p =.05) in the exercise training group (n =70) relative to the control group (n =72) were not matched by greater improvements in functional independence, mobility, or psychologic function, at either 12 weeks or follow-up.	"The benefits of improved cardiovascular fitness did not appear to extend to measurable change in function or psychologic state."	Data suggest the improvements in exercise capacity (improved cardiovascular fitness) did not translate into measurable changes in terms of function or improved psychological outcomes(s).
Blake 2009 (4.5)	Relaxation Exercises	RCT	No COI.	20 individuals with brain injury	Control group mean age: 46.20±11.27 years. Exercise group±10.52 years. 15 males, 5 females.	Exercise group: received supervised Quigong instruction once per week for one hour Vs Control group: attended non-exercise social and leisure activities one hour per week for 8 weeks	Follow up at 8 weeks.	Groups were comparable at baseline. After the intervention, mood was improved in the exercise group when compared with controls (U=22.0, P=0.02). Improvements in self-esteem (Z=2.397, P=0.01) and mood (Z=–2.032, P=0.04) across the study period were also evident in the exercise group only. There were no significant differences in physical functioning between groups. In view of the sample size, these findings are inconclusive.	"This study provides preliminary evidence that a brief Qigong exercise intervention programme may improve mood and self-esteem for individuals with traumatic brain injury. This needs to be tested in a large-scale randomized trial."	Small sample size. Data suggest Quigong exercise may improve mood and self esteem but no difference in physicial functioning between groups.

Evidence for the Use of Aerobic Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow -up:	Results:	Conclusion:	Comments:
Bateman 2001 (5.5)	Aerobic Exercise	RCT	No sponsorship or conflict of interest.	N = 157 who had suffered a one-time brain injury within the past 10 to 38 weeks	Mean age for exercise group 41.7 years and for control group 44.7 years. 60 females, 97 males.	Cycle ergometer aerobic exercising group (n=70) Vs. Relaxation exercise group	24 weeks (12 weeks post training)	At alpha level .05 the exercising group did not have statistically significant improvements in mobility or psychologic function at weeks 12 or 24.	"The benefits of improved cardiovascular fitness did not appear to extend to measurable change in function or psychologic state."	Data suggest the improvements in exercise capacity (improved cardiovascular fitness) did not translate into measurable changes in terms of function or improved psychological outcome.
Canning 2003 (4.5)	Aerobic Exercise	RCT	Partially funded by the Motor Accidents Authority of New South Wales. No conflict of interest.	N = 24 participants who suffered a severe TBI within past 12 months and currently are attending inpatient rehabilitation	Mean age for control group 25.6 and for exercise group 24.75. 6 females, 16 males.	Experimental exercise group who had four weeks of sit-to-stand and step-up training exercises (n = 13) Vs. Control group with no additional training exercises (n = 11)	None	The exercise group produced a statistically higher improvement in number of repetitions of sit-to-stand movements in three minutes compared to the control group's improvement ($p < 0.05$). The exercise group improved by 62% while the control group improved by 18%.	"Intensive task-specific training is recommended as an important component of rehabilitation early following severe traumatic brain injury."	Small sample size. Data suggest intensive sit to stand training is beneficial for TBI patient s in retraining motor performance. No long term follow up.
Driver 2004 (4.5)	Aerobic Exercise	RCT	No mention of sponsorship or conflict	N = 16 who suffered a brain injury at	Mean age for study population 37.65. 8 females, 8 males.	Exercise group who completed three one-hour aquatic exercise sessions per week for 8 weeks	None	The exercise group had several measures of body movement, including elbow flexion, hip flexion, knee flexion, and body composition, which	"By providing an exercise programme that meets regularly, is safe and fun, it is possible to positively impact	Small sample size. Data suggest physical fitness improved in aquatic exercise group.

			of interest.	least one year prior		with a personal instructor (n = 8) Vs. Control group who participated in a vocational rehabilitation class focusing on writing and reading for 8 weeks (n = 8)		improved significantly when comparing pre- and post-scores ($p < 0.05$). All comparisons were measured using paired sample t-tests.	the functional capacity of people with a brain injury. Results also indicate that people with a brain injury can respond to a training stimulus as physical work capacity, ROM and muscular strength and endurance improved. Consequently, aquatic exercise programmes can play an integral part in the rehabilitation programmes currently available to outpatients with a brain injury."	
Blake 2009 (4.5)	Aerobic Exercise	RCT	No mention of COI. Funded by the Headway House, Nottingham.	N = 20 with chronic TBI	Mean age for exercise group 44.5 (1 female, 9 males). Mean age for control group 46.20 (4 females, 6 males)	Exercise group who underwent supervised one hour Qigong instruction sessions once a week for 8 weeks (n = 10) Vs. Control group who underwent one hour non-exercise activities, including group discussion, drawing, and writing, once a week for 8 weeks (n = 10)	8 weeks	The exercise group had statistically improved mood ($p = 0.02$) and self-esteem ($p = 0.01$) when compared to the control group. These comparisons were created using the Mann-Whitney U-test. However there was no significant difference between the two groups in regards to physical function improvement.	"This study provides preliminary evidence that a brief Qigong exercise intervention programme may improve mood and self-esteem for individuals with traumatic brain injury. This needs to be tested in a large-scale randomized trial."	Small sample size. Data suggest Qigong exercise may improve mood and self esteem but no difference in physicial functioning between groups.

Evidence for the Use of Aquatic Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Driver 2004 (4.5)	Aquatic Aerobic Exercise	RCT	No mention of sponsorship or conflict of interest.	N = 16 who suffered a brain injury at least one year prior	Mean age for study population 37.65. 8 females, 8 males.	Exercise group who completed three one-hour aquatic exercise sessions per week for 8 weeks with a personal instructor (n = 8) Vs. Control group who participated in a vocational rehabilitation class focusing on writing and reading for 8 weeks (n = 8)	None	The exercise group had several measures of body movement, including elbow flexion, hip flexion, knee flexion, and body composition, which improved significantly when comparing pre- and post-scores ($p < 0.05$). All comparisons were measured using paired sample t-tests.	"By providing an exercise programme that meets regularly, is safe and fun, it is possible to positively impact the functional capacity of people with a brain injury. Results also indicate that people with a brain injury can respond to a training stimulus as physical work capacity, ROM and muscular strength and endurance improved. Consequently, aquatic exercise programmes can play an integral part in the rehabilitation programmes currently available to outpatients with a brain injury."	Small sample size. Data suggest physical fitness improved in aquatic exercise group.

Evidence for the Use of Rest

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Thomas 2015 (6.5)	TBI	RCT	Sponsored by Injury Research Center of the Medical College of Wisconsin. No COI.	N = 99 with mild TBI / concussion.	Aged 11 – 22 years, 65 males and 34 females.	Intervention or strict rest for 5 days (N = 50) vs Control or usual care for 1-2 days of rest, followed by stepwise return to activity (N = 49).	10 days	At 10-day period, strict rest group reported greater PCSS scores / higher total number of postconcussive symptoms / and higher daily PCSS clustered at day 4: 187.9 vs 131.9 [C], $p < 0.03$ / 79.4 [I] vs 50.2 [C], $p < 0.03$ / and 13.95 [C] vs 21.51 [I], $p < 0.03$. Subgroup analysis; higher postconcussive symptom score at day 10 randomized to strict rest (15.2 [I] vs 7.7 [C], $p < 0.04$). Those who presented to ED with immediate signs of concussion and those with past history of concussion randomized to strict rest (11.0 [I] vs 14.6 [C], $p = 0.22$ and 15.1 [I] vs 5.6 [C], $p < 0.05$.	"Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care."	Data suggest strict bed rest after acute concussion not beneficial in speeding up recovery or discharge vs usual care.

Evidence for the Use of Body Weight Support Treadmill Training

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Brown 2005 (5.5)	Body Weight Support Treadmill Training	RCT	No mention of COI or sponsorship.	N = 19 in postacute phase of TBI rehab	Mean age for COGT group 42.56 (3 female, 6 male). Mean age for BWSTT group 38.00 (3 female, 7 male).	Conventional over ground gait training (COGT) (n = 9) Vs. Body weight-supported treadmill training (BWSTT) (n = 10)	3 months after initiation of treatment	Mean increase in velocity was 0.8 cm/s for COGT and 2.8 cm/s for BWSTT. There was no significant difference in velocity overall (p=0.573). There was no between group differences in velocity changes (p=0.837). Mean stride difference was -3.6 cm for COGT and -1.0 for BWSTT. Both differences were significant (p=0.036). No significant between group differences (p=0.198). A significant difference between groups in step length change was observed (p=0.011) with COGT decreasing by 7.3 cm and BWSTT increasing by 8.9. No significant difference in function reach was observed within groups (p=0.106) or between groups (p=0.957). No significant improvement in FAC levels were observed overall (p=0.331) or between groups (p=0.641). There was no significant difference observed for mean TUG scores overall (p=0.178) or	"[T]he BWSTT was not found to be more effective than the COGT when provided more than 3 months to individuals greater than 6 years post-TBI. On the contrary, gait symmetry improved more in the COGT group. Three months of physical therapy exercises tailored to the individual's needs, along with either the BWSTT or COGT, resulted in a narrower step width (approaching the norm) during ambulation for individuals with chronic TBI. Gait velocity and FAC did not change significantly for either group	Small sample sizes, resulting in many results likely underpowered. Pop. Is 6+yrs post-TBI. Data suggest COGT better than BWSTT for improving gait symmetry, but some findings better with treadmill.

								between groups (p=0.872).	after only 3 months of intervention."	
Esquenazi 2012 (4.5)	Body Weight Support Treadmill Training	RCT	No COI. Study was supported by grants from MossRehab Research Fund Disclosure and Department of Defense, CDC.	N = 16 with TBI and baseline over group walking self-selected velocity of ≥ 0.2 m/s to 0.6 m/s	Mean age for RATT 37.1 ± 10.6 (5 female, 3 male). Mean age for MATT 41.9 ± 16.8 (4 female, 4 male)	Robotic-assisted treadmill training (RATT), 45 minutes 3 times a week (n=) Vs. Manually assisted treadmill training, 45 minutes 3 times a week (n=)	6 to 8 weeks	All parameters produced no significant between-group differences. The average SSV increased in RATT by 49.8% (p=0.01) and by 31% (p=0.06) for MATT. RATT group average maximal velocity increased by 14.9% (p=0.06) and MATT group increased by 30.8% (p=0.01). RATT group step-length asymmetry ratio improved by 33.1% (p=0.01) and by 9.1% (p=0.73) for MATT group. RATT group distance walked increased by 11.7% (p=0.21) and MATT group increased by 19.3% (p=0.03). Mobility improvement was present for both groups (p=0.03).	"The results of this study demonstrate greater improvement in symmetry of gait (step length) for RATT and no significant differences between RATT and MATT with regard to improvement in gait velocity, endurance, and SIS. Our study provides evidence that participants with a chronic TBI can experience improvements in gait parameters with gait training with either MATT or RATT."	Small Sample. Data suggest comparable results for both RATT and MATT on all outcome measures except greater improvement of step length (gait symmetry) from RATT was observed.

Evidence for the Use of Constraint-Induced Movement Therapy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sterr, 2002 (4.0)	Traumatic Brain Injury	RCT	No mention of industry sponsorship. No COI.	N=18	11 males, 4 females. Mean age of 3h/d: 68.4±7.0 years Mean age of 6h/d: 49.9±18.5 years.	3H/D Group: (n=8) Vs. 6H/D Group: (n=7)	Weekly For 1 month	ANOVA for AOU and QOM showed treatment gain by a strong time effect respectively (p<.01, P<.01). Treatment effect was greater for 6h/d groups than for 3h/d group. Median pre-post performance time gain was 2.34 seconds for 6 h/d group, but only .64 seconds for 3 h/d group. Interaction was not significant. Beneficial effects were greater in 6 h/d group than in 3 h/d group.	"The 3-hour CIMT training schedule significantly improved motor function in chronic hemiparesis, but it was less effective than the 6-hour training schedule."	Small sample. Data suggest 6 hour training CIMT significantly improved motor function in chronic hemiparesis patients compared to 3 hour CIMT training group.

Evidence for the Use of Systematic Instruction

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Powell, 2012 (7.0)	Systematic Instruction	RCT	No mention of COI and sponsored by the National Institutes of Health, National Center for Medical and Rehabilitation Research, Award #5R03HD054768.	N=29 persons with moderate-severe cognitive impairments due to acquired brain injury.	Mean age: 42.31±13.43 years. 17 males, 12 females.	Systematic Instruction Group: (n=15) 12, 45-minute individual training sessions on PDA Vs. Conventional Instruction Group: (n=14) 12, 45-minute individual training sessions on PDA	30 days	No significant differences were observed in either group except in the 30 day follow-up posttest. Systematic instruction participants showed better PDA skills.	"These results demonstrate that systematic instruction applied to ATC results in better skill maintenance and generalization than trial-and-error learning for individuals with moderate-severe cognitive impairments due to acquired brain injury."	Data suggest systematic instruction training better than trial and error learning for ATC (assistive tech. for cognition) and TBI patients.

Evidence for the Use of Television Assisted Rehabilitation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Lemoncello 2011 (5.0)	Television Assisted Prompting	RCT	Research was funded by a grant from the US department of Education, National Institute on Disability Rehabilitation & Research. No COI.	N=23	Group 1: 7 males, 5 females; Mean age 47.2±14.5. Group 2: 5 males, 6 females; Mean age 47.6±18.1.	Group 1: received Television Assisted prompt (TAP) (N=12) VS. Group 2: received typical practice (TYP) (N=11)	Follow-up at baseline, 4 and 8 wks.	Task completion was higher in TAP group (df=520, mean=0.72, SE=0.02) than with TYP (df=520, mean=0.73, SE=0.02). TAP group completed more experimental tasks compared with preferred or non-preferred tasks (p=0.01). Satisfaction survey at conclusion of study suggest that participants found TA system useful in for reminders, easy to use, and yielded greater flexibility in daily scheduling.	This study suggested that when ProM reminders are delivered automatically and via a familiar medium, the television, adults with ABI completed a greater number of tasks than when participants used self-selected or typical reminder strategies.	Crossover RCT. Data suggest TAP showed advantage for memory prompting over no prompting and higher task completion.

Evidence for the Use of Action Sequences

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follo w-up:*	*Results:*	*Conclusion:*	*Comments:*
Zlotowitz 2010 (4.0)	Action Sequences	RCT	No COI and no mention of sponsorship.	N=16 patients with acquired brain injury	Mean age: 38.63±14.41 years. 11 males, 5 females.	Group A: Modelling Condition Vs. Group B: Moulding Condition	none	There was no significant difference between groups for recall of sequence after short delay. (z=1.19, P>.05) Patients were more accurate in sequence recall in modelling condition that for moudling condition after longer delay. (Group A: mean=2.63, SD=1.23; Group B: mean=1.56, SD=1.63; Z=1.91, P=0.028).	"The use of a modelling instructional technique to teach brain-injured participants an action sequence during their rehabilitation may be more effective for their longer term performance than a moulding instructional technique."	Crossover. Small sample (n=16). Mixed patients (TBI, stroke, abscess, etc.). Data suggest brain injured patients may improve learning via modeling instead of molding technique.

Evidence for the Use of Cognitive Behavioral Therapies

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Vanderploeg 2008 (8.0)	Cognitive Behavioral Therapies	RCT	Supported by the Defense and Veterans Brain Injury Center, Uniformed Services University of the Health Sciences, Bethesda, MD, the Department of Veterans Affairs, Veterans Health Administration, and a Department of Defense award administered through the Henry Jackson Foundation (grant no. MDA 905-03-2-0003).	366, 18+yo with mod- severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	18+yo	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; 1-on-1 sessions v. functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All had 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until discharge home or to community transitional rehab program or completed 60 days specific protocol Tx.	Follow-up at 1 year.	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).	"…[N]o difference between cognitive-didactic and functional-experimental approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Trend to higher education level and less alcohol in cognitive rehabilitation arm may have biased in favor of CR, although baseline cognitive measures comparable. Data suggest minimal differences between groups.

Powell 2012 (7.0)	TBI	RCT	Sponsored by the National Institutes of Health, National Center for Medical and Rehabilitation Research, Award #5R03HD054768. No mention of COI.	N = 29 with acquired brain injury.	Mean age 42.31 years for the total group. 17 males, 12 females. Mean age is 42.93 years for the Systematic Instruction Group. 9 males, 6 females. Mean age is 41.64 years for the Conventional Instruction group. 2 males, 2 females.	Systematic Instruction Group – emphasized mastery, incorporating all of the previously described design and delivery elements tailored to the instruction of ATC (N = 15) vs Conventional Instruction Group – emphasized exploratory learning, not mastery (N = 4).	30 day follow-up	Pre-test performance for both the groups was not statistically significant. p = 0.60. The main effect of treatment condition on post-test performance was not statistically Significant, p = 0.16. Accuracy at the 30-day follow-up: significant from pre to post-test. P < .01. Statistically significant treatment condition. p < 0.1. At fluency at post-test and 30 day follow up difference between two groups was p = 0.81 post-test and p=.05 at 30 day follow up. Fluency rates between two groups were not statistically significant at post-test, but were at follow-up. P=.051.	"The results from this study suggest that systematic instruction applied to ATC results in better retention and generalization of trained skills than conventional instruction, with the potential to significantly improve client outcomes."	Data suggest systematic instruction training better than trial and error learning for ATC (assistive tech. for cognition) and TBI patients.

Ponsford 2016 (5.5)	Cognitive Behavioral Therapies	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))	"Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI."	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54 vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease anxiety and depression.

Jean 2010 (5.5)	TBI	RCT	Sponsored by the Alzheimer Society of Canada (ASC) co-funded by the Fonds de la Recherche en Sante´ du Que´bec (FRSQ) and the Canadian Institutes of Health Research (CIHR)-Institute of Aging (IA). MEB supported by doctoral grant, MS and CH supported by research grant and SW supported by doctoral training grant.	N = 22 with mild cognitive impairment of the amnestic type (MCI-A).	Aged 50 or older; 11 males and 12 females.	Experimental group learned face–name associations using a paradigm combining errorless (EL) learning and spaced retrieval or SR (N = 11) vs Control group trained using an errorful (EF) learning Paradigm (N = 11).	10-weeks	All participants improved their capacity to learn face–name associations, ($p < 0.001$).	"The absence of difference between groups on all variables might be partly explained by the high variability of scores within the experimental group."	Data suggest comparable efficacy.

Bédard 2013 (5.0)	Cognitive Behavioral Therapy	RCT	This study was funded by the Ontario Neurotrauma Foundation (grant ABIMIND2-476) NO COI	N = 76 individuals with depression symptoms after a TBI	Mean age: Treatment group 47.1 Control Group: 45.81 Gender (M:F): 42:34	Treatment group (N=38) received intervention based on mindfulness-based stress reduction, and the manual for MBCT by Segal and colleagues. Intervention lasted for 10 weeks. Control group (N= 38) was a wait-list control arm. The control group would not receive intervention until treatment group was finished with their 10-week treatment.	3 months	Parallel group analysis of Beck Depression Inventory-II for intervention group vs control group, 6.63 vs 2.13, (P= 0.029). Improvements were maintained at the 3 month follow up.	"These results are consistent with those of other researchers that use mindfulness-based cognitive therapy to reduce symptoms of depression and suggest that further work to replicate these findings and improve upon the efficacy of the intervention is warranted."	Data suggest mindfulness-based cognitive therapy may reduce depressive symptoms associated with TBI.

Bell 2008 (score=5.0)	Cognitive Behavioral Therapies	RCT	Supported by the Centers for Disease Prevention and Control. No COI.	313 from a level I trauma center, admitted within 48 hours of the injury, injury likely a MTBI	Mean age: 32.47 years; 235 males, 78 females.	Scheduled phone contacts over first 3 months post-injury, along with standard patient instruction handout, a wallet card with the study's toll-free phone number, and CDC booklet "facts about Concussion and Brian Injury and Where to Get Help" (n = 146) vs Usual ED standard of care for MTBI – patient instruction handout and standard outpatient treatment (n = 167)	Follow up at 2 days and 2, 4, 8, and 12 weeks post-injury.	Post-traumatic symptom composite mean difference between control and treatment groups: 6.6 (95% CI: 1.2-12.0, p=0.016). General health composite mean difference between control and treatment groups: 1.5 (95% CI: -2.2-5.2, p=0.417)	"Telephone counselling, focusing on symptom management, was successful in reducing chronic symptoms after MTBI."	Significant baseline dissimilarity between groups as the treatment group had a higher baseline GCS than the control group. Also, the study design changed throughout the course of the trial as originally there were to be three groups, which were then reduced to two. Data suggest the interventional group had improved post-MTBI outcomes than the control.

Ashman 2014 (4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by National Institute for Disability and Rehabilitation research grants H133B040033 and H133B000001. NO COI.	N= 77 individuals with TBI and a diagnosis of depression	Cognitive Behavioral Therapy (CBT) group: 47.1 Supportive psychotherapy (SBT) group: 48.1 Gender (M:F) 32:42	CBT group (N=29) received 16 sessions of treatment focused on cognitive restructuring techniques to challenge and reshape automatic thoughts into more rational self-statements. SPT group (N=26) received 16 sessions of client-centered psychotherapy treatment. Treatment focused on improving self-esteem, maximize adaptive capacities, and maintaining the individual's best possible level of functioning.	3 months	After treatment, 35% of participants in CBT group no longer met criteria for depression vs 17% of participants in SPT group. However, difference in remission rates was not statistically significant (P =.16) Changes in the Beck Depression Inventory-II scores were not significant between CBT group and SPT group. (P=.632)	"Both forms of psychotherapy were efficacious in improving diagnoses of depression and anxiety and reducing depressive symptoms. These findings suggest that in this sample of individuals with TBI, CBT was not more effective in treating depression than SPT, though further research is needed with larger sample sizes to identify different components of these interventions that may be effective with different TBI populations."	High dropuout rate, substantial intergroup variability. Data suggest comparable efficacy between groups.

Tiersky 2005 (4.5)	Psychological Therapy	RCT	No COI. Supported by the National Institute on Disability and Rehabilitation Research and the Henry Kessler Foundation.	N = 20, mild or moderate TBI	11 female, 9 male. Mean age 46.85±10.51 years	Cognitive-behavioral psychotherapy and cognitive remediation (n = 11) vs Control (n = 9), all followed for 11 weeks	11 weeks, 1 and 3 months	Outcome measures at end of treatment: GSI – CBP+CR 0.86±0.41, control 1.74±1.00 (P=0.045), Depression – CBP+CR 1.12±0.45, control 2.11±1.14 (P=0.046), Anxiety subscale – CBP+CR 0.72±0.42, control 1.53±1.02 (P=0.066), PASAT – CBP+CR 135.55±30.71, control 110.88±60.28 (P=0.257), Problem solving – CBP+CR 13.06±2.67, control 12.58±2.21 (P=0.685), Attention Questionnaire CBP+CR 19.42±11.56, control 29.29±9.94 (P=0.082)	”Cognitive behavioral psychotherapy and cognitive remediation appear to diminish psychologic distress and improve cognitive functioning among community-living persons with mild and moderate TBI.”	Data suggest TBI patient may benefit from CBT and cognitive remediation in terms of reducing anxiety and depression.

Fann 2015 (4.5)	Cognitive Behavioral Therapy	RCT	This study was supported by the National Institutes of Health (grant R21HD53736) and the Department of Education, National Institute on Disability and Rehabilitation Research (grant H133G070016). NO COI	N = 100 adults with Major Depression after a Traumatic Brain Injury	Mean Age: 45.8 years old Gender (M:F) 63:37	Intervention groups received therapy adapted from Simon and Ludman's telephone care management and CBT protocol over the telephone (CBT-T, N=40) or in person (CBT-IP, (N=18) Usual Care group (N=42) were encouraged to continue using the rehabilitation and primary care services.	24 weeks	CPT-T group had significant improvement on the patient reported Symptom Checklist-20 (SCL-20) in comparison to the UC group at follow up (treatment effect = 0.36, 95% CI: 0.01–0.70; p = 0.043) Participants who completed more than 8 CBT sessions significantly improved SCL-20 scores compared to UC group (treatment effect = 0.43, 95% CI: 0.10–0.76; p = 0.011)	"In-person and telephone-administered CBT are acceptable and feasible in persons with TBI. Although further research is warranted, telephone CBT holds particular promise for enhancing access and adherence to effective depression treatment."	Data suggest telephone CBT may be beneficial in decreasing depression in TBI patients.

Radice-Neumann 2009 (4.5)	Psychological Therapy	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State University of New York.	N = 19 with acquired brain injury, minimum 1 year post-injury	8 female, 12 male. Mean age 43 years	Facial Affect Recognition "FAR" (n = 10) vs Stories of Emotional Inference "SEI" (n = 9), both treatments given for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (*P*=.225, *P*=.312), LEAS-Self (*P*=.064, *P*=.732), LEAS-Other (*P*=.340, *P*=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, *P*=.004). DANVA2-AF: Significant performance change found in FAR (*P*<.001) and SEI (P=.006). DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR *P*=.584, SEI	"Training can improve emotion perception in persons with ABI. Although further research is needed, the interventions are clinically practical and show promise for the population with ABI."	Small groups. No sham/placebo. Data suggest specific training may enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improvement in ability to infer how they would feel in a given context.

						scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)		*P*=.166). LEAS-Self: Both significant change over time (FAR and SEI both P=0.019). LEAS-Other: Significant change over time for FAR (P=0.004). No change in SEI (P=.579). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (*P* = .042). No change perceived in SEI (*P* = .363).		

Mittenberg 1996 (score=4.0)	Cognitive Behavioral Therapies	RCT	No mention of sponsorship or COI.	58 with mild head trauma	Mean age: 46.35 years; 40 males, 18 females.	Treatment group: given 10 page manual, "Recovering From Head Injury: A Guide for Patients", met with therapist to review expected symptoms, cognitive-behavioral model of symptom maintenance and treatment, techniques to reduce symptoms, instructions for gradual return to normal activities (n=29) vs Control group: received routine hospital treatment and discharge instructions (n=29)	Follow up at 6 months post-injury.	Postconcussion Symptoms for Control and Treatment groups, respectively: Frequency of initial symptoms – 4.38, 3.69 (p=0.42), Duration of average symptoms (days) – 51.19, 33.18 (p=0.05), Frequency of symptoms 6 months posttreatment – 3.10, 1.62 (p=0.02), Days per week symptomatic at 6 months – 1.33, 0.53 (p=0.01), Severity of average symptom at 6 months (0-10 scale) – 1.72, 0.80 (p=0.02)	"Telephone counselling, focusing on symptom management, was successful in reducing chronic symptoms after MTBI."	Standard care bias. Relatively small sample size. Data suggest interventional group achieved better outcomes (fewer symptomatic days and less severity of symptoms) vs controls.

Ruff 1990 (3.5)	Psychological Therapy	RCT	No mention of COI. Supported by grant from the Robert Wood Johnson Foundation.	N = 24, moderate to severe head injury with at least 1 hour of coma duration	7 females, 17 males. Mean age experimental group 28.3 years, control group 31.1 years	Experimental group – cognitive retraining on attention, visuospatial abilities, learning and memory, and problem solving. Small groups of 2-4, 12 hours per week for 8 weeks, 2 hour of group therapy and 20-30 minute "wrap-up" sessions at the end of the day (n=12) vs. Control group – also received group and "wrap-up" session therapy, training focused on psychosocial functioning and activities	8 weeks after intervention began	Test—re-test correlations in Katz Adjustment Scale (KAS) subset; Social Obstreperousness: Patient rating r=0.87 (P<0.001), Relative rating r=0.88 (P<0.001), Patient vs. Relative rating r=0.01 (P>0.01). Acute Psychoticism: Patient r=0.68 (P<0.001), Relative r=0.76 (P<0.001), Patient vs Relative r=0.45 (P>0.01). Withdrawn Depression: Patient r=0.78 (P<0.001), Relative r=0.65 (P<0.1), Patient vs Relative r= -0.07 (P>0.01). Both groups did not perceive changes in emotional and psychosocial function from	"In this study, self-ratings according to the KAS proved to be reliable for both relative and patient ratings. Nonetheless, very little agreement existed between patient and relative ratings, as indicated by zero correlations for global scales of social obstreperousness and withdrawn depression. Furthermore, relatives but not patients reported significant gains."	Baseline differences between groups for coma duration (25.5 vs. 48.3 days), otherwise data suggest potential efficacy.

						of daily living (n=12). All participants' relatives also were involved in evaluation.		interventions (SO: U=58 P>0.10, AP: U=64 P>0.10, WD: U=62.5, P>0.10). Relatives of both groups also did not perceive changes (SO: U=55 P>0,10, AP: U=48.5 P>0.10, WD: U=36, P>0.10).		

Evidence for the Use of Cognitive-Motor Dual-Tasking

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Couillet, 2010 (5.0)	Cognitive Motor Dual-Tasking	RCT	Sponsored by grants from the Programme Hospitalier de Recherche Clinique and by Assistance Publique-Hopitaux de Paris. No mention of COI.	N = 12 patients in the stages of subacute or chronic after a severe TBI.	Mean age of AB group: 23.8 (N=5) BA group: 26.7 (N=7) No mention of Sexes	An AB vs. BA crossover design was used. Each phase was six weeks and consisted of four one hour training sessions a week for a total of 24 hours of training. A phase was the control phase, consisting of cognitive tasks that did not use the patient's divided attention or working memory. B phase consisted of specific dual attention training.	Follow up at 6 weeks, 12 weeks, and one month after the end of the trial.	Effect of time and the group x time interaction in Divided attention subtest of the TAP: Mean Reaction Time: AB group: F(3, 21) = 21.5, (p < .0001); BA group: F(3, 21) = 20.7, (p < .0001) Number of Omissions: AB Group: F(3, 18) =22.3, (p < .0001) BA group: F(3, 18) = 13.2, (p < .0001) Effect of time and the group x time interaction were both significant for the go–no go dual-task reaction times: AB group: F (3, 18) =12.3, (p <.0001). BA group: F(3, 18) = 17.5, (p <.0001,) Digit Span Dual Task: AB group: F(3, 18) =84.6, (p<.0001); BA group: F(3, 18)= 28.4, (p<.0001)	"[T] the specific rehabilitation programme for divided attention had specific effects on divided attention and was useful and helped patients to deal more rapidly and more accurately with dual-task situations."	Crossover trial. Small sample size. Data suggest training can improve dual task performance by enhancing attention.
Evans, 2009	Cognitive Motor	RCT	Sponsored by Cambridgeshi	N = 19 patients with	Treatment group:	Treatment group received 2 dual-task	A baseline assessment	Pre-training (T1) and post training (T2)	"Results suggest that	Small sample with

(3.5)	Dual-Tasking		re NHS Research and Development Support Team. No COI.	impairments in cognitive-motor dual tasking impairments due to a neurological injury.	Mean age 44.4 Control group Mean Age: 45.11 Sex (M:F) 17:2	practice sessions a day, 5 days a week for 5 weeks. Practice sessions consisted of 2min walking sessions, with increasing cognitive demands. Control group was assessed once a week by a therapist, and patients kept a diary of their daily experiences with dual-tasking.	was created before training and a follow up was conducted 5 weeks from baseline.	scores among the treatment vs control groups: (T1, T2 for treatment vs T1,T2 control) Sentences and walking combined (13.9, 19.9 vs 15.44, 15.33 ($p<0.05$)) Tones and Walking Combined (17.2, 19.1 vs 15.33, 20.11 ($p<0.05$)) Memory Span & Track task approached significance (93.0, 94.01 vs 84.68, 90.44 ($p<0.10$))	the intervention may lead to improvement, but that any improvement may be limited to this task and not generalize to other cognitive–motor task combinations."	variable therapist contact time. Sparse methods Trend towards dual-tasking improvement from interventional group.

Evidence for the Use of Attention Regulation Training

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Novakovic-Agopian, 2011 (5.0)	Attention Regulation Training	RCT	Sponsored by the Office of Research and Development Rehabilitation R&D Service Department of Veterans Affairs, and the California PacificMedical Center Foundation. COI, Drs Novakovic-Agopian, Chen, Abrams, and McKim, andMs Rossi are affiliated with the Veteran's AdministrationMedical Center, San Francisco, California.	N = 16 patients with chronic acquired brain injuries for more than 6 months.	Age range 24-63 years old, 7 males & 9 females, and mean age of 50.	Goal training (n=8) vs Education goals (n=8)	Follow-up was taken at baseline, at week 5, and at week 10 for both short-term and long-term effects.	At week 5 no significant difference between the groups for Working Memory (P<0.0001), Mental Flexibility (P = .009), Inhibition (P=0.005), and Sustained Attention (P=0.01). Significant differences were found in the Memory Domain for changes for Learning at P=0.02 and Delayed Recall at P=0.01. At week 10 significant difference between the groups for Attention and Executive Function Domain (P < .0001) and the following subdomains in Working Memory (P=0.0008), Mental Flexibility (P=0.0008), Inhibition (P=0.01), and Sustained Attention (P=0.01).	"Training in goal-oriented attentional self-regulation is theoretically driven and feasible in a research setting. Pilot results suggest improvements in cognitive and functional domains targeted by the intervention."	Pseudorandom crossover. Pilot RCT with small sample. Mixed pop., primarily TBI. Data suggest goal-oriented attentional self regulation improves attention and executive function.
Shum, 2011 (5.0)	Attention Regulation Training	RCT	Sponsored by the National Health and	N = 45 patients with moderate to severe TBI	Age range 19-57 years old, 37 males & 8 females, and	4 groups of intervention at (n=12), (n=11), (n=11), &	Follow up was at week 4 and week 8	No significance between the pre-intervention rating and the change score among the 4 groups.	"The results provide evidence that prospective	Data suggest memory improvement from short duration as

			Medical Research Council Project Grant (no: 277002). No CoI.		mean age of 38.	(n=11) subjected to CAMPROMPT, CAMPM, and SPRS. CAMPROMPT= Cambridge Behavioural Prospective Memory Test; CAPM=Comprehensive Assessment of Prospective Memory; SPRS= Sydney Psychosocial Reintegration Scale;		The self-aware S-A plus compensatory Training was tested for CAMPROMPT: Pre-inter 26.50 (19.50; 28.75) P=0.808, change 3.50 (0.25; 9.75) P=0.034, CAPM: Pr-inter 2.03 (1.74; 2.48) P=0.664, Change –0.15 (–0.48; 0.00) P=0.692 and SPRS: Pre-inter 44.50 (37.00; 51.25) P=0.295, and Change 6.00 (0.00; 14.25) P=0.110.	memory can be improved in patients with traumatic brain injury using a compensatory approach in a relatively short duration and low intensity intervention."	well as low intensive interventions.
Niemann 1990 (3.5)	Attention Regulation Training	RCT	No mention of sponsorship or COI.	N = 29 outpatients suffering from moderate to severe traumatic brain injury.	Mean age for experiment and control groups; 28.9 and 34.3.	Experimental group or measures of attention + memory, 9 weeks for 2-hour sessions per week (N = 13) vs Control group or measures or attention, 9 weeks for 2-hour sessions per week	9 weeks after initial intervention	The attention group improved vs memory group on four measures of attention, Wilks's lambda = 64, approximated: F (4, 21) = 2.93, p < 0.02, one-tailed.	"The experimental design evaluated outcome by juxtaposing a multiple baseline procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on 2nd set of neuropsychological tests."	No sham or control group. Results equivocal regarding efficacy.

						(N = 13). Measures of attention: d2 test, Paced Auditory Serial-addition task revision (PASAT-R), Divided Attention Test and Trail Making Test Part B test. Memory tests: Rey Auditory Verbal Learning Test-modified (RAVLT-M), and Learning Block span learning test (BSLT).				
Chen, 2011 (3.5)	Attention Regulation Training	RCT	Sponsored by the Veteran's Administration Rehabilitation Research and Development and the California Pacific Medical Centre Foundation. No CoI.	N = 12 patients with chronic acquired brain injuries greater than 6 months.	Age range 24-63 years old, 5 males & 7 females, and mean age of 48.	Goals Training (n=5) Vs Education (n=7) and patients were switched at 5 weeks.	Follow-up given at the end of assessment 1 at 5 weeks, and assessment 2 at 10 weeks.	Significant improvements results were shown on behavioral measures of attention and executive control. No significant results between education and goals training at P=0.41 vs the crossover between goals training and education at P=0.40.	"[M]odulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training." "These results suggest that enhanced modulatory control over visual processing and a rebalancing of prefrontal functioning may underlie improvements in attention and executive control."	Mixed population of TBI, stroke, hemorrhage, resection or chemotherapy . Data suggest goal-directed attention training regulation improves modulary control over neural processing.

Evidence for the Use of Motivational Interviewing

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zatzick 2014 (6.5)	Motivational Interviewing	RCT	Grants supplied by National Institute on Alcohol Abuse and Alcoholism R01/AA016102 and National Institute of Mental Health K24/MH086814 were given to support this article. No declaration of interests.	N = 878	208 females, 670 males. Mean age is 36.9.	Intervention sites (n=10, patient n=469). Vs control sites (n=10, patient n=409)	Follow up after baseline at 6 and 12 months post-injury.	In the first year following injury, intervention group participants had a significant 8% reduction in Alcohol Use Disorders Identification Test (AUDIT) hazardous drinking cut-offs compared to control group. Intervention group also had a significant increase in abstinent from drinking days over the next year post-injury (*P* = 0.02).	"[T]hese findings suggest that a brief trauma center intervention based upon MI (motivational interviewing) principles can yield relevant population level reductions in alcohol consumption and related hazardous drinking outcomes."	Population mixed between TBI and others. Assessment via interviews. Data suggest modest (8%) reduction in problem drinking patients, especially non-TBI patients.
Ponsford 2016 (5.5)	Motivational Interviewing	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))	"Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI."	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54 vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease

										anxiety and depression.
Tweedly 2012 (5.5)	Motivational Interviewing	RCT	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	"There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach statistical significance…. Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population."	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.
Hsieh 2012 (score=5.5)	Motivational Interviewing	RCT	This study was supported in part by grants from the National	N=27, participants with TBI in past. No	21 males, 6 females; mean age 38.0±13.2.	Group 1: received motivational interviewing and cognitive behavioral therapy. (N=9)	Baseline, week 3, week 12, week 21.	NDC+CBT group indicated significant reduction on primary outcome HADS-Anxiety (effect size: 0.24; 95%CI:	"The results provided preliminary support for the adapted CBT	Data suggest motivational interviewing or CBT may be effective for TBI

			Health and Medical Research Council and Monash University, and a scholarship from the Victorian Brain Injury Recovery Association (Australia). No COI.	current psychosis.		vs. Group 2: received non-directive counseling and cognitive behavioral therapy. (N=10) vs. Group 3: treatment as usual. (N=8)		-0.64 to 1.12); MI+CBT group also showed significant reduction on HADS-Anxiety (effect size: 0.50; 95%CI:-0.49 to 1.50). No significant reduction on DASS-Anxiety measurement in both groups (p>0.05). Female participants in NDC+CBT group showed lower HADS (p=0.00) and DASS (p=0.03), comparing with male patients.	programme, and the potential utility of MI as treatment prelude. Longer follow-up data are required to evaluate the maintenance of treatment effects."	related anxiety as both treatment groups outperformed the TAU group.
Bombardier 2009 (5.0)	Motivational Interviewing	RCT	Supported by a grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 126 with TBI, discharged from inpatient rehabilitation	32 female, 94 male. Mean age 36 years	Motivational Interviewing via phone call at day 1 and again at months 1, 2, 3, 5, 7, and 9 (n = 62) vs Control group (n = 64)	1 year	Brief Symptom Inventory-Depression (BSI-D), Neurobehavioral Function Inventory-Depression subscale (NFI-D), Mental Health Index-5 (MHI-5). Pre-post changes on BSI-D subscale showed significant between group differences (Control 0.45±0.95, Telephone 0.08±0.72, P=0.019). Posttreatment BSI-D score: control 1.03±1.05, telephone 0.44±0.66 (P=0.000). Posttreatment NFI-D score: control 32.3±12.9, telephone 24.0±9.1 (P=0.000). Posttreatment MHI-5 score: control 20.2±5.9, telephone 23.4±4.8 (P=0.002). Pooled difference in treatment outcome via BSI-D score	"Telephone-based interventions using problem-solving and behavioral activation approaches may be effective in ameliorating depressive symptoms following TBI. Proactive telephone calls, motivational interviewing, and including significant others in the intervention may have contributed to its effectiveness."	High dropouts Data suggest the use of scheduled telephone interventions utilizing problem solving and behavioral activation techniques may help reduce TBI depressive symptoms.

								changes did not statistically vary by age, sex, or coma severity (P > 0.15 for all). Significant difference in white vs nonwhite participants, white reporting higher scores (P = 0.002).		
Ponsford 2012 (score=4.5)	Motivational Interviewing	RCT	Authors declare no conflict of interest.	N=60, TBI rehabilitation patients.	No mention of sex; mean age of 35.	Group 1: Motivational interview technique to limit alcohol use and supplemental information (N=18) vs. Group 2: Only received supplemental information (N=15) vs. Group 3: Informal discussion (control). (N=15)	Participants were assessed baseline and 6 months after.	No significant difference was found between intervention and control groups of overall alcohol consumption. But low relative risk of drinking (frequent or heavier drinking) was associated with action stage of readiness to change ($p<0.001$). Extra education (1 year) indicated to associated with higher relative risk of drinking (frequent drinking: p=0.019; heavier drinking: p=0.040).	"[R]eadiness to change and depression represent potentially important factors on which to focus efforts to minimize alcohol use following TBI. The knowledge that individuals with higher rather than lower education may be at greater risk of heavier post injury drinking is also noteworthy."	Data suggest a person's readiness to change and treatment of depression is key in treating alcohol use post TBI.
Bell 2005 (score=4.0)	Motivational Interviewing	RCT	Supported by the National Institute of Disability and Rehabilitation Research, US Department of Education No COI.	N=171 participants with primary diagnosis of TBI.	132 males, 39 females; mean age 36±15.	Group 1: received motivational interviewing through telephone. (N=85) vs Group 2: received treatment as usual. (N=86)	Baseline and 1 year.	Patients with scheduled telephone intervention indicated better primary composite outcomes (p=0.002) including perceived quality (p=0.006) and functional status (p=0.003), comparing with patients with standard follow-up care. Other measurement (GCS and EuroQol scores) indicated no significant change in both groups.	"In this study, we demonstrated the successful use of scheduled telephone counseling and education in improving outcomes for people with moderate to severe TBI and their families. Results are similar to that for other	Usual care bias. Data suggest moderate to severe TBI patients and families may benefit from scheduled telephone interventions to improve functional status and overall well-being.

									medical populations (eg, diabetes, heart disease, arthritis, depression)."	
Sander 2012 (3.5)	Motivational Interviewing	RCT	This work was supported by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education (grants H133B031117, H133B090023, H133A070043, and H133A070029). No COI.	N = 104	85 males, 19 females; Mean age is 35.75 years.	Standard of Care (N = 50) Vs. Intervention group (N = 54).	Follow up period of 3 months.	History of alcohol binging was not significant (p=.55). There was an effect on group treatment and control on AEQ-III GP. Treatment vs control (p=.01). Group effect and binge history did not interact (p=.06). Treatment wasn't effected by injury severity, history of binges, attribution or site (p=.25). After adjustment there was still no effect (p=.86).	"Brief intervention can be effective for educating on the negative impact of alcohol use for people with severe TBI who have emerged from posttraumatic amnesia. Attribution of the injury to alcohol use could potentially increase readiness to change in some settings, and might be used to generate discussion about the negative impact of alcohol use."	Brief treatment (10min video) followed up by education and a motivational interview did not show efficacy to improve problem alcohol use or readiness to change.
Corrigan 2005 (3.0)	Motivational Interviewing	RCT	Funding for this project was provided by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration,	N= 195	138 males, 57 females. Mean age is 36.6 years.	195 participants randomly assigned into 4 groups. (1) Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incetive.	Appointments unspecified and varied by participant preference. Follow up at 3 and 6 months.	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview (45%) and attention control (45%) groups. Significance indicated through client signing an individualized service	"Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational interview and control groups….	Data suggest financially compensated and barrier reduction groups were more likely to sign on to a substance abuse treatment program post TBI than the

			via Grant 5 KD1 TI12013. No mention of COI.					plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign (*M* = 22.8 days, *SD* = 14.7), (*M* = 44.0 days, *SD* = 35.8) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman's (1997) conception of how engagement in treatment can affect later retention."	motivational interview or attention control groups.

Evidence for the Use of Emotional Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tornås 2016 (score=7.0)	Emotional Training	RCT	Supported by the Norwegian Extra Foundation for Health and Rehabilitation, EXTRA funds. No mention of COI.	N=70 patients with verified acquired brain injury.	Mean age: 42.89 years; 38 males, 32 females.	Goal Management Training group (GMT) (n=33) vs. Brain Health Workshop (BHW) (n=37).	Follow-up at 6 months.	BRIEF-A scores in three index reduced significantly in both groups. Behavioral regulation index in GMT group reduced from 60.87 ± 11.16 to 53.87 ± 10.54 ($p<0.001$) vs. BHM group reduced from 62.24±11.72 to 58.62±10.89 ($p<0.05$). Metacognitive index in GMT group reduced from 63.68±9.65 to 57.90±11.25 ($p<0.01$) vs. BHM group reduced from 66.76±9.69 to 63.74±9.88 ($p<0.01$). Global executive composite in GMT group reduced from 63.32±9.24 to 56.68±10.86 ($p<0.001$) vs.BHW group reduced from 65.97±10.2 to 62.85±10.01 ($p<0.05$). Dysexecutive Questionnaire (DEX) score in GMT group reduced from 28.33 ±11.75 to 21.7 ±12.02 ($p<0.001$); in BHM group reduced from 29.06 ±13.32 to 28.3±14.17 (not statistically significant).	"[G]MT combined with external cueing is an effective metacognitive strategy training method, ameliorating executive dysfunction in daily life for patients with chronic ABI."	Data suggest GMT plus external cuing may be beneficial for chronic TBI patients to restore some executive function.
Tornås 2016 (score=6.0)	Emotional Training	RCT	Supported by the Norwegian	N=70 individuals	Mean age: 43±13 years;	Goal Management	Follow-up at baseline,	Dysexecutive Questionnaire (DEX)	"The present results have	Baseline differences

			Extra Foundation for Health and Rehabilitation through EXTRA funds. No mention of COI.	with TBI and executive dysfunction.	38 males, 32 females.	Training (GMT) (N=40) Vs Brain Health Workshop (BHW) (N=40)	post intervention (8 weeks), and 6 months.	Baseline vs Follow up, GMT: 4.55±2.69 vs 2.94±2.34 (p<0.001). Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) baseline vs follow-up, GMT: 60.03±11.49 vs 53.97±9.75 (p<0.001). QOL Total score, baseline vs follow-up, GMT: 3.26±0.54 vs 3.57±0.53 (p<0.001). Cognitive subscale score: 2.97±0.68 vs 3.33±0.73 (p<0.01). ADL score: 3.12±0.70 vs 3.59±0.66 (p<0.001). Emotional Subscale score: 3.75±0.88 vs 4.10±0.69 (p<0.01). Physical Subscale Score: 3.50±0.76 vs 3.70±0.83 (p<0.05).	promising implications because they suggest that a relatively brief metacognitive intervention targeting sustained attention and emotional regulation is effective in improving emotional regulation and QOL even years after injury.	between groups for time in years since injury (8.9 vs. 6.8).
Westerhof-Evers 2017 (score=4.5)	Emotional Training	RCT	No mention of sponsorship. The authors declared no COI.	N=61 patients with traumatic brain injury from moderate to severe.	Mean age: 43.2±13 years; 83 males, 17 females.	T-ScEmo Intervention group (n=30) vs. Cogniplus group (n=29) vs. Healthy control group (n=42).	Follow-up at 3, and 5 months.	Primary outcome "The Awareness of Social Inferences Test" (TASIT)-Short score indicated no significant change in the two treatment groups. T-ScEmo group had TASIT-short score changed from 63.1±7 to 63.7±7 (p=0.31) vs. Cogniplus group had TASIT-short score changed from 61.4±6 to 62.3±7 (p=0.28).	"[I]mpairments in social cognition can be effectively dealt with by using a comprehensive treatment protocol, leading to improvements in everyday life social functioning."	Data suggest significant improvement in social cognition with T-ScEmo in terms of facial affect recognition, theory of mind, proxy-rated empathic behavior, societal participation and treatment

										goal attainment with gains lasting up to 5 months.
Radice-Neumann 2009 (score=4.5)	Emotional Training	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State University of New York.	N = 19 with acquired brain injury, minimum 1 year post-injury	Mean age: 43 years; 12 male, 8 female.	Facial Affect Recognition "FAR" (n = 10) vs Stories of Emotional Inference "SEI" (n = 9), both treatments given for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (P=.225, P=.312), LEAS-Self (P=.064, P=.732), LEAS-Other (P=.340, P=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, P=.004). DANVA2-AF: Significant performance change found in FAR (P<.001) and SEI (P=.006). DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR P=.584, SEI P=.166). LEAS-Self: Both significant change over time (FAR and SEI both P=0.019). LEAS-Other: Significant change over time for FAR (P=0.004). No change in SEI (P=.579). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (P = .042).	"Training can improve emotion perception in persons with ABI. Although further research is needed, the interventions are clinically practical and show promise for the population with ABI."	Small groups. No sham/placebo. Data suggest specific training may enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improvement in ability to infer how they would feel in a given context.

								No change perceived in SEI (P = .363).		
Neumann 2015 (score=3.5)	Emotional Training	RCT	No COI. Sponsored by the National Institute on Disability and Rehabilitation Research.	N = 203 with moderate to severe TBI	Mean age: 39.8 years; 151 male, 52 female.	Faces Intervention – program to teach participants to recognize emotions from facial expressions (n=24) vs. Stories Intervention – program to teach participants to decipher emotions from the context of short stories (n=23) vs. Cognitive Training Control – individual training without an emotional education component (n=24). All interventions were one-on-one computer-assisted treatments given by therapist, administered for one hour, three times per week, for three	3 and 6 months	Diagnostic Assessment of Nonverbal Accuracy-2 Adult Faces mixed model MANCOVA results: Faces vs. Control interventions – Group – F1,44=5.72 (p=0.031), Effect size partial η2=0.11, Time – F2,90=0.92 (p=0.421), Effect size partial η2=0.02, Group x Time – F2,90=(1.14) (p=0.380), Effect size partial η2=0.02. Stories vs. Control interventions – Group – F1,44=1.63 (p=0.239), Effect size partial η2=0.04, Time – F2,88=0.58 (p=0.614), Effect size partial η2=0.01, Group x Time – F2,88=(1.22) (p=0.350), Effect size partial η2=0.03. Emotional Inference from Stories Test mixed model MANCOVA results: Faces versus Control interventions – F1,44=1.10 (p=0.349), Effect size partial η2=0.02, Time – F2,90=4.25 (p=0.059), Effect size partial η2=0.09, Group x Time – F2,90=(1.57) (p=0.553), Effect size partial	"The Faces Intervention effectively improved facial affect recognition in participants with chronic post–traumatic brain injury, and changes were maintained for 6 months. Future work should focus on generalizing this skill to functional behaviors."	More males randomized to faces group than females. Data suggest that the faces intervention enhanced facial affect recognition in chronic TBI patients and this improvement was sustained for 6 months suggesting faces better than either stories or control groups.

						weeks (totaling to 9 sessions).		η2=0.03. Stories vs. Control interventions – Group – F1,44=2.62 (p=0.167), Effect size partial η2=0.06, Time – F2,88=9.65 (p=0.001), Effect size partial η2=0.18, Group x Time – F2,88=(1.78) (p=0.253), Effect size partial η2=0.04.		

Evidence for the Use of Goal Setting

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
McPherson 2009 (6.0)	Goal setting	RCT	Sponsored by the Health Research Council of New Zealand. No COI.	N = 34 with moderate to severe traumatic brain injury.	Mean age for goal management / identity orientated / and usual care: 29 / 28 / and 40 years; 17 males and 7 females.	Goal management training (N = 12) vs Identity Orientated goal training, identity map for intervention delivery and scripted a six-step process for clinicians to aid mapping process (N = 10) vs Usual Care current rehabilitation plan (N = 12).	6 - 8 weeks	Goal attention scale, mean values: goal management vs identity oriented goal vs and usual care: base / post / follow-up; 26.38 (2.62) vs 26.15 (2.15) vs 28.34 (4.94) / 47.56 (14.11) vs 50.76 (13.71) vs 57.69 (12.25) / 43.97 (16.08) vs 48.48 (11.65) vs 51.63 (11.51).	"These theoretically informed approaches to goal setting showed promise but were time intensive and at times difficult for practitioners to utilize."	Pilot study. No significant differences reported. Data suggest no differences between usual care and either of 2 goal setting approaches (Goal Mgt. training for structure) and (Identity oriented goal training for process). Both were time intensive and often difficult to utilize.
Tornas 2016 (6.0)	Goal Setting	RCT	Supported by the Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds. No mention of COI.	N=70 individuals with TBI and executive dysfunction.	38 males, 32 females; Mean age of 43±13.	Goal Management Training (GMT) (N=40) Vs Brain Health Workshop (BHW) (N=40)	Follow-up at baseline, post intervention (8 weeks), and 6 months.	Dysexecutive Questionnaire (DEX) Baseline vs Follow up, GMT: 4.55±2.69 vs 2.94±2.34 ($p<0.001$). Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) baseline vs follow-up, GMT: 60.03±11.49 vs	"The present results have promising implications because they suggest that a relatively brief metacognitive intervention targeting sustained attention and emotional regulation is effective in improving emotional	Baseline differences between groups for time in years since injury (8.9 vs. 6.8).

								53.97±9.75 (p<0.001). QOL Total score, baseline vs follow-up, GMT: 3.26±0.54 vs 3.57±0.53 (p<0.001). Cognitive subscale score: 2.97±0.68 vs 3.33±0.73 (p<0.01). ADL score: 3.12±0.70 vs 3.59±0.66 (p<0.001). Emotional Subscale score: 3.75±0.88 vs 4.10±0.69 (p<0.01). Physical Subscale Score: 3.50±0.76 vs 3.70±0.83 (p<0.05).	regulation and QOL even years after injury.	
Ownsworth 2008 (5.0)	Goal Setting	Community Life Based Goals	Sponsored by a grant from the Centre of National Research on Disability and Rehabilitation Medicine (CONROD and a National Health and Medical Research Council Public Health Fellowship. No mention of COI.	N = 35 with brain injury units and community-based rehabilitation services over 12 months	Age range 21-62 years old, 19 males & 16 females, and mean age of 43.89.	Individual Intervention (N = 10) vs Group Intervention (N = 11) vs Combined Intervention (N = 10)	3 months	Pre-post comparison and pre-follow-up comparison, PCRS: P=0.482 and P=0.150 respectively compared to P<0.025 and P=0.109 for Group and P=0.463 and P=0.114 for Combined groups.	"These findings generally support the efficacy of brief intervention formats following acquired brain injury, although further research is needed to examine clients' suitability for particular interventions."	Small sample sizes. Wait-list control bias. Data not well reported as compared to controls. Authors interpretations that trend towards better results with individual than group approach.

Doig 2011 (4.5)	Goal Setting	Randomized Cross over trial	Sponsored by Alexandra Hospital Foundation and the Queensland Health Community Rehabilitation Research Scheme. Principle researcher was in receipt of a University of Queensland Postgraduate Research Scholarship while conducting research.	N=14 diagnosed with TBI as evidence by loss of consciousness.	12 males, 2 females; Mean age of 24.5 (19.7-29.2)	Group 1 6 1-hour weekly sessions Home-based goal oriented therapy, followed by hospital based therapy of same amount of time (N=7) Vs Group 2 6 1-hour weekly hospital based goal oriented therapy following by home-based therapy (N=7)	1, 6, 12, and 18 weeks	Group 1, vs Group 2, Week 6, Goal Attainment Scale (GAS): 36.1 (31.7-42.8) vs 35.5 (28.9-40.9) ($p<0.05$). Group 1 & 2, baseline vs Wk 18: 36.1 (21-38) vs 50.0 (46.2-58) ($p<0.01$), & 35.0 (28.9-40.9) vs 53.6 (50-55) ($p<0.01$). Mayo Portland Adaptability Index (MPAI), Group 2, baseline vs week 18: 47 (37-50) vs 39 (33-48) ($p<0.05$). Canadian Occupational Performance Measurement (COPM) performance, Group 2, baseline vs wk 12 & 18: 4.0 (3.3-3.5) vs 7.2 (6.5-8.3) ($p<0.01$) & 8.6 (8.0-9.5) ($p<0.05$). COPM satisfaction, group 2, baseline vs wk 12 & 18: 4.0	"The results of this pilot investigation indicated that the outpatient therapy program was equally effective when carried out at home compared with a day hospital setting in terms of goal achievement, psychosocial reintegration, ability and adjustment and effect on environmental barriers."	Repeated measures crossover design small smaple. Data suggest comparable efficacy between groups.

								(2.0-4.7) VS 7.5 (6.2-7.7) (p<0.01) & 8.6 (8.0-10.0) (p<0.01).		
Gauggel 2001 (4.5)	Goal Setting	RCT	No mention of sponsorship or COI.	N=62 patients with Cerebral Vascular Accidents (CVA) and Closed Head Injury (CHI). N=47 control patients with orthopedic disorders and no TBI	No mention of gender; Mean age for Brain-Damaged groups: 41.5±13.8 and 41.7±14.4. Orthopedic Injury: 42.2±12.4 and 44.3±13.5.	High, Specific goals set for TBI patients (N=32) Vs "Do your best" goals given to TBI patients (N=30)	2 weeks after Neuropsych test and Respone time blocks a few days follwing	Response latency, Goal by block interaction, F(1,105)=31.65 (p=0.0001). Indicating participants with high goals responded faster. Goal X Bock interaction F(1,105)=9.14(p <0.01) indicating that high goals led to faster Response time. Goal Setting, chronic vs acute patients, mean personal goal (SD): -18.2% (11.1) vs -11.1% (6.0) t(23)=-2.26, (p=0.03).	"[O]ur experiment provides support for an application of the goal setting approach to the field of neuropsychology. The goal setting technique seems to be a useful tool for the investigation of motivation and self-regulation in brain-damaged patients.	Data suggest the speaker and high goal setting group responded faster than the "do your best goal" group.

Hart 2002 (3.5)	Goal Setting	Randomized Prospective Trail	Supported by grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N=10 people with moderate to severe TBI.	8 males, 2 females; Mean age of 31.5 (19-45)	Participants got a voice organizer to remind them of goals set by clinician (N=5) Vs No voice organizer or cue recall (N=5)	Follow-Up of 1 week	Mean Recall Score, Recorded vs unrecorded cue recall groups: 5.5±1.9 vs 2.1±1.6 (p<0.001). Mean Recall Score, recorded vs unrecorded free recall group: 4.4±3.0 vs 0.5±0.8 (p<0.001). All 10 patients reported liking the recall device.	"Portable electronic devices have the potential to assist with treatment areas beyond tasks involving prospective memory"	Small sample (n=10). Sample had variable time since injury (3mo to 18yrs). No long term F/U (only 1 week recall F/U).
Gauggel 2002	Goal Setting	Non-RCT	No mention of sponsorship or COI.	N=87 patients with Cerebral Vascular Accidents (CVA) and Closed Head Injury (CHI).	No mention of gender; Mean age for High, Specific goal: 39.0±15.6. Self-stated goal group: 38.6±15.9. "Do your best" goal group: 47.4±13.7.	High, Specific goals set for TBI patients (N=30) Vs "Do your best" goals given to TBI patients (N=29) Vs Self-stated goals for TBI patients (N=28)	All trials done in one day.	Goal Commitment, High, Specific group, assignment of goal vs last trail: M=23.4 (4.9) vs M=24.2 (4.5) r=0.72 (p<0.001). All three groups performed very low error rates. ANCOVA, Group effect, F(2, 83)=7.57 MSE=65.9, (p=0.001). High Specific Goal performed more calculation in trial 4 vs Do you best (p<0.0001)	"[B]rain-damaged patients do not necessarily have goal setting difficulties in a simple laboratory task that provides sufficient performance feedback. Moreover, it seems that brain-damaged patients can influence their own motivation quite well if they pay adequate attention to their own performance, the conditions under which they occur, and the immediate and distal effects they produce."	Exclude. Methods indicate trial not completely randomized. Rather assigned to groups and then some randomized.

								and self-group (p<0.009).		

Evidence for the Use of Peer-Mentoring Program

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Simpson 2011 (6.5)	Mentoring - TBI	RCT	Sponsored by a National Health and Medical Research Council Health Professional Fellowship grant. No COI.	N = 17 with severe TBI and experienced posttraumatic amnesia and moderate to severe hopelessness	Mean age: Treatment group 39.41 Wait List group 44.08 No mention of Sex	Treatment group (N = 8) received 20 hours of group based therapy, consisting of 10 weekly 2hour sessions. vs Wait List Group received standard care from Brain Injury Rehabilitation Unit. (N = 9)	3 months	Significant group-by-time interaction was found for BHS in the treatment group ($F_{1,15} = 13.20$, ($p = 0.002$)), At follow up 75% of patients in the treatment group retained the benefits from treatment. Suicide ideation, depression, social problem solving, self-esteem, hopefulness displayed no significant group-by-time interactions or main effects.	"This trial provides initial evidence for the efficacy of a psychological intervention in reducing hopelessness among long-term survivors with severe TBI."	Small sample. Data suggest treatment gains maintained 3 months post-intervention for 75% of patients evidenced by reduction in mean Beck Hopelessness Scale.
Hanks 2012 (4.0)	Behavioral Programs	RCT	Sponsored by the U.S. Department of Education-National Institute of Disability Research and Rehabilitation —The Traumatic Brain Injury Model Systems Project. No COI.	N = 199 with TBI.	Mean age for control and mentoring group: 40.90 ± 17.33 / 38.46 ± 17.60 years, 136 males and 22 females.	Mentoring (N = 96) vs No mentoring (N = 62). Outcome measures: Peer Mentoring Questionnaire; Brief Symptom Inventory-18; Family Assessment Device (FAD); Coping Inventory for Stressful Situations; Short Michigan Alcohol	2 years	Differences in subjective perception of community integration and levels of depression or anxiety, ($p = 0.35$). 88% in the mentoring group reported positive experience. Those who received mentoring had better behavioral control and less chaos in the living environment / lower alcohol use / less	"Mentoring can be an effective way to benefit mood and healthy coping after TBI, and it can help to prevent maladaptive behaviors, such as substance abuse and behavioral dyscontrol, in the living situation."	Data suggest equal in efficacy.

						Screening Test; Medical Outcomes Study 12-Item Short- Form Health Survey; and Community Integration Measure.		emotion-focused / avoiding coping / and good physical quality of life: p = 0.04 / 0.01 / 0.04 / 0.03 / and 0.4.		
Struchen 2011 (3.0)	Mentoring - TBI	RCT [761]	Sponsored by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education. No mention of COI.	N = 30 with TBI	Mean age of Peer Partners: 31.7 Sex (M:F) 24:6	Active peer partnering group (N=12) participants were matched with a social mentor, and received 3 months of active social mentoring. Social mentors aimed to foster social networking and social interaction with their matched peer. vs The wait list group (N=18) did not receive active mentoring and completed a weekly social activity survey (WSAS).	2 months	No statistically significant main or interaction effects were observed for social integration, as measured by the Social Integration subscale of CHART-SF,Wilks lambda F1,25 = 2.10, (p = 0.16). No statistically significant interactions or main effects of time and/or group were observed for various measures of social network size and social activity level. A significant change was observed in the CES depression scale for the active mentoring group F1,25 = 9.73, (p < 0.01), however, an increase of depressive symptoms was observed after peer mentoring. The active mentoring group showed a significant increase of perceived social support after mentoring. F1,25 =4.66, (p<0.05).	"Satisfaction ratings for the SPM program were uniformly high and selected positive findings encourage further investigation of social mentoring as an intervention to effect improvements in social integration."	Sparse methods. Pilot study with small sample size and injury severity differences between groups. Data suggest increased social support after mentoring observed but depression symptoms increased as well. Trend towards increased social life satisfaction.

Evidence for the Use of Video Feedback

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Schmidt 2012 (7.0)	TBI	RCT	Sponsored by a partial grant from the Occupational Therapists Board of Queensland. JS supported by fellowship by the Wenkart Foundation, Australia and NAL was supported by the Balnaves Fellowship provided by the Cerebral Palsy Alliance, Australia. No COI.	N = 54 with TBI and impaired self-awareness.	Mean age 40 (13) years; 46 males and 8 females.	Video plus verbal feedback group following 4 meal preparation sessions (N = 18) vs Verbal feedback plus 4 meal sessions (N = 18) vs Experiential Feedback plus 4 meal sessions (N = 18).	Unknown	Effect of feedback intervention on online awareness (measured by number of errors); mean difference for the video feedback group vs verbal vs experimental group: mean difference = 19.7; 95% CI = 9.2-30.1 vs mean = 12.4; 95% CI = 1.8-23.0).	"The results suggest that the video plus verbal feedback approach used in this study was effective in improving self-awareness in people with TBI."	Baseline dissimilarity in yrs post injury (1.5 vs. 4.7 vs. 5.8). Data suggest combining video and verbal feedback superior to verbal or experiential alone for improving self awareness.
Schmidt 2015 (4.5)	TBI	RCT	Sponsored by a grant awarded by the Occupational Therapists Board of Queensland. NO COI.	N = 32 with TBI and impaired self-awareness.	Mean age 42.2 (13.1) years; 27 males and 5 females.	Group 1, video plus verbal feedback group following 4 meal preparation sessions (N = 10) vs Group 2, verbal feedback plus 4 meal sessions (N = 10) vs Group 3, experiential Feedback plus 4 meal sessions (N = 10).	8-10 weeks	Maintenance of gains in online awareness: group 1 vs group 2 (mean difference 20.6, 95% CI 8.8 to 32.3) vs group 3 (mean difference 14.4, 95% CI 3.1 to 25.6). Differences in number of errors group 2 vs 3 (mean	"A combination of video plus verbal feedback is an effective technique for achieving maintained gains in self-awareness in people with TBI."	Same study population as Schmidt 12. Baseline dissimilary between groups post injury (2.6 vs. 8.4 vs. 8.1). Data suggest verbal plus video feedback best for self-awareness in TBI patients by 8-10 weeks post-intervention.

								difference 6.2, 95% CI −5.0 to 17.5).		

Evidence for the Use of Memory Rehabilitation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lannin 2014 (8.0)	Memory Rehabilitation	RCT	This work was supported by a grant from the Royal Rehabilitation Centre Sydney Foundation. No COI.	N = 42	33 males, 9 females; Mean age is 33.5 years.	Control Group. Non-electronic memory aids. (N = 21) vs Experimental Group. PDA. (N = 21)	1 or 2 years post intervention	From baseline to end of 8 week assessments: Control group had GAS t-score of 41.7 to 49.5. Trial had 41 to 53 (P=.0001).	"Occupational therapy training in the use of a handheld computer improved patients' daily memory function more than standard rehabilitation."	No long term follow-up. Data suggest use of handheld computerized equipment for memory aid significantly improved memory goals.
das Nair 2012 (6.0)	Memory Rehabilitation	RCT	Sponsored by grants from The Stroke Association, Remedi (2006/05), Universities UK (Overseas Research Students Award Scheme), and the University of Nottingham. No COI.	N = 72 with memory problems following traumatic brain injury, stroke or multiple sclerosis.	Mean age 47.7, (10.2) years; 32 males and 40 females.	Compensation, 10 sessions (N = 24) vs Restitution treatment programmes, 10 sessions (N = 24) vs A self-help group control 10 sessions (N = 24).	7-months	No significant effect of treatment on the Everyday Memory Questionnaire, (p = 0.97). At 7-months, mean score for compensation vs restitution vs self-help; 41.0 vs 36.6 vs 44.1. Internal memory Aids questionnaire, (p = 0.002). Treatment groups used more internal memory aids vs to self-help, (p < 0.01). Measure of mood / adjustment / and activity of daily living, (p > 0.05).	"These results show few statistically significant effects of either compensation or restitution memory group treatment as compared with a self-help group control."	Dissimilar time since diagnosis between groups. Mixed population of TBI, MS and Stroke patients. At 7 months data suggest similar efficacy between all groups for mood, memory functions and dialing living activities although the compensation and restitution groups used significantly more internal memory aids than did the self help group.
Tawmley 2014	Memory Rehabilitation	RCT	Supported by the	N = 34	32 males, 2 females; mean age	Supported Employment	No follow up	CogSMART is rated highly among the patients that use it.	"We tentatively conclude	Data suggest addition of Cog SMART may

(4.0)			DOD (award W81XWH-08–2-0193). No mention of COI.		is 31.9 years.	and CogSMART (N = 16) vs Enhanced Supported Employment (N = 18)		Cohen d effect sizes scores for group differences were .97 and .72. For supported employment and CogSMART showed small improvement.	that CogSMART may improve postconcussive symptoms and prospective memory performance. Psychoeducation regarding TBI and postconcussive symptoms and training in compensatory strategies appear to be perceived by Veterans as helpful."	improve post concussive symptoms and prospective memory for veterans with mild-moderate TBI.
Sumowski 2014 (score=3.5)	Memory Rehabilitation	Experimental	Supported by the Kessler Foundation and Children's Specialized Hospital. No COI.	N = 10	6 males, 4 females; mean age is 43.4 years.	Retrieval Practice (N = 10) vs Massed Restudy (N = 10) vs Spaced Restudy (N = 10).	No follow up	46.3% subjects recalled of verbal paired associates through retrieval practice, 12.5% through masses restudy, and 15% through spaced restudy (P = .00001).	"RP represents a promising memory strategy for survivors of TBI with memory impairment. In addition to the apparent effectiveness of RP, this strategy appears simple/straightforward to apply (quizzing oneself or someone else), cost-effective, safe, and noninvasive. RCTs of RP training are needed."	Not an RCT. Data suggest RP improved memory in severe TBI patients. Very small sample size (N=10).

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Vas, 2011 (4.5)	TBI	Higher-Order Reasoning Training	This research was funded by the Prothro-McDermott fund of the Dallas Foundation, Wood-Hayner-Yates TBI Research Fund, Julie and EdHawes, and theDee Wyly Research fund.	N = 35 participants with TBI, at least 1-year postinjury	Age range 20-65 years old, 16 males & 12 females, and mean age of 43.	Strategic Memory and Reasoning Training (SMART) (n=18, discontinued training: n=4) Vs Brain Health Workshop (BHW, control) (n=17, discontinued training: n=3)	Follow-up given end of assessment within 3 weeks, and at 6 months post training.	Significant results found in SMART group in posttraining (*P* = .007) and at 6 months posttraining (*P* = .004) when compared to pretraining. No significant results found in BHW at posttesting (*P* = .44), or at 6-months (*P* = .52) compared to pretraining.	"First, our findings revealed that 15 to 18 hours of SMART enhanced gist-reasoning in adults with TBI. Second, the effects of SMART generalized to untrained domains such as on the working memory measure of listening span and ratings of increased participation in daily activities. Third, there appeared to be sustained benefit (6 months posttraining) of SMART as compared to the control group (BHW)."	High dropout rate in both groups. Data suggest chronic TBI patients (at least 2 yr. post injury) benefit from SMART measured by gist-reasoning and measures of executive and lifestyle functions.

Evidence for the Use of Attention Process Training

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sohlberg 2000 (3.5)	Attention Process Training [770]	RCT Cross-over	No mention of sponsorship or COI.	N = 14 with 10 weeks of brain injury.	Age range between 18-60 years of age, gender not specified.	Condition A, 24 hours of attention process training over 10 weeks (N = 7) vs Condition B, 10 hours of therapeutic support and education over 10 weeks (N = 7).	10 weeks	Greater number of changes reported in memory and attention (1.59) vs psychological functions (.59), ($p < 0.0001$). The effect of intervention was significant, ($p = 0.05$) with greater (Paced Serial Addition Task) or PASAT scores after APT vs brain education.	"APT influenced self-reports of cognitive function and had a stronger influence on performance of executive attention tasks than was found with the brain injury education therapy."	Small sample. Data suggest most patients improved. APT influenced cognitive self reports and performance of attention related tasks and brain injury education improved psychological functions.

Evidence for the Use of Recreational Computing

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Gray 1992 (3.5)	Recreational Computing	RCT	Sponsored by a grant from the Scottish Home and Health Department, Chief Scientist Office. No mention of COI.	N = 31 with attentional dysfunction following traumatic or non-traumatic brain damage of acute onset.	Mean age for experimental / control groups: 16.18 (7.58) / 34.14 (18.44), 24 male and 9 female.	Experimental or computerized attentional retraining group of 14 sessions of 75 minutes each (N = 17) vs Control or recreational computing group of 14 sessions of 75 minutes each (N = 14).	6 months	Post test results show, in favor of the experimental group there was difference for the WAIS-R Picture Completion (P = 0.031) and for PASAT Information Processing Rate (IPR) (P = 0.023). At follow-up, for the experimental group IPR / total score at 4 improved during intervention and at follow up phase, (p = 0.004 and 0.001 / 0.007 and 0.018). And IPR shows improvement at 6-months for control group, (p = 0.034).	"[B]y 6-month follow-up the experimental group performed better on two tests related plausibly to attentional function, namely PASAT and the arithmetic subtest of the WAIS-R."	Small sample. Data suggest that at 6 months, experimental group performed better on tests related to attentional function (PASAT) and (WAIS-R).

Evidence for the Use of Computerized Attention Training with Visual, Auditory, and Divided Training

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Niemann 1990 (4.0)	Computerized Attention Training	RCT	No mention of sponsorship or COI.	29 outpatients suffering from moderate to severe traumatic brain injury.	Experimental group mean age: 28.9±8.2 years. Control Group: 34.3± 12 years.	Experimental Group: attention training (Six 2-hr sessions) Vs. Control Group: memory training (Six 2-hr sessions)	Baseline measures taken 2 times after completion of treatments.	Attention group improved more significantly than memory group on four measures of attention: Wilks's lambda=64, approximate F(4,21) =2.93, p<.025, one-tailed. Subsequent univariate *F* tests revealed a significant difference between the attention group and the memory group on the TMT-B, *F(l,* 24) = 5.25, *p* < .015, one-tailed. This significance was felt acceptable despite the fact that	"The experimental design evaluated outcome by juxtaposing a multiple baseline procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on a 2nd set of neuropsychological tests. The experimental group improved significantly in comparison with the control group on measures of attention."	Data suggest moderate-severe TBI patients in experimental group improved significantly in comparison to controls in attention measures.

								the adjusted level of .013 for multiple comparisons was not met. The reversed pattern between the two groups on four memory measures was not confirmed, Wilks's lambda = .88, approximated *F(4, 2*1) = < 1, *p* > .50. In contrast with the baseline measures, the tests of the SDNTB were administered only before and after the training. The result of the 2 X 2 MANOVA was nonsignificant for the group effect, Wilks's lambda = .79, approximated *F(3,* 22) = 1.94, *p* > .10, two-tailed; the trial effect,		

								Wilks's lambda = .88; approximated *F(3,* 22) = .96, *p* > .40, two-tailed; and the Group X Trial interaction, Wilks's lambda = .98, approximated F(3, 22) = . 16; *p* > .90, two-tailed.		
Gray 1992 (3.5)	Computerized Attention Training	RCT	Sponsored by a grant from the Scottish Home and Health Department, Chief Scientist Office. No mention of COI.	N = 31 with attentional dysfunction following traumatic or non-traumatic brain damage of acute onset.	Mean age for experimental / control groups: 16.18 (7.58) / 34.14 (18.44), 24 male and 9 female.	Experimental or computerized attentional retraining group of 14 sessions of 75 minutes each (N = 17) vs Control or recreational computing group of 14 sessions of 75 minutes each (N = 14).	6 months	Post test results show, in favor of the experimental group there was difference for the WAIS-R Picture Completion (P = 0.031) and for PASAT Information Processing Rate (IPR) (P = 0.023). At follow-up, for the experimental group IPR / total score at 4 improved during intervention and at follow up phase, (p = 0.004 and	"[B]y 6-month follow-up the experimental group performed better on two tests related plausibly to attentional function, namely PASAT and the arithmetic subtest of the WAIS-R."	Data suggest that at 6 months, experimental group performed better on tests related to attntional function (PASAT) and (WAIS_R).

								0.001 / 0.007 and 0.018). And IPR shows improvement at 6-months for control group, (p = 0.034).		
Ruff 1989 (3.5)	Computerized Attention Training	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA F(1,37)=.07, P>.05 and F(1,37=0.2, P> .05 respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

								attention, spatial integration, and consistency of retrieval.		

Evidence for the Use of Vestibular Rehab Treatment

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Schneider 2014 (7.0)	Vestibular Therapy	RCT	This study was funded by the Alberta Centre for Child, Family and Community Research, grant number 09SM-Emery. No COI.	N=31	(18 males, 13 females); Median age of 15 (12-30).	Group 1 (N=15) received standard care for concussion from physiotherapist and also received cervical spine physiotherapy and vestibular rehabilitation. Vs. Group 2 (N=16) received the standard protocol for care by same physiotherapist.	Baseline, once a week for 8 weeks.	Greater proportion of individuals in group 1 were cleared medically to return to sport within 8 weeks, 66.2% vs <10% (95%CI 40-92.3) ($p<0.001$). Group 1 10.27 time more likely to be cleared (1.51-69.56, $p<0.001$). Time since injury was same for both groups, and patients had zero symptoms when cleared to play.	"A greater proportion of adolescents and young adults with persistent symptoms of dizziness, neck pain and/or headache, who were treated with a combination of vestibular rehabilitation and cervical physiotherapy treatment, were medically cleared to return to sport by 8 weeks following initiation of treatment than individuals with the same kind of symptoms who continued with rest instead."	Data suggest combination therapy (cervical and vestibular PT) shortened time to medical clearance to resume sports activity.

Evidence for the Use of Computer and Video Games

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Gil-Gomez 2011 (5.5)	Video & Computer Games	RCT	No Sponsorship or COI.	N=20	(11 males/6 females) Mean Age 47.3±17.8	eBaViR balance system using the Wii Balance Board (WBB) vs Control group that did normal physiotherapy.	Follow up at baseline and after 20, hour long sessions (3-5 a week)	ANOVA measurements showed significant time effect favoring WBB group for Berg Balance scale (p=0.00), Brunnel Balance assessment (p=0.048), Anterior Reach Test (p=0.005), Stepping test (paretic) (p=0.021), Stepping Test (non-paretic) (p=0.046), 1 minute walking test (p=0.007), Time "Up and Go" test (p=0.004), and 30-second Sit-to Stand Test (p=0.003). No difference in dynamic balance time effect in control and WBB group.	"[T]he study assessed the influence of a WBB-based virtual rehabilitation system (eBaViR) on standing balance rehabilitation with ABI patients and showed that virtual rehabilitation is capable of substantially improving the condition of the patients."	Small sample. Data suggest Patients who used eBaVIR had a significant improvement in static balance compared to patients in traditional therapy group. Both groups showed dynamic balance improvement.
Cuthbert 2014 (5.5)	Video & Computer Games	RCT	Study funded by the Craig Hospital Foundation. No COI.	N=20	(13 males/7 females) Group 1: 31.5 (23-56) Group 2: 31.0 (19-64)	Patients received 15 minute (Extra Stand Balance Care) ESC balance training Vs VRT group which utilized games on the Wii Fit and Wii Sport interactive in addition to standard physical therapy.	Follow-up at baseline, 2, and 4 weeks.	No significant difference in Extra Standard Balance Car and VRT in Patient satisfaction. Time improvement higher in VRT group for Berg Balance Scale (0.19 pts/day, p=0.03). overall improvement in BBS between groups not significant. Both groups had comparable Dynamic Stability improvements, no adverse effects within both groups.	"[F]urthermore, these data help to provide support for the growing trend of using VR-based activities in physical rehabilitation. The VR intervention applied here utilized many of the theories of neurological and physical recovery that have driven this trend, including repetitive practice, self-observation and biofeedback."	Small sample. Data suggest slight preference for use of VR therapy for balance over traditional therapy.
Baniqued 2014 (3.0)	Video & Computer Games	Quasi rando	Study supported	N=209	(47 males/162 females)	completed a working memory and	Total of 10, 20 minute sessions. 2-	WM-REAS 2 group vs active control group; effort ratings higher in WM-REAS 2	"[N]evertheless, with the aggressive marketing of brain games and the liberal	Data suggest training games resulted in

			by grant from The Office of Naval Research And National Science Foundation Neuroengineering IGERT Fellowship grant.		Group 1: 21.16±2.25 Group 2: 21.35±2.61 Group 3: 20.80±2.10 Group 4: 20.70±2.19	reasoning game (WM-REAS 1 Vs. Adaptive working memory and reasoning game (WM-REAS 2) Vs. Active control casual games Vs. No-contact control group.	3 sessions per week. Follow up at session 1, 5, and 10.	(p<0.017). Overall, feedback indicating three training groups. WM-REAS group higher ANOVA gain scores vs other groups (F(3,166)=5.613 p=0.001). Reduced lag blink in Wm-REAS 2 group (p<0.001). Post-experiemtnal survey showed 3 active groups, changed the way they perform daily activities in a good way.	application of prelim- inary training results, we caution against using video games or other computer-based programs as a sole or primary approach to improving brain function, particularly if it leads to a more sedentary lifestyle or in the words of Weis and Cerankosky (2010) “displace(s) activities that might have greater educational value.”	improvement which was only slightly noted on transference to untrained tasks. There was found to be better performance in attention requiring games and decreased attention blinks.

Evidence for the Use of Virtual Reality

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cuthbert 2014 (5.5)	Computer and Video Games	RCT	Study funded by the Craig Hospital Foundation. No COI.	N=20 with diagnosis of TBI.	(13 males/7 females) Group 1: 31.5 (23-56) Group 2: 31.0 (19-64)	Patients received 15 minute (Extra Stand Balance Care) ESC balance training Vs VRT group which utilized games on the Wii Fit and Wii Sport interactive in addition to standard physical therapy.	Follow-up at baseline, 2, and 4 weeks.	No significant difference in Extra Standard Balance Car and VRT in Patient satisfaction. Time improvement higher in VRT group for Berg Balance Scale (0.19 pts/day, p=0.03). overall improvement in BBS between groups not significant. Both groups had comparable Dynamic Stability improvements, no adverse effects within both groups.	"[F]urthermore, these data help to provide support for the growing trend of using VR-based activities in physical rehabilitation. The VR intervention applied here utilized many of the theories of neurological and physical recovery that have driven this trend, including repetitive practice, self-observation and biofeedback."	Small sample.Data suggest slight preference for use of VR therapy for balance over traditional therapy.
Grealy 1999 (4.5)	Virtual Reality	RCT Crossover design	No mention of sponsorship or COI.	13 brain-injured patients	Mean age: 32.08 years. 7 males, 6 females.	VR exercise group vs No-exercise Control Group	None	Mean scores decreased significantly after exercise (RT: t12 = 3.21, p <.01; MT: t12 = 2.66, p < .05) while no significant changes were seen in the control condition (RT: t12 = .38,	"Exercising in a virtual environment offers the potential for significant gains in cognitive function."	Small sample. Data suggest that even while exercising in a virtual reality environment, there is significant improvement in cognitive function as experimental group performed better than controls for

								p > .05; MT: t12 = .07, p > .05). Postexercise times were also found to be significantly faster than those achieved after the control trials (RT: t12 = 2.22,p < .05; MT: t12 = 1.79, p< .05). However, RT and MT both remained slow after exercise.		reaction times, movement times and verbal and visual learning tasks.
Jacoby 2013 (4.5)	Virtual Reality	RCT	No mention of sponsorship or COI.	12 people who had sustained TBI and was hospitalized in Department of Brain Injury	Mean age experimental group: 27.83±12.06 years. Mean age of control group: 30.67±13.13 years. 8 males, 4 females.	Experimental group (Ten 45-min VR-based treatment sessions) Vs. Control Group (10 sessions of occupational therapy cognitive training)	None	No significant differences were found between the groups in total score of MET-SV before and after intervention. A larger effect was seen in participants in the experimental group improved more in their final scores on MET-SV relative to initial scores (M=46.21%, SD=37.06, median=62.28), compared to control group	"(c)ognitive treatment in occupational therapy that focuses on mediating strategies to improve executive functions, may lead to an improvement in the ability to perform IADL activities among people following TBI."	Small sample. Data suggest a trend toward VR therapy vs Cognitive retraining OT without VR results in improved complex daily activities.

								(M=13.52%, SD=19.93, median=14.35) (z=-1.761, p=0.046; ES=.51)		
Yip 2013 (4.5)	Virtual Reality	RCT Single-blind	Sponsored by a General Research Grant of the Research Grant Council, Hong Kong. No COI.	N = 37 with acquired brain injury.	18 to 55 years old, 24 male and 13 female.	Virtual reality-based prospective Memory (VRPM) group pretest and posttest, two times a week for about 30 to 45 minutes (N = 19) vs Control group regular reading and table games activities during the treatment phase (N = 18).	5-6 weeks (unclear)	VRPM showed improvement of the immediate recall PM tasks / performance of both evet and time based PM tasks / ongoing tasks / and number of time checks: $p < 0.05$ / 0.001 / 0.01 / and 0.001. No significant difference found in any outcome measure in the control group.	"The present study initially supported the positive training effect of a VR-based cognitive rehabilitation programme in PM among people with acquired brain injury."	Small sample. Data suggest VR training resulted in improved VR based and PM outcome measures in ABI patients.
Man 2013 (4.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	40 participants with mild or moderate brain injury	Ages between 18-55. No mention of gender.	Artificial intelligent virtual reality based vocational training system (AIVTS) Vs. Psycho-educational vocational training programme (PEVTS)	3 months	ANOVA measures indicated no group x time interaction effect on primary and secondary outcomes. AIVTS group performed better than PEVTS group. No group interaction effect or group difference (F=0.95, p=.33), but a difference over time (F=5.19,	"These results support the potential use of a VR-based approach in memory training in people with MCI. Further VR applications, limitations and future research are described."	Data suggest VR based approach group performed better than therapist led group in terms of memory processes.

								p=0.014). For AIVTS, pre-test (mean=79.66, SD=16.33) and post-test (mean=83.45, SD=14.32) showed differences (t=-2.59, p=0.018). For PEVTS, pre-test (mean=78.40, SD=13.52) and post-test (mean=78.55, SD=14.00) showed no differences (t=-0.058, p=0.955). Friedman's Test for individual groups of AIVTS and PEVTS over three points showed chi-squares and statistical significance were, respectively, 11.14 (p=0.04) and 8.00 (p=0.018).		
Thornton 2005 (4.0)	Virtual Reality	Quasi randomization	Sponsored by the Ontario Neurotrauma Foundation and through a Premier's Research	N = 27 with TBI.	Aged 18 – 66 years, 19 male and 8 female.	An activity-based (ABE) programme, plus conventional tools of balance (N = 12) vs	6 weeks	Activities-specific Balance Confidence Scale [360] mean score increased from 74.6 to 76.4 and 78.2 and 74.8 to	"Both exercise programmes offered benefits in addition to improved balance."	Quasi randomization, small sample. Sparse methods .Data suggest similar efficacy between group for balance

			Excellence Award (to HS). MT was supported by an Ontario Neurotrauma Foundation Student Fellowship. HS is a Career Scientist with the ministry of Health and Long-term Care of Ontario. No other COI.			Virtual reality (VR) delivered balance exercise programme (N = 15).		80.2 and 81.2 for VR group. 2 participants in each group made clinically significant improvements of nine points or more on the Lower Extremity Functional Scale (LEFS) between the baseline and post intervention testing, (p-value not given).		improvement but VR group demonstrated better quantitative improvement and expressed increased confidence and improved enjoyment.
Fong 2010 (4.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	24 persons in the community with acquired brain injury	Mean age of Part I: 43.0±10.7 years. Mean age of Part II: 52.6±6.2 years. 17 males, 7 females.	Part I: Early (VR-ATM program first, followed by real ATM) Vs. Late (Real ATM first, then VR-ATM) Part II: Six 1 hour sessions over 3 weeks. VR Training Vs. Computer-assisted instruction	No	Part I: Average reaction time for real ATM was 15.5 seconds. Failed attempts with real ATM had an average reaction time of 26.5 seconds. Sensitivity of VR-ATM was 100% for cash, and 83.3% for money transfers. Part II: Mann-Whitney test indicated no significant differences in cognitive performance between participants in	"We found the VR-ATM to be usable as a valid assessment and training tool for relearning the use of ATMs prior to real-life practice in persons with ABI."	Small sample. Data suggest VR-ATM may be useful for ABI patients to relearn how to use ATMs.

								VR-ATM and CAI groups. (p=0.288-.911) No statistically significant difference was found in the post-test correct percentage scores between VR-ATM and CAI groups. (p=.059)		
Cox 2010 (3.5)	Virtual Reality	RCT	Sponsored by a grant from DARPA (Defense Advanced Research Projects Agency) through a Phase 1 SBIR (Small Business Innovation Research) Program. No mention of COI.	N = 11 male with TBI.	Mean age / range: VRDSRT and Control; 26.2 / 23-31 and 26.6 / 21-39, all male.	Virtual reality drying simulation rehabilitation training (VRDSRT) group received residential rehabilitation and VRDSRT, 4-6, 60- to 90-min rehabilitation training sessions (N = 6) vs VRDSRT control group or residential rehabilitation only (N = 5).	Unclear	The composite score improved significantly for VRDSRT group vs control, (p < 0.01). VRDSRT demonstrated a reduction in road rage / risky driving behaviors; (p = 0.01 / 0.04). Driving performance improved in VRDSRT group, (p < 0.01).	"VRDSRT showed promising results with respect to retraining driving performance and behavior among military personnel recovering from TBI."	Small sample. Data suggest VRDSRT may be useful in retraining TBI patients in driving.
Mahajan 2011 (3.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	20 participants who were at least 1 year post traumatic brain injury	Mean age: 30.62±10.91 years. 12 males, 8 females.	Isometric joystick Vs. Conventional joystick	None	The mean trial time for the MSJ was 3.4% higher than the mean trial time for the IJ, after	"The customizable isometric joystick seems to be a promising	Small sample. Data suggest participants could drive a virtual wheelchair using an IJ which may be

								controlling for wheelchair icon speed. As expected, a significant main effect of task width (P<.005, F1,135=5968.25) was found. The average trial time on wider tasks was 110.38% higher than the average trial time on narrow tasks. All other interactions were not significant. The joystick _ task-width interaction effect was significant for RMSE (P=.035, partial η^2=.109) No significant differences were found in other outcome measures when compared across the 2 joystick groups. From the mixed model analysis for trial time, the interactions of joystick and task width with the covariate absolute average	interface for driving a powered wheelchair for individuals with TBI."	useful for driving real wheelchairs.

								speed were not significant. However, a significant difference in log of trial times between the 2 joysticks (main effect: *P*=.038, F1,135=4.38) was observed. No statistically significant differences were seen between the 2 joysticks in the following driving performance measures: boundary collisions, number of HPM violations, and number of times the wheelchair got stuck.		

Evidence for the Use of Verbal Labeling Training nnn

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Schmidt 2012 (7.0)	Compensatory Interpersonal Process Recall (IPR), Videotape of social interaction, viewing tape, feedback, corrections and practice	Pragmatic RCT	Study was partially funded by grant from the Occupational Therapists Board of Queensland. No COI.	N = 54 participants with a TBI and also impaired self-awareness	Mean age video feedback group 42.7 years, verbal feedback group 41.6 years, and experiential feedback group 37.5. 46 males, 8 females.	Video Feedback (n=18) c Vs. Verbal Feedback (n=18) Vs. Experiential Feedback (n=18)	Meal tasks completed within 2 to 4 days. After final task no mention of long-term follow-up.	The video feedback group had statistically higher intellectual awareness compared to the verbal and experiential groups ($p < 0.01$). Between the verbal and experiential groups there was no statistically significant difference between intellectual awareness (mean difference = -2.4, 95% CI = (-7 – 2.1).	"In conclusion, this RCT demonstrated that the combination of video plus verbal feedback is most effective in enhancing both online and intellectual awareness compared with other feedback methods. A reassuring finding is that the intervention was not accompanied by a significant increase in emotional distress."	Data suggest virtual feedback plus video was effective in self awareness improvement

Evidence for the Use of Memory/Reasoning Tasks, Games, Computer Games

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Dou 2006 (3.5)	Memory/ Reasoning Tasks	Quasi-experimental design	No mention of sponsorship or COI	37 patients with TBI	Mean age: 38.067±12.32 years. 27 males, 10 females.	Computer-Assisted Memory Training Group (CAMG) with 1 month training program Vs Therapist-administered Memory Training Group (TAMG) with 1 month training program Vs. Control Group (CG)	1 month	Test results revealed statistically significant differences between the control and the two training groups in NCSE scores (for TAMG and CG, F=4.762, p=0.015; for CAMG and CG, F= 5.166, p=0.02). No statistically significant differences between the CAMG and TAMG (F=1.496, p=0.256). Comparing the post-training to the follow-up using a pair sample t-test, no statistically significant differences were found in each of the three groups and during the follow-up. Slight improvement in RBMT score for all groups was observed. statistically significant difference between the CAMG and CG (F=11.747, p=0.0001) and between the CAMG and CG (F=11.849, p=	"In conclusion, treatment efficacy has been demonstrated when using a combined EL and EE memory rehabilitation model, although there is no significant difference between CAMG and TAMG. This new development may guide improvements in memory rehabilitation in patients with TBI. Future studies should also be carried out to determine its role in Chinese people, especially those with moderate to severe TBI."	Quasi-experimental design. Baseline differences in time post injury between groups. Data suggest CAMG performed better than CG in the NCSE and RBMT. No difference found between CAMG and TAMG. Data suggest a combination of a computerized approach and errorless learning may be best for memory improvement in TBI patients.

								0.0001) in the total RBMT score, but no statistically significant differences were found between the CAMG and TAMG (F=1.358, p=0.287). Again, no statistically significant differences were found in each of the three groups.		
Ruff 1989 (3.5)	Memory/ Reasoning Tasks	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA F(1,37)=.07, P>.05 and F(1,37=0.2, P> .05 respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Evidence for the Use of Handheld Computers for Memory

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Lannin (8.0)	Memory Rehabilitation	RCT	This work was supported by a grant from the Royal Rehabilitation Centre Sydney Foundation. No COI.	N = 42 with acquired brain impairments.	33 males, 9 females; Mean age is 33.5 years.	Control Group. Non-electronic memory aids. (N = 21) vs Experimental Group. PDA. (N = 21)	1 or 2 years post intervention	From baseline to end of 8 week assessments: Control group had GAS t-score of 41.7 to 49.5. Trial had 41 to 53 (P=.0001).	"Occupational therapy training in the use of a handheld computer improved patients' daily memory function more than standard rehabilitation."	No long term follow-up. Data suggest use of handheld computerized equipment for memory aid significantly improved memory goals.

Evidence for the Use of Computer Memory Retraining Group (CMRG)

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Ruff 1994 (4.0)	CMRG	Randomized cross-over study	Research supported by IBM. No COI.	N=15	Mean Age 26.9 (17-47). No mention of Gender.	Group A received attention training follow by memory training. Vs Group B got the reverse order of treatments stated above.	Baseline and post treatment, 3 measure administered in 7 day intervals pre and post treatment.	Both groups improved. Memory II improved ($F(2)=4.52$, $p=0.021$). Response times decreased. Attention levels, Group A performed better in 7 & 2 attention test by 0.10, Group B did not improve. Behavioral rating improved by evaluator and subjectively between groups. No depression between groups in study, and Wechsler Memory Scale test scores improved in both groups.	"The efficacy of the attention training was demonstrated on multiple levels. On the computerized measures, small but consistent gains were evident. The results of the psychometric measures were mixed."	Small sample. Data suggests computer technology may assist TBI patients regain some attention and memory fun
Tam 2004 (3.5)	CMRG	RCT	No mention sponsorship or COI.	26 persons with brain injury (not including control group of 8 persons)	Mean Age of Self-Pace: 40.5 years. Mean age of Feedback: 33.3 years. Mean age of Personalized: 32.6 years. Mean age of Visual: 39.8 years. Mean age of Control: 45 years. 18	Completed 1 of 4 computer-assisted memory training strategies Self-paced Group (work at own pace in non-threatening environment Vs Feedback Group(immediate feedback in	No mention of follow-up.	Feedback group showed most substantial improvement within analogy memory performance. No statistical significance with memory improvement in all four groups By RBMT testing method for pre- and post-program RBMT scores. Feedback	"This attempt to develop and evaluate different computer applications for memory retraining was made and the effectiveness of applying customized computer technology in memory	Data suggest customized therapeutic computer-assisted memory retraining is key in memory skill retraining outcomes and using computers is an effective method to assist in cognitive rehab.

					males, 14 females.	clear, consistent, non-judgmental fashion) Vs Personalized Group (multimedia presentation of actual people, object, and living environment) Vs Visual Presentation Group (attractive, bright, and colorful presentation) Vs Control Group with no specified memory rehab		group showed statistically significant improvement in self-efficacy; self-paced, visual, and personalized groups did not show similar change.	rehabilitation was critically evaluated. Results of the present study showed that the unique customized therapeutic characteristics of computer-assisted memory retraining (e.g. self-paced practice, performance feedback, salient visual presentation and personalized training contents) are positive attributes of memory skill retraining outcomes."	

Evidence for the Use of Restorative Imagery Training

Author Year (Score):	*Category:*	Study type:	*Conflict of Interest:*	*Sample size:*	*Age*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Chiaravalloti 2015 (8.0)	Cognitive Rehabilitation	RCT	Sponsored by Department of Education, and endorsement by the Federal Government under the NIDRR Grant H133A070037. No COI.	N=69, Participants with moderate-severe Traumatic Brain Injury (TBI).	Participants ranged from 18 to 59 years old. Treatment Group 37.17 (11.24) and 77% male. Control Group 40.68 (11.28) and 71% male.	Treatment Group (n=35) 10 1-on-1 treatment session twice a week 45-60 mins long. Skill 1 was taught utilizing imagery to facilitate learning through reading and highly visual story from the list of words and then apply their newly acquired imagery skills to visualize. Skills applied mSMT to real-world memory-demanding tasks, utilizing both context and imagery to remember the information that story. vs Control Group (n=34) 10 1-on-1 treatment session twice a week 45-60 mins long. Participants received Non–training-oriented tasks consisted of reading the same stories and answering questions about their content.	Long-term follow-up 6 months after following treatment completion.	The treatment group showed significant improvement when compared to the placebo group: $F(1, 69) = 4.45$, $P < .025$ 1-tailed, partial $\eta 2 = 0.064$ medium effect; CI = −1.71 to −0.047; No significant treatment results from CVLT learning slope [$F(1, 69) = 0.686$, NS, $\eta 2 = 0.011$ small effect; CI = −0.154 to 0.373]. 49% of participants in the treatment group showed an improvement compared to 18% of the control group: $\chi 2[170] = 7.42$, $P = .006$, Cohen's $w = 0.33$, medium effect. No significant difference for RBMT in everyday memory from treatment group vs control group: $\chi 2(2) = 7.36$, $P = .025$, Cohen's $w = 0.43$.	"Based on widely accepted classification systems for treatment study design,67-69 the present results provide class I evidence supporting the efficacy of the mSMT to improve learning and memory in TBI patients with impaired learning. Thus, this study extends the evidence for efficacy of the treatment protocol to a sample of people with TBI. Future research should examine the optimal methodology for increasing the maintenance of the treatment effect over time and development of new treatment protocols that can be similarly successful in TBI patients."	Baseline comparability differences with respect to months since injury (Treatment group 119.97 (128.91) and Control group 101.97 (70.78) Data suggest mSMT improves memory and learning in TBI patients.

Oostra 2012 (4.0)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI.	N=37, Patients with moderate-severe Traumatic Brain Injury (TBI).	TBI Group 31.2_12.3 and 16:4 male: female. Control Group 32.1_14.2 and 13:4 male: female.	Rehabilitation TBI Group (n=20) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions vs Healthy Control Group (n=17) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group	Follow-up time frame not mentioned	Sub-scores for MIQ-RS for kinesthetic and visual were more significant at *P*<.05 in the control group than the TBI group, with a mean total score SD of 82±10 and 72±13, respectively. MIQ-RS visual (t18= -2,92; *P*<.01) and MIQ-RS total (t18= -2,48; *P*=.024) in patients with frontal brain damage [11385]. Statistically significant correlation between the number of imagined stepping movements and the duration of time periods in both groups (F1,35_153, *P*_.001) by the TDMI test. TBI group showed significantly less imagined stepping movements than the control group (F1,35_15.5, *P*_.001). Imagery stepping time and actual stepping time in both groups (TBI group, *r*=0.82, *P*<.001 and control group, *R*=0.80, *P*<.001).	"The present findings indicate that while TBI patients may still perform motor imagery, our cohort showed a decrease in the 3 motor imagery modalities, with a decrease of motor imagery vividness, temporal congruence, and accuracy. Our results, however, suggest that patients with TBI retain ability for motor imagery and hence may benefit from motor imagery training to improve their motor preparation and execution of movement and thus their functional ability."	Data suggest that the TBI group exhibited decreased motor imagery modes, specifically in vividness, temporal congruence and accuracy. TBI patients retain the ability for motor imagery and may benefit from motor imagery training.

Evidence for the Use of Games, Art and Self-Expression

Author Year (Score):	*Category:*	Study type:	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow -up:*	*Results:*	*Conclusion:*	*Comments:*
Ryan 1988 (4.0)	Self Expression	RCT	No mention of COI.	20 patients with head injuries with mild to moderate neuropsychological impairment	Control group mean age: 31.4 years. Experimental group mean age: 34.3 years. 14 males, 6 females.	Control Group (games, art, group discussions, relaxation exercises, self-expression) Vs. Experimental Group (retraining memory, attention and spatial integration exercises)	Immediately following the 6 week treatment.	No significant differences were observed in the T-tests, RLSE, DRS, or GOAT tests. MANOVA results revealed a significant overall effect (T (2, 36) =7.13, p<.05 indicating both groups improved over time. Experimental group did not demonstrate significant improvement over the control group. All ANOVA examinations did not reveal significant differences for either group. Results from the 2 groups x 2 severity ratings x 3 assessments MANOVA showed highly significant interaction between treatment and level of severity over the three testing conditions. (T-(2, 32) =20.13, p<.001. Subjects with mile neuropsychological impairments benefited more from memory remediation compared to more severely impair patients.	"(t)he present data demonstrates that remediation techniques in the area of memory do not necessarily enhance memory independent of severity and that a further neurobehavioral rating of severity is required."	Data suggest the mild TBI group received benefit from the experimental intervention but not those with moderate to severe impairments.

Evidence for the Use of Computer Assisted Cognitive Rehabilitation

Author Year (Score):	*Category:*	Study type:	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Vanderploeg 2008 (4.5)	Computer Assisted Cognitive Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with mod- severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive33.2±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions vs Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All received 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until ready to discharge home or to community transitional rehabilitation program or completed 60 days specific protocol treatment.	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).	"[N]o difference between cognitive-didactic and functional-experimental approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term functional cognitive outcomes for the cognitive treatment arm.

De Luca 2014 (4.0)	Computer Assisted Cognitive rehab	RCT	No mention of sponsorship or COI	35 subjects affected by traumatic or vascular brain injury (MMSE score from 10-26 absence of severe spasticity with Ashworth Scale ≤3).	Mean age 35.97±14.26 years. 19 males, 16 females.	Experimental treatment with 24 sessions of pc-cognitive training 3 times a week for 8 weeks including conventional rehab. Vs. Standard Treatment performing only conventional rehabilitation.	2 months after rehabilitation treatment.	Tests at baseline in whole sample showed moderate cognitive dysfunction (MMSE 22.21± 4.79) with more impairment in language production, visual attention, memory span, and memory abilities. Functional status of entire sample was severely impair: ADL 2.88±1.97. IADL 1.97±1.45. BI 35.26±30.08. MRI showed mostly unilateral hemispheric lesions in all patients. Observed overall improvement in cognitive and functional status in both groups, with significant differences. Experimental group presented highly significant improvement in all test. Control group had significant recovery only for LCF, AC, ADL, IADL, and BI tests. At T0, no significant differences between groups. At T1, LCF score was only significant difference (p=0.009). Greater cognitive improvement for experimental than control group.	"Our data suggest that cognitive pc-training may be a promising methodology to optimize the rehabilitation outcomes following brain injury."	Data suggest cognitive PC training may improve outcomes following brain injury. Both groups showed improvement but greater memory span was seen in experimental group.

Lundqvist 2010 (4.0)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI	21 individuals suffering from acquired brain injury	Mean age: 43.2 years. 10 males, 11 females.	Group I (systematic WM training for 5 wks) Vs Group II (control group- no training)	5 months	Significant difference was observed in non-trained WM tests, PASAT, Listening Span, Block Span, and CWIT. Picture Span observed significant difference after 4 wks training, but not at follow up (p=0.012). A t-test paired samples showed that the relative long-term WM training effect was significantly higher for PASAT compared to Digit Span, t(19)=1.87m p<0.05, and for Listening Span compared to Digit span t(19)=1.88, p<0.05. At baseline, performance level of Digit Span was M=8.3 (SD=1.4)(n=21) and after 20 wks training level was M=8.9 (SD=0.89) (n=20). All 21 individuals increased their WM index when comparing the Start index (baseline) and the Max index. The Start index was M ¼ 73.7 (SD ¼ 9.7) and the Max index was M ¼ 93.4 (SD ¼ 13.7). The difference varied between 9.0–35.0. Best results obtained during 2nd part of training; 74% of subjects' peak index was obtained during last 30% of training. Nine percent of subjects reached peak index already during first 50% of training. Results from the COPM interviews show a difference in estimated performance of prioritized occupations,	"Structured and intense computerized working memory training with QM improves subjects' cognitive functioning as measured by neuropsychological WM-demanding tests, WM-related activities (occupational performance, satisfaction with performance) and overall health. The training probably has an impact on the rehabilitation outcome, returning to work, as well as on daily activities for individuals with verified WM impairments."	Small sample. Data suggest that structural and intense WM training showed significant improvements in neuropsychological WM-test results at both 4 and 20 weeks post training, However, quality of life did not change but overall health quality as was rated by patients.

								before training vs 20 weeks after training, $p < 0.05$. An even bigger difference was found in estimated satisfaction with performance before vs 20 weeks after training, $p < 0.001$. There was no difference ($p > 0.05$) in health-related quality-of-life, as measured by the EQ-5D questionnaire, while there was a significant difference in the health self-rating VAS ($p < 0.05$).		
Tam 2004 (3.5)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI	26 persons with brain injury (not including control group of 8 persons)	Mean Age of Self-Pace: 40.5 years. Mean age of Feedback: 33.3 years. Mean age of Personalized: 32.6 years. Mean age of Visual: 39.8 years. Mean age of	Completed 1 of 4 computer-assisted memory training strategies Self-paced Group (work at own pace in non-threatening environment Vs Feedback Group(immediate feedback in clear, consistent, non-judgmental fashion) Vs Personalized Group (multimedia presentation of actual people, object, and living environment) Vs Visual Presentation Group (attractive, bright, and colorful presentation)	No mention of follow-up.	Feedback group showed most substantial improvement within analogy memory performance. No statistical significance with memory improvement in all four groups By RBMT testing method for pre- and post-program RBMT scores. Feedback group showed statistically significant improvement in self-efficacy; self-paced, visual, and personalized groups did not show similar change.	Small sample. "This attempt to develop and evaluate different computer applications for memory retraining was made and the effectiveness of applying customized computer technology in memory rehabilitation was critically evaluated. Results of the present study showed that the unique customized	Data suggest customized therapeutic computer-assisted memory retraining is key in memory skill retraining outcomes and using computers is an effective method to assist in cognitive rehab.

					Control: 45 years. 18 males, 14 females.	Vs Control Group with no specified memory rehab			therapeutic characteristics of computer-assisted memory retraining (e.g. self-paced practice, performance feedback, salient visual presentation and personalized training contents) are positive attributes of memory skill retraining outcomes."	
Ruff 1989 (3.5)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA $F(1,37)=.07$, $P>.05$ and $F(1,37=0.2$, $P> .05$ respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Batchelor 1988 (3.5)	Cognitive Rehabilitation	Quasi-RCT	No mention of sponsorship or COI	34 patients with severe to extremely sever closed-head injuries	Experimental group mean age: 22.6±6.9 years. Control group mean age: 26.2±11.0 years. 27 males, 7 females.	Experimental group (computer assisted cognitive treatment) Vs Control group (non-computer cognitive treatment)	3 days after completion of treatment.	A significant difference was revealed between the number of years of education of the two groups (t (32) =2.25, P<.05) with the difference favoring the control subjects. Significant improvement in the level of performance of experimental and control subjects at time of posttreatment assessment compared with pretreatment assessment. Pre and posttreatment scores of the experimental and control subjects were compared using an analysis of covariance. No significant differences emerged between adjusted posttest scores between groups.	"(S)tudy failed to support hypothesis that computer-assisted cognitive therapy is any more effective in remediating disorders of memory, attention, information processing, and higher cognitive functioning in severely head-injured patients than are non-computerized techniques."	Data suggest computer-assisted techniques no more effective than noncomputerized techniques in cognitive rehab of severely closed head injured patients.
Dou 2006 (3.0)	Cognitive Rehabilitation	Quasi-experimental design	No mention of sponsorship or COI	37 patients with TBI	Mean age: 38.067±12.32 years. 27 males, 10 females.	Computer-Assisted Memory Training Group (CAMG) with 1 month training program Vs Therapist-administered Memory Training Group (TAMG) with 1 month training program Vs. Control Group (CG)	1 month	Test results revealed statistically significant differences between the control and the two training groups in NCSE scores (for TAMG and CG, F=4.762, p=0.015; for CAMG and CG, F= 5.166, p=0.02). No statistically significant differences between the CAMG and TAMG (F=1.496, p=0.256). Comparing the post-training to the follow-up using a pair sample t-test, no statistically significant differences were found in each of the three groups and during the	"In conclusion, treatment efficacy has been demonstrated when using a combined EL and EE memory rehabilitation model, although there is no significant difference between CAMG and TAMG. This new development may guide improvements in memory	Quasi-experimental design. Baseline differences in time post injury between groups. Data suggest CAMG performed better than CG in the NCSE and RBMT. No difference found between CAMG and TAMG. Data suggest a combination of a computerized approach and errorless learning may be best for memory improvement in TBI patients.

								follow-up. Slight improvement in RBMT score for all groups was observed. statistically significant difference between the CAMG and CG (F=11.747, p=0.0001) and between the CAMG and CG (F=11.849, p= 0.0001) in the total RBMT score, but no statistically significant differences were found between the CAMG and TAMG (F=1.358, p=0.287). Again, no statistically significant differences were found in each of the three groups.	rehabilitation in patients with TBI. Future studies should also be carried out to determine its role in Chinese people, especially those with moderateto-severe TBI."	

Evidence for the Use of Psychosocial Functioning

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Powell J 2001 (7.5)	Psychosocial Functioning	RCT	No mention of COI. The research assessor was funded by a grant from the Medical Research Council, and the treatment programme was funded by the Department of Health.	N= 110 Patients who sustained severe TBI between 3 months and 20 years previously, and had no other neurological conditions.	Mean age: 34.5; (Males 71, Females 23)	Outreach group (N=54) vs. Information group (N=56) (No other description of study design and comparison groups)	Follow up for an average of 24.8 months	The outreach participants were significantly more likely to show gains on the BI (Barthel index) and the BICRO-39 (brain injury community rehabilitation outcome-39) total score and self-organization and psychological wellbeing subscales. There were likewise strong trends ($p<0.10$) for BICRO personal care and mobility, and on the FIM+FAM for personal care and cognitive functions. Differential improvements were not seen for indices of socializing, productive employment, anxiety, or depression. Median changes on individual subscales were small, reflecting the diversity of the clinical population; however, 40% of outreach but only 20% of information participants made a clinically significant improvement of 2+ points on at least one BICRO-39 scale. Time since injury was unrelated to the magnitude of gains.	This is the first RCT of multidisciplinary community rehabilitation after severe TBI, and suggests that even years after injury it can yield benefits which outlive the active treatment period.	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury occurrence not correlated to amount of gains.

Evidence for the Use of Group Sessions

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Dahlberg 2007 (5.5)	Group sessions for problem solving, discussion of social isolations and frustrations	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. COI.	N = 52 patients with TBI at least 1 year post-injury who had social communication deficits and received rehabilitation treatment.	Mean age group sessions 42.43, control 39.91. 44 males, 8 females.	Weekly group sessions for 12 weeks (each 1.5 hours) focused on improving communication skills (n = 26) Vs. Control group receiving no treatment (n = 26)	3, 6, and 9 months	Analysis of treatment effects via independent t tests showed significant differences between two groups in 7 out of 10 of The Profile of Functional Impairment in Communication (p values ranging from .001 - .024). There was also a statistical difference between two groups for the Social Communication Skills Questionnaire-Adapted measurement (p = .005).	"TBI subjects who received social communication skills training had improved communication skills that were maintained on follow-up. Overall life satisfaction for participants was improved."	Data suggest significant improvement in treatment group for communication skills and overall life satisfaction.
Rath 2003 (5.5)	Group sessions for problem solving, discussion of social isolations and frustrations	RCT	Funded by grant from the National Institute of Child Health and Human Development. No COI.	N = 60 outpatients with TBI who were at least 1 year post-injury and also considered higher-level (more cognitively demanding).	Mean age of entire sample 43.6. 23 males, 37 females.	Innovative Group Treatment focused on "emotional self-regulation" and "clear thinking", (N = 32) Vs Conventional Group Treatment (N = 28)	24 weeks and 6 months	The innovative group had higher self-esteem (p < .05) where the self-esteem for the conventional group was not significant at the same level (p < .08). The innovative group also showed higher problem-solving self-appraisal measures (p = .005).	"Our findings suggest that our treatment is a promising method for improving problem solving, one that may have practical applications for improving the function of people with TBI."	Data suggest treatment group (innovative group) improved problem solving compared to conventional group.

Anson 2006 (3.5)	Group sessions for problem solving, discussion of social isolations and frustrations	Non randomized	No mention of sponsorship or COI.	N = 31 participants with TBI who received outpatient therapy	Mean age of Group A 38.9, Group B 37.8. 26 males, 5 females.	Group A, receiving 10 90 minute Coping Skills Group sessions twice a week for 5 weeks, baseline phase being 5 weeks (n = 15) Vs. Group B, receiving same Coping Skills Group sessions for 5 weeks, baseline phase being 10 weeks (n=16) Vs. Control, on a waiting list	5, 10 weeks	Several ANOVA analyses were performed. Post-hoc analysis, utilizing the Bonferroni adjustment, showed a significant difference within coping skills between pre- and post-treatment ($p < 0.05$). Skills did not remain stable due to a significant decrease from post-treatment to follow-up ($p < 0.05$).	"The results suggest that it may be possible to modify coping strategy use following brain injury, through CBT."	Small sample. Data suggest no appreciable improvement in anxiety, depression, self esteem or psychological function but coping strategy and ability to understand emotions improved.
Ruff 1989 (3.5)	Group Sessions for Problem Solving	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA $F(1,37)=.07$, $P>.05$ and $F(1,37=0.2$, $P> .05$ respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Evidence for the Use of Compensatory Skills Training

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cantor 2014 (5.5)	Compensatory Skills Training	RCT	Sponsored by the Centers for Disease Control and Prevention. No COI.	N = 98 with TBI and executive dysfunction.	Mean age 45.3 ± 14.0, 37 male and 61 female.	Immediate start or IS, Short-Term Executive Plus (STEP) cognitive rehabilitation program; including problem solving, emotional regulation, individual sessions of attention and compensatory strategies training (N = 49) vs Waitlist or WL program (N = 49).	12 weeks	Intent-to-treat indicated significant treatment effect for the composite executive function measure, (p = 0.008). Secondary analysis indicated significant treatment effects for executive function scale, (p = 0.049), and the problem solving strategies, (p = 0.016).	"The STEP program is efficacious in improving self-reported post-TBI executive function and problem solving."	Data suggest STEP efficacious in improving self reported post TBI problem solving and executive function.
Bergquist 2009 (3.5)	Compensatory Skills Training	RCT Crossover	Sponsored by a TBI Model System grant from the National Institute for Disability and Rehabilitation Research (NIDRR). No COI.	N = 14 with medically documented traumatic brain injury over an 18-month period.	Average age 48 years, 7 male and 7 female.	Baseline: Neurobehavioural Functioning Inventory (NFI), Community Integration Questionnaire (CIQ) and Compensation Techniques Questionnaire (CTQ), Followed with	Unclear	There was no significant differences in changes in functioning on any of these measures in the Calendar Condition vs the Diary Condition, (p > 0.05). Significant improvements in functioning in calendar use, (p = 0.02) and using a cue card for compensation techniques (p = 0.01) at	"These results suggest that the Internet may be an effective delivering mechanism for compensatory cognitive rehabilitation, particularly among individuals who are already utilizing some basic	Small sample Data suggest comparable efficacy.

						Intervention that included; internet-based intervention: Active condition (calendar) or control (diary) group for a total of 30 sessions of one intervention type using instant messaging with a therapist over the internet, plus 30 sessions of the alternative intervention type.		the baseline vs final assessment periods.	compensatory strategies."	
Helffenstein 1982 (2.5)	Compensatory Skills Training	RCT	No mention of sponsorship or COI.	N = 16 with nonprogressive brain injury.	Age range from 17-35, 13 male and 3 female.	Experimental group received 20 one-hour session of Interpersonal Process Recall or IPR (N = 8) vs Control group received 20 one-hour session of 'nontherapeutic' attention (N = 8).	1 month	Experimental group demonstrated significantly greater change in a) reduction of trait anxiety, b) increase in overall self-concept, c) increase in self-concept related to 'social self, d) increase in self- concept related to 'normal' self, improvement in interpersonal and communication skills.	"[T]wenty hours of IPR treatment did facilitate growth and improvement of interpersonal and communication al skills beyond that which would have been expected had there been no formal intervention."	Small sample. Data suggest IPR group demonstrated improved anxiety, self concept, interpersonal and communication skills compared to control group.

Evidence for Vision Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Keller 2010 (3.5)	TBI	RCT	No mention of sponsorship or COI.	N = 20 with visual field deficits.	Mean 59, Range 16 – 85, 8 females 12 Males	Audiovisual Stimulation Training, 20 training sessions (30 minutes) over 3 weeks (N = 10) vs Visual only stimulation training using the same apparatus, 20 training sessions (30 minutes) over 3 weeks (N = 10).	Assessed before and after 3 week training	Audiovisual stimulation training had statistically significantly better outcomes for visual exploration (85.3% v 64.1%, p = 0.001), reading time (75 seconds v 178 seconds, p = 0.003), search time per object (2.9 seconds v 4.9 seconds, p = 0.009), and activities of daily living total score (1.5 v 5.0 p = 0.036) outcomes as well as differences in number and amplitude of saccades from electro-oculography evaluations	"Audiovisual exploration training in patients with visual field defects resulting from occipital lobe lesions after recent stroke improves performance in a variety of activities of everyday life"	All stroke patients. Data suggest multimodal audiovisual training appears more effective for recovery of function compared to visual training alone.
Roth 2009 (3.5)	TBI	RCT	No COI. Study was funded by Adolf Messer foundation.	N = 30 with postchiasmatic lesions	Mean 60, range 34-76, 11 females, 19 males	Explorative saccade training, 2 sessions of 30 minutes per day, 5 days a week (N = 15) vs Flicker-stimulation training, 2 sessions of 30 minutes per day, 5 days a week (N = 15).	Assessed before, immediately after initial training and after 6 week training	No significant differences between two primary treatments for any outcomes at the 6-week follow-up. Significant differences were seen between blind and seeing side assessments.	"[I]n patients with hemianopic orientation disorder, compensatory EST selectively improves exploration behavior on the blind side in everyday tasks."	MIxed population that is mostly stroke. Data suggest compensatory EST improves daily life activity performance.

Thiagarajan 2013 (3.0)	Visual Training	Experimental	No COI. Sponsored by the U.S. Army, Department of Defense, College of Optometrists in Vision Development, and SUNY College of Optometry Graduate Program.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29; 4 males and 8 females.	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean of laboratory-based objective measure of symmetric vergence (baseline vs. after OMT): Peak velocity – Convergence (C) 13.0±1.9, 18.0±0.9 (p=0.01) / Divergence (D) 11.6±1.1, 13.5±0.8 (p<0.01), Time Constant – C 399±68, 228±14 (p=0.01), D 378±35, 312.22 (p<0.01), Steady-state Variability – C 0.90±0.07, 0.75±0.04 (p=0.04), D 0.81±0.05, 0.78±0.02 (p=0.54), Response Amplitude C 3.93±0.07, 3.96±0.08 (p=0.43), D 3.93±0.06, 3.93±0.08, (p=1.00)	"The significant improvement in most aspects of vergence eye movements following OMT demonstrates considerable residual brain plasticity via oculomotor learning."	Small sample crossover study. Sparse method, significant dropouts and compliance to protocol issues.
Thiagarajan 2014 (2.5)	Visual Training	Experimental	No COI. Sponsored by the US Army, DOD.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29; 4 males and 8 females.	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean visagraph parameters (at baseline, at post-OMT, p-value): Reading rate [wpm] (142, 17, p<0.01), Comprehension [%] (81, 85, p=0.31), Fixations/100 words (164, 135, p=0.02), Regressions/100 words (30, 23, p=0.11), Fixation duration [seconds] (0.27, 0.27, p=0.91), Grade level efficacy (4.1, 6.3, p=0.01)	"OBVR had a strong positive effect on oculomotor control, reading rate, and overall reading ability. This oculomotor learning effect suggests considerable residual neuroplasticity following mTBI.	Small sample crossover study, sparse methods.

Thiagarajan 2014 (2.0)	Visual Training	Experimental	No COI. Sponsored by the US Army, DOD.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29±3;	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean saccade ratio for SRML reduced after OMT ($t(11)=3.83$, $p=0.002$). Mean SRSL did not reduce ($t(11)=2.06$, $p=0.06$). Mean increase in peak velocity ±2.5° horizontal after OMT ($t(11)=2.35$, $p=0.03$). Saccadic gain (SG) increased for ±2.5° horizontal ($t(11)=2.4$, $p=0.03$) and ±2.5° vertical ($t(11)=3.54$, $p=0.004$). SG increased for ±5° vertical saccades ($t(11)=2.16$, $p=0.05$). Saccadic latency did not change for horizontal ($t(11)=1.65$, $p=0.12$) or vertical ($t(11)=1.06$, $p=0.30$) random saccades	"The versional-based OMT had a significant, positive effect on most aspects of versional tracking. These findings are suggestive of improved rhythmicity, accuracy and sequencing of saccades following OMT in mTBI as a result of oculomotor learning."	Small sample, sparse methods.

Evidence for Oculomotor Training

Thiagarajan 2014 (4.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT crossover	No COI. Supported by U.S. Department of Defense (DoD) grant, the College of Optometrists in Vision Development, and SUNY graduate program.	N = 12 with mild TBI, injury onset of over 1 year, displayed at least one clinical sign of accommodative dysfunction	8 female, 4 male Mean age overall 29 ± 3 years	Oculomotor training (OMT) Vs. Placebo training (P) Each session 60 minutes, two sessions per week, 9 hours for one treatment total	15 weeks	Placebo training produced no significantly different measures ($p > 0.05$). OMT produced an increase of about 30% in peak velocity for increasing ($t(11) = 3.61$, $p = 0.01$) and decrease ($t(11) = 3.65$, $p = 0.01$) steps of accommodation.	"These results provide evidence for a significant positive effect of the accommodatively based OMT on accommodative responsivity. Such improvement is suggestive of oculomotor learning, demonstrating considerable residual brain-visual system plasticity in the adult compromised brain.	Small sample, crossover design. Data suggest OMT improved most measures related to accomodation responsivity which may be the result of oculomotor learning.

Evidence for the Use of NSAIDs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Cormio 2007 (score = 4.5)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N=23 febrile comatose, GCS≤8, at least one reactive pupil, Temp≥38C, 12 with severe TBI and 10 with SAH.	ages 14-75yo.	Diclofenac low-dose infusion: initial IV bolus 0.2 mg/kg diluted in 100 ml NS then a continuous infusion of 75 mg in 50 ml normal saline until internal temperature was lower than 38ºC for at least 12 hours (N=10) vs. boluses of NSAIDs: 0.2 mg/kg diclofenac sodium infusion, 100 mg ketoprofene, and 1000 mg proparacetamol all diluted in 100 ml normal saline (N=12).	Follow-up 24 hours following the stop of antipyretic therapy.	Percentage of time >38ºC was 4% vs. 34% (p<0.0001). Maximum temperatures also lower with continuous infusion. Favorable outcomes (good result, moderate disability): 70% DCF vs. 83% controls (NS) at 6mo.	"Low dose DCF infusion is a potential useful strategy for a successful control temperature better than intermittent NSAIDs dosing, minimizing potentially brain-damaging effects of fever."	Data suggest considerably better febrile control with continuous IV NSAID infusion vs. NSAID boluses. However, not powered to detect differences in other endpoints.

Evidence for the Use of Dextromethorphan

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Pioro 2010 (Score=6.0)	Dextromethorphan	RCT	Supported by Avanir Pharmaceuticals. Pioro received research support and compensation for consulting from Avanir Pharmaceuticals. Other authors also received compensation for work on this project.	N = 326 with clinically significant pseudobulbar affect (PBA), a score ≥ 13 on the Center for Neurological Study—Lability Scale (CNS-LS), and either an amyotrophic lateral sclerosis (ASL) diagnosis within the last 30 months or a multiple sclerosis (MS) or probable MS diagnosis	Mean age = 51.41 years; 149 males, 117 females.	30mg dextromethorphan plus 10mg quinidine (DM 30mg + Q 10mg, DMq-30) (N = 110) vs DM 20mg + Q 10mg (DMq-20) (N = 107) vs placebo (N = 109). Each patient took one capsule each morning during week 1. For weeks 2-12 patients took one capsule each morning and another at night.	Weeks 2, 4, 8, and 12.	Mean change in daily episode rate for DMq-30, DMq-20, and placebo, respectively: -4.1, -3.9, -3.0 ($p = 0.0099$, $p = 0.0048$, respectively). Via longitudinal negative binomial model, reduction in PBA episode rate for DMq-30 vs. placebo was 46.9% ($p < 0.0001$) and for DMq-20 vs. placebo was 49.0% ($p < 0.0001$).	"DMq markedly reduced PBA frequency and severity, decreasing the condition's detrimental impact on a patient's life, with satisfactory safety and high tolerability. The findings expand the clinical evidence that DMq may be an important treatment for patients suffering from the socially debilitating symptoms of PBA."	Results determined from patient diary entries. Only a 12 week time period. Placebo controlled RCT. Data suggest DMq reduced the frequency and severity of PBA.
Pope 2012 (Score=2.0)	Dextromethorphan	RCT	Supported by Avanir Pharmaceuticals, Inc. Pope is an employee of Avanir Pharmaceuticals, Inc. Other authors were also employees of this company.	N = 52 healthy test subjects with body weight ≥60 kg for males, ≥52 kg for females, BMI 19-20 kg/m^2, non-smoker, and could abstain from alcohol for the length of the trial	Mean age = 36.1 years; 39 males, 24 females.	Group 1 – given a dose of 5 mg memantine once daily, which was titrate over 3 weeks to 10 mg twice daily for 11 days, DMQ 30 mg (dextromethorpahn 30mg/quinidine 30mg) twice daily was also	No long-term follow-up.	Only 17 patients from each group were evaluated (total n included 34). Ratio of AUC12 values 90% confidence intervals for memantine (group 1, day 40 vs. day 32), dextromethorpahn (DM) (group 2, day 40 vs. day 8), dextrorphan (DX) (group 2, day 40 vs.	"Minimal pharmacokinetic and pharmacodynamic interactions were observed between memantine and DMQ, suggesting they can be coadministered without dose adjustment.	Open label RCT. Small sample. Significant AEs in group I (78.3%) and in group II (92.9%).

						given for another 8 days (N = 23) vs Group 2 – given DMQ 30mg twice daily for 8 days, then administered memantine, titrated like group 1, for 11 additional days (N = 29)		day 8), and quinidine (group 2, day 40 vs. day 8), respectively: 0.850-1.036, 1.041-1.160, 1.020-1.167, 1.153-1.349. To be pharmacokinetically similar, the 90% CI had to fall within predefined range of 0.8—1.25.		

Evidence for the Use of Proton Pump Inhibitors

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Chan 2002 (9.5)	Proton Pump Inhibitors (PPIs)	RCT	No mention of sponsorship. No COI.	N = 102 patients with RA, OA, and other forms of arthritis with ulcer bleeding. 2 participants withdrew after randomization.	Mean age 62.5. 33 males, 67 females.	Omeprazole 20mg plus amoxicillin 1g plus clarithromycin 500mg vs. omeprazole 20mg and placebo antibiotics each BID for 1 week	Every 8 weeks for a period of 6 months.	H pylori eradicated in 90% vs. 6% controls.6-month probability of ulcers 12.1% (95% CI 3.1-21.1) in eradication group vs. 34.4% (21.1-47.7) in controls (p = 0.0085); 6-month probabilities of complicated ulcers 4.2% (1.3-9.7) vs. 27.1% (14.7-39.5), p = 0.0026.	"Screening and treatment for H pylori infection significantly reduces the risk of ulcers for patients starting long-term NSAID treatment."	One week treatment 6 months diclofenac SR. Data suggests antibiotics plus omeprazole effective.
Labenz 2002 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of sponsorship or COI.	N = 832 patients who tested positive for H pylori. Mean age 55. 660 participants included in intention to treat analysis.	Mean age 55. 252 males, 408 females.	Omeprazole 20mg BID vs. amoxicillin 1g BID vs. clarithromycin 500mg BID for 1 week (OAC), plus 4 weeks of placebo QD (OAC-P); OAC for 1 week plus 4 weeks omeprazole 20mg QD (OAC-O); omeprazole 20mg QD for 1 plus 4 weeks [532]; or placebo for 5 weeks (P-P)	Follow up at Week 1 and Week 5.	Relative risk reduction (%) (95% CI) and absolute risk reduction (%) (95% CI) for the treatment groups was as follows: OAC-P: 79 (4.5-95), 4.6 (0.7-8.5); OAC-O: 80 (11.1-96), 4.7 (0.8-8.6); O-O: 100, 5.8 (2.1-9.5).	"In H pylori infected patients, all three active therapies reduced the occurrence of NSAID associated peptic ulcer and dyspeptic symptoms requiring therapy."	All diclofenac 50mg twice a day for 5 weeks. Other arms treatment for 1 week. Three treatment arms all reduced risk comparably. Results may not be generalized beyond H pylori infected patients.
Scheiman 2006 (9.0)	Proton Pump	RCT	Sponsored by AstraZeneca R&D. No	VENUS study: N = 805; PLUTO study:	Mean age 65.4. Venus study: 266 males, 539	Esomeprazole 20mg vs.	No follow up.	16.5% (95% CI: 9.7–23.4) on COX-2s or placebo developed	"For at-risk patients, esomeprazole was	Two RCTs with large sample size.

	Inhibitors (PPIs)		mention of COI.	N = 573 for at-risk patients (≥60 years and/or ulcer history).	females. Pluto study: 130 males, 443 females.	Esomeprazole 40mg vs. Placebo QD for 6 months.		ulcers over 6 months vs. 0.9% (95% CI: 0–2.6) esomeprazole 20mg and 4.1% (95% CI: 0.6–7.6) esomeprazole 40mg ($p < 0.001$, $p = 0.002$) vs. placebo, respectively.	effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors."	Study suggests efficacy.
Regula 2006 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by ALTANA Pharama AG. COI, Regula Jaroslaw, Butruk Eugeniusz, Dekkers Cornelius PM, de Boer Sybrand Y, Raps Dieter, Simon Laszlo, have in the past received grants from ALTANA. Terjung Andreas, Thomas Kathy B., Luhmann Reinhold, and Fischer Renate are employees of ALTANA.	N = 595 rheumatic patients on continual NSAIDs with at least 1 more re-cognized risk factor that contributes to GI injury.	Mean age 66. 172 males, 423 females.	Pantoprazole 20mg vs. pantoprazole 40mg vs. omeprazole 20mg QD for 6 months	Follow up at 3 and 6 months after treatment.	At 6 months, probability of therapeutic remission 90% pantoprazole 20mg QD, 93% pantoprazole 40 mg QD, and 89% omeprazole 20mg QD. Probabilities of endoscopic failure 9% vs. 5% vs. 7% respectively (NS).	"For patients taking NSAIDs continually, pantoprazole 20 mg o.d., pantoprazole 40 mg o.d., or omeprazole 20 mg o.d. provide equivalent, effective, and well-tolerated prophylaxis against GI lesions, including peptic ulcers."	Large population of rheumatoid arthritis, osteoarthritis, multiple conditions and spine for 6 months of treatment. Suggests equal efficacy.
Yeomans 2008 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by AstraZeneca. COI, Neville Yeomans is an advisor for AstraZeneca, and previously to	N = 991 participants ≥60 years without baseline gastro-duodenal ulcer receiving	Mean age 69.5 ± 6.5. 566 males, 425 females.	Esomeprazole 20mg QD vs. Placebo for 26 weeks.	No follow up.	Twenty-seven (5.4%) in placebo group with gastric or duodenal ulcer during 26-week treatment vs. 8 (1.6%) inesomeprazole group (life-table estimates: 6.2%vs 1.8%; p =	"Esomeprazole 20 mg once daily reduces the risk of developing gastric and/or duodenal ulcers and symptoms associated with	Large population. Suggests efficacy.

			Merck Sharp & Dohme and Pfizer. Angel Lanas, Sander Veldhuyen van Zanten, Konstantin Tchernev, Dimitrios Karamanolis, and Chris Hawkey have received financial support from AstraZeneca. Emma Naucler and Lars-Erik Svedberg are employees of AstraZeneca.	aspirin 75-325mg daily.				0.0007). At 26 weeks, cumulative proportion with erosive esophagitis lower for esomeprazole vs. placebo (4.4% vs. 18.3%, respectively; p <0.0001).	the continuous use of low-dose aspirin in patients aged > or =60 yr without preexisting gastroduodenal ulcers."	
Dorta 2000 (8.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by the Swiss Cancer League/Cancer Researh Switzerland and Astra Hassle AB.	N = 12 healthy volunteers.	Median age 29. 7 males, 5 females.	Two-week course of omeprazole (40mg) plus "separate 2-week course of an identical looking placebo." Water-soluble diclofenac (50mg) taken 2nd week.	No follow up time.	No differences in healing scores after administration of placebo/diclofenac (median = 6; range 0-6) and omeprazole/ diclofenac (median = 9; range 0-6; p = 0.17) were found.	"In healthy subjects, omeprazole does not accelerate the healing of pre-existing mucosal lesions or prevent the development of small diclofenac-induced mucosal lesions."	Crossover study with small sample size. Short-term treatments of unclear clinical significance .
Bianchi Porro 2000 (8.5)	Proton Pump Inhibitors (PPIs)	RCT	No mention of sponsorship or COI.	N = 104 with RA or OA.	Mean age 59.5. 18 males, 86 females.	40mg pantoprazole Vs. Placebo QD for 12 weeks	Weeks 4 and 12	Difference in probability of remaining free of peptic ulcer 5% (95% CL-13%, = 23%) at 4	"Pantoprazole 40mg once daily was well tolerated and is more effective than placebo in the	RA or OA 12 week treatment. Suggests efficacy.

								weeks and 13% (-9%, = 33%) at 12 weeks.	prevention of peptic ulcers in patients with rheumatic diseases who require continuous, long-term, treatment with NSAIDs."	
Hawkey 2005 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	All but one author were employees or consultants to AstraZeneca. Study was funded by a grant from AstraZeneca R&D, Mölndal, Sweden.	2 RCTs: N = 608 and N = 556 (NASAI, SPACE 1) Con-tinuous NSAID users free of gastro-duodenal ulcers, erosive esophag-itis, and H pylori	Sell 2004 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by Novartis Pharma. No mention of COI.	N = 245 THA	Mean age 63 years. 110 men, 135 women.
Sell 2004 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by Novartis Pharma. No mention of COI.	N = 245 THA	Mean age 63 years. 110 men, 135 women.	Cholestyramine-bound diclofenac 75mg QD vs. BID for 14 days post op	6 months.	In diclofenac 150mg, 19% slight heterotopic ossification (Booker 1, none more severe) vs. 75mg which had 17% grade 1 and 4% grade 2 Booker. No clinical difference after 6 months.	"Although the two doses displayed similar efficacy the author recommends the lower dose because of the lower instance of adverse gastrointestinal event (23% vs. 38%, p=0.02)."	Co-administration of proton pump inhibitors likely resulted in lower side effect profile. No placebo control.

Stupnicki 2003 (6.5)	Proton Pump Inhibitors (PPIs)	RCT	Supported by ALTANA Pharma AG, Konstanz, Germany. No mention of COI.	N = 515 Rheumatic patients likely to take NSAIDs continuously for at least 6 months	376 female, 139 male Median age pantoprazole group 64 years, misoprostol group 64 years	Pantoprazole 20mg plus placebo vs. misoprostol 200µg	3 and 6 months	Pantoprazole superior to misoprostol (p = 0.005) for endoscopic failure. Estimated remission rates 3 and 6 months, 98 and 95% (pantoprazole); 95 and 86% (misoprostol). Discontinuations for likely/definitely drug-related adverse effects: 13/257 (5%) pantoprazole vs. 33/258 (13%) misoprostol.	"Pantoprazole 20 mg o.d. is superior to misoprostol 200 microg b.i.d. in the prevention of NSAID-induced gastrointestinal lesions and symptoms in patients on continuous long-term treatment with NSAIDs due to rheumatic diseases and at risk to develop such lesions or symptoms."	Six-month treatment. Study suggests pantoprazole superior to misoprostol.
Desai 2008 (6.5)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by an Independent Investigator Research Grant from Pfizer, Inc., and by grant from the Digestive Disease Research Foundation.	N = 70 Healthy adults aged 50-75 not taking chronic NSAIDs	37 female, 33 male Mean age NPX 500mg BID plus omerprazole 58.2 years, placebo 58.9 years	Naproxen 500mg BID plus omeprazole 20mg QD vs. naproxen 500mg BID plus placebo for a 6.5-day treatment	14 days	Less gastroduodenal ulcers in naproxen plus omeprazole vs. naproxen plus placebo [11.8% (4 ulcers/34 subjects) vs. 46.9% (15/32), RR = 0.25, p = 0.002]. NPX plus OMP associated with decreased risk of ulceration and erosion [5 erosions [38.2% (13/34) vs. 81.3% (26/32), RR = 0.47, P B 0.001].	"[O]MP at the U.S. OTC dosage of 20 mg daily begun on Day 1 of NSAID treatment reduces both GDUs and dyspepsia with OMP. Therefore, in view of the relatively low cost, availability, and good safety profile of OTC OMP, co-prescription of a PPI in relatively healthy older patients requiring short-term non-specific NSAID therapy may be reasonable."	"Pilot Study"; unclear whether endoscopy data translate to clinical outcomes to support conclusion.

Bianch Porro 1998 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 114 Arthritic disorders requiring indomethacin, diclofenac, or ketoprofen	87 female, 16 male Mean age omeprazole group 53.1±12 years, placebo group 51.6±9.2 years	Omeprazole 20mg QD vs. Placebo for 3 weeks. All patients given indomethacin 100mg, ketoprofen 150mg, and diclofenac 150mg	7 days	26/57 (46%) of omeprazole vs. 20/57 (35%) of placebo group with normal gastroduodenal mucosa (score = 0). Clinically significant gastric lesions (score 3-4) in 6/57 (11%) omeprazole vs. 11/57 (19%) on placebo.	"Omeprazole 20mg once daily is significantly more effective than placebo in the prevention of gastric and duodenal ulcers due to chronic NSAIDs treatment and may provide clinical advantages, in terms of tolerability, over currently available prophylactic therapies."	Three weeks of treatment added to NSAID. Data support treatment.
Graham 2002 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	Graham's research is supported by by Abbott Laboratories, Astra USA, Astra-Merck, Enteric Products Inc, Glaxo Wellcome Inc, Meretek Diagnostics, Merck Sharp & Dohme, Merck, Proctor & Gamble, SmithKline Diagnostics, and TAP Pharmaceutical Products Inc. Agrawal's	N = 535 Patients without H pylori and long-term users of NSAIDs with history of gastric ulcer	348 female, 187 male Mean age of placebo group 60.5±11.8 years, misoprostol group 59.4±12.0, lansoprazole 15mg group 61.6±12.1, lansoprazole 30mg group 60.2±11.8	Placebo plus Misoprostol 200µg QID vs. 15 or 30mg of lansoprazole QD for 12 weeks	Months 1, 2 and 3	Patients on NSAIDs. Either dose lansoprazole remained free from gastric ulcer longer vs. placebo (p <0.001).Misoprostol group remained free of gastric ulcers longer than placebo (p <0.001), 15mg lansoprazole (p = 0.01), or 30mg lansoprazole (p = 0.04).	"Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 microg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, proton pump inhibitors and full-dose misoprostol are clinically equivalent."	Not blinded to misoprostol . H pylori negative.

			research is supported by Pharmacia, Pfizer Inc, and TAP Pharmaceuticals. Campbell's research is supported by AstraZenica, Merck, TAP Pharmaceuticals, Wyeth-Ayerst, and Janssen Pharmaceutica. Overall study supported by grant from TAP Pharmaceutical Products Inc.							
Bergmann 1992 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by grant from Houde Laboratories Paris La Defense.	N = 12 Healthy volunteers	5 female, 7 male Age range 22-32 years	Lansoprazole 30mg QD vs. placebo plus aspirin for 1 week	1 week	Mean Lanza scores 0.67±0.98 with lansoprazole vs. 2.25±1.1 with placebo ($p < 0.005$).	"[I]t is possible to distinguish the functional and morphologic effects of a gastrotoxic drug such as aspirin during experimental studies in humans. Lansoprazole prevents hemorrhagic lesions without reinforcing the mucosal barrier."	Crossover study with small sample size (n = 12). Short experimental design of 1 week.

Niwa 2008 5.5	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 10 Healthy subjects	0 female, 10 male Age range 20 to 40 years	Rebamipide 300mg plus diclofenac 75mg plus omeprazole 20mg vs. placebo plus diclofenac 75mg plus omeprazole 20mg QD for 1 week	4 weeks	Number of subjects with small-intestinal mucosal injuries significantly higher in placebo group (8/10) than rebamipide group (2.10) (p = 0.023).	"Rebamipide had significantly higher efficacy than placebo in preventing NSAID-induced small-intestinal mucosal injury."	Crossover trial with small sample size (n = 10). Evaluation of small intestine. 7 day treatment. Data suggests efficacy for small intestine.
Miyake 2005 5.0	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 26 RA in patients treated over a long term with NSAIDs	14 female, 12 male Mean age famotidine group 65.6 years, lansoprazole group 62.6 years	Famotidine 20mg BID vs. lansoprazole 15mg QD for 24 weeks	24 weeks	8% (1/13) peptic ulcer onset rate infamotidine vs. 2/13 (15%) lansoprazole (NS).	"In Japan, normal-dose H2RA is expected to be a new PU preventive treatment strategy in patients requiring long-term NSAID therapy."	RA patients on NSAIDs with peptic ulcers scars 24-week treatment; small sample (n = 26). Under-reported study.
Scheiman 1994 (4.5)	Proton Pump Inhibitors (PPIs)	RCT	No COI. Supported by NIH grant and by Merck Sharpe and Dohme Research Laboratories.	N = 20 Healthy volunteers	9 female, 11 male Mean age 27±6 years	Omeprazole 40mg QD vs. placebo plus aspirin 650mg QID for 2 weeks	2 weeks	Omeprazole reduced PUD 55% vs. 10% (p <0.01). Endoscopic evidence of intraluminal bleeding or ulceration in 70% of placebo vs. 15% of omeprazole (p <0.001).	"Omeprazole 40mg/day significantly prevented both gastric and duodenal injury due to 2600mg aspirin/day over the two-week period of our study…Omeprazole 40mg/day prevented 95% of subjects from developing ulceration, 85%	Crossover, short 2 week study.

									from having >15 erosions (all ≤3mm in size), and 55% from having >5 erosions. In the subjects given placebo, 25% developed gastric ulcers, 70% had grade 3 injury or worse, and all 95% had at least grade 2 injury."	
Pilotto 2000 (4.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by the host institutions.	N = 69 H pylori positive patients with no severe gastro-duodenal lesions	40 female, 29 male Mean age PAC group 74 years, P group 76.9 years	Pantoprazole 40mg QD plus amoxicillin 1g BID and clarithromycin 250mg BID for 1 week vs. pantoprazole 40mg QD for 1 month	1 month	Higher incidence of severe gastroduodenal damage in Group PAC vs. Group P (29% vs. 9%, p <0.05). Percent of patients worsened, unchanged, improved after 1 month Group PAC: 46%, 46%, and 9% vs. Group P: 7%, 65%, 29% (p <0.0008).	"One month of pantoprazole was more effective than a proton pump inhibitor-based triple therapy in the prevention of gastroduodenal damage in elderly H. pylori-positive NSAID users."	Triple therapy for 1 week pantoprazole for 1 month reduces strength of conclusion regarding what is efficacious vs. efficacy of 1 month when 1 arm still actively treated.

Evidence for the Use of Sucralfate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Agrawal 1991 (6.5)	Sucralfate	RCT	Supported by grant from G. D. Searle & Company. This company provided study design and data analyses.	N = 356 OA patients receiving ibuprofen, piroxicamor naproxen with abdominal pain	115 female, 241 male Median age misoprostol group 60 years, sucralfate group 60 years	Misoprostol 200µg vs. Sucralfate 1g QID	3 months	Gastric ulcer developed in 2/122 (1.6%, 95% CI, 0.3% to 6.4%) on misoprostol vs. 21/131 on sucralfate (16%, CI, 10.4% to 23.7%). Difference in ulcer rates: 14.4% (CI, 10.4% to 19.5%.	"In patients receiving chronic NSAID therapy for osteoarthritis, treatment with misoprostol for 3 months was associated with a significantly lower frequency of gastric ulcer formation, compared with treatment with sucralfate (P less than 0.001)."	OA patients. Study suggests misoprostol is effective compared with sucralfate.
Lanza 1988 (5.5)	Sucralfate	RCT	No COI or sponsorship mentioned.	N = 30 Healthy volunteers	No gender distribution described. Age range 18-47.	Misoprostol 200µg vs. sucralfate 1g vs. placebo, co-administered with 650mg of aspirin 4 times a day 7 days	2 hours after medication administration	Misoprostol superior to sucralfate (p = 0.0001) and placebo (p = 0.00001). Differences in success rates between misoprostol and sucralfate and misoprostol and placebo (44%; 100%) and (61%; 100%), respectively.	"[M]isoprostol at a dose of 200µg, 4 times a day, when dosed concurrently with aspirin, was highly effective in protecting the gastroduodenal mucosae from aspirin-induced injury."	Suggests misoprostol is superior to placebo and sucralfate. Sucralfate not blinded.
Miglioli 1996 (5.0)	Sucralfate	RCT	No COI or sponsorship mentioned.	N = 107 With arthritis	89 female, 18 male Mean age 55.2±9.7 years	Diclofenac 200mg a day vs. naproxen 1g a day plus sucralfate gel 1gm BID vs. Placebo for 14 days	Repeated assessments after administration.	More GU/DU ulcers in placebo group (p <0.05). More on placebo had heartburn and epigastric pain at final evaluation (51 vs. 30% and 49 vs. 28%; p <0.05).	"Sucralfate gel reduces both the incidence of acute gastroduodenal mucosal lesions and symptoms in patients with arthritis receiving short-term nonsteroidal anti-inflammatory drugs."	Data support efficacy in prevention.

Evidence for the Use of H2 Blockers

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rixen 1996 (7.5)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 20 with severe head injury and GCS <10	Mean age: 36 years. 8 male, 7 female	Continuous infusion of ranitidine at 6.25 mg/hr (n = 9) vs. Placebo (n = 11)	Not reported	Ranitidine increased CD4+ lymphocytes (33% to 49%; p < 0.05) and decreased CD8+ lymphocytes (41% to 27%; p < 0.05).	This study demonstrates an immunostimulatory effect of the histamine2receptor antagonist, ranitidine, both at the cellular and mediator levels in patients after head injury."	Small sample. Data suggest ranitidine improved lymphocyte function post severe head injury pointing to an immunostimulatory effect of ranitidine.
Ehsanullah 1988 (6.0)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 297 RA or OA without lesions in the stomach and duodenum	158 female, 139 male Mean age ranitidine group 57 years, placebo group 60 years	Ranitidine 150mg twice a day vs. Placebo twice a day. NSAID drug treatment: naproxen 750mg a day; piroxicam 20mg a day; diclofenac 100mg a day; indomethacin 100mg a day.	4 and 8 weeks	Cumulative incidence of peptic ulceration at 8 weeks 10.3% (27/263); 2/135 (1.5%) developed duodenal ulceration in the ranitidine group vs. 10/126 (8%) taking placebo. Frequency of gastric ulceration same (6%) for the 2 groups at 8 weeks. Fewer gastric lesions in ranitidine group.	"Ranitidine 150 mg twice daily significantly reduced the incidence of duodenal ulceration but not gastric ulceration when prescribed concomitantly with one of four commonly used non-steroidal anti-inflammatory drugs."	RA or OA. Also treatments with naproxen, diclofenac, indomethacin or piroxicam. Suggests ranitidine prevents DU, not GU.
Robinson 1989 (5.5)	H2 Blockers	RCT	No mention of COI. Supported partially by grant from Glaxo Inc., Research Triangle Park,	N = 144 Patients with normal endoscopic findings requiring NSAIDs	93 female, 51 male Mean age ranitidine male 50.1±3.1 years/female 47.0±2.5, placebo male	Ranitidine 150mg twice a day vs. Placebo plus ibuprofen, indomethacin	Week 8	47/57 (82%) of ranitidine had no mucosal damage in the duodenum by study end vs. 32/49 (65%) on placebo.	"[R]anitidine therapy (150mg bid) was effective in preventing duodenal, but not gastric injury resulting from eight weeks of NSAID treatment."	8 weeks treatment also included with NSAID (ibuprofen, naproxen, sulindac, indomethacin, piroxicam).

			North Carolina		45.9±3.2/female 43.1±2.0	, naproxen, sulindac, or piroxicam for 8 weeks				
Robinson 1991 (4.5)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 673 Patients receiving NSAIDs for arthritic or musculo-skeletal conditions	412 female, 261 male Mean age 51.2 for ranitidine group, 50.7 for placebo	Ranitidine 150mg twice daily vs. Placebo for 4 weeks or 8 weeks.	4 and 8 weeks	Protective effect against duodenal mucosal lesions including duodenal ulcers (3 studies) and gastric mucosal lesions including gastric ulcers (1 study) observed vs. placebo.	"[R]antidine is effective in preventing NSAID-associated duodenal ulcers and may be appropriate prophylaxis for certain high-risk patients."	4 RCTs for 4 weeks or 8 weeks treatment. Data suggests protective for DU not GU.

Evidence for the Use of Magnesium

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Temkin 2007 (Score = 9.0)	Magnesium	RCT	Sponsored by the NINDS/NIH. No COI.	N = 499 Age 14 and older admitted with moderate or severe traumatic brain injury.	Mean age magnesium 34.3±16.6 years, placebo 34.4±17.8 years.	(N = 250) Magnesium sulfate 1.0-1.85 mmol/L or 1.25-2.5 mmol/L vs. (N=249) Placebo 1.0-1.85 mmol/L or 1.25-2.5 mmol/L for 5 days.	Follow-up at 1, 3, and 6 months.	No significant results for higher doses of magnesium than placebo -7 to 14; p=0.70; No significant results for lower doses of magnesium than placebo -10.5 to -2; p=0.007; Both at 95% CI	"[W]e undertook a double-blind, single institution trial designed to test the hypothesis that magnesium supplementation given within 8 h of significant head injury would attenuate mortality and improve functioning. By using a broad array of measures, we did not prove our hypothesis."	Moderate to severe TBI. Large sample size. Data suggest lack of efficacy.

Van Norden 2005 (Score = 3.5)	Magnesium	RCT	Sponsored by the Netherlands Heart Foundation. No mention of COI.	N = 186 patients age > 18 using magnesium therapy.	Mean age magnesium 57 years, placebo 56 years.	(N = 94) Magnesium sulfate 1.0-2.0 mmol/L Vs. (N = 92) Placebo 1.0-2.0 mmol/L for 14-18 days.	Follow-up for 18 days.	64 mmol magnesium sulfate a day, serum magnesium levels of 1.0–2.0 mmol/L can easily be maintained without severe side effects (nausea, headache, and muscle weakness).	"With an intravenous dosage schedule of 64 mmol magnesium sulphate a day, serum magnesium levels of 1.0–2.0 mmol/L can easily be maintained without severe side effects for an extended period in a vast majority of patients with SAH."	Study described as partially completed trial. Sparse details

Evidence for the Use of Progesterone

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Skolnick 2014 (Score = 9.5)	Progesterone	RCT, multinational, prospective, double-blind, parallel-group	Sponsored by BHR Pharma, a division of Besins Healthcare. No mention of COI.	N = 1179 with severe TBI. Patients had Glasgow Coma Score ≤8.	Age range 16 to 70 years.	Progesterone group (N = 591) vs. Placebo group (N = 588). Treatments were given intravenously.	Follow-up for 90 days, 180 days, and 6 months.	The primary outcome: at 6 months, the GOS score was not statistically significant between both groups [OR 95% CI: 0.96 (0.77–1.18)]. 50.4% patients in the progesterone group had favorable GOS score and 50.5% in the placebo group. 22.2% patients in the progesterone group and 22.3% in the placebo group, were in vegetable state or died.	"Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials."	Data suggest lack of efficacy.

Wright 2014 (Score = 8.5)	Progesterone	RCT Double-blinded, multicenter	Sponsored by the National Institute of Neurological Disorders and Stroke, the National Center for Advancing Translational Sciences of the National Institutes of Health, and the Emory Emergency Neurosciences Laboratory in the Department of Emergency Medicine. COI, Dr. Wright reports receiving royalties from a patent related to progesterone for the treatment of traumatic brain injury (U.S. patents 7,473,687, 7,915,244, and 8,455,468), which is licensed to BHR Pharma.	N = 882 with severe, moderate to severe, or moderate acute TBI (Glasgow Coma Scale score of 4 to 12, on a scale from 3 to 15, with lower scores indicating a lower level of consciousness). Patients started with the study within 4 hours after blunt injury.	Age range 17 – 94 years.	Intravenous progesterone (N = 442) vs. Placebo group (N = 440). Treatments were administered for 96 hours.	Follow-up for 6 months.	Primary outcome: 51.0% of the progesterone group had favorable outcomes vs. 55.5% of the placebo group [−4.5 (95% CI: −11.1 to 2.1)]. Progesterone group had fewer favorable outcomes vs. placebo group according to a relative benefit of 0.95 (95% confidence interval [CI], 0.85 to 1.06; p = 0.35). At 6 months, the mortality was 17.2% in the study population, ranging from 13.0% in the moderate-injury group to 27.6% in the severe-injury group.	"This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI."	Data suggest lack of efficacy and increased phlebitis

Xiao 2008 (Score = 8.5)	Progesterone	RCT, prospective	Sponsored by the Scientific Research Fund of Zhejiang Provincial Education Department, China. No COI.	N = 159 with Patients entered the study within 8 hours of injury with a Glasgow Coma Score ≤ 8.	Mean age 30 (11) years in the progesterone group and 31 (9) years in the placebo group.	Progesterone group: 1.0 mg/kg via intramuscular injection and then once per 12 hours for 5 consecutive days (N = 82)vs. Placebo group (N = 77).	Follow-up for 3 and 6 months.	At 3 mo., progesterone group had better recovery rate vs. placebo [21 (25) vs. 10 (12)], (p = 0.044). Dichotomization of GOS scores showed favorable outcomes for 47% in progesterone group vs. 31% placebo group (p = 0.034). At 6 mos., dichotomization of GOS scores showed favorable outcomes for 58% in progesterone group vs. 42% placebo (p = 0.048). At 3 and 6 mos., mean modified FIM scores were significant between progesterone group (8.02 ± 1.73 and 9.87 ± 1.17) vs. placebo group (7.35 ± 1.89 and 8.95 ± 1.05), (p	"[The] data suggest that acute severe TBI patients with administration of progesterone hold improved neurologic outcomes for up to 6 months. These results provide information important for further large and multicenter clinical trials on progesterone as a promising neuroprotective drug."	Data suggest better outcomes with progesterone with death and disability.

								< 0.05 and p < 0.01).		
Wright 2005 (Score = 7.0)	Progesterone	RCT	Sponsored by the National Institute for Neurological Disorders and Stroke, National Institutes of Health, and the General Clinical Research Center at Emory University and Grady Memorial Hospital. No mention of COI.	N = 36 with a closed head injury arising from blunt trauma, or a moderate to severe brain injury (Index Glasgow Coma Score [GCS] 4-12). Patients arrived in the emergency department in less than 11 hours post injury.		Progesterone infusion (N = 32, 11 females and 21 males) vs. Placebo infusion (N = 4). The treatments were administered over 12 hours and repeated every 12 hours.	Follow-up at 30 days.	The mean value for CL was found to be 1.73 ± 0.72 L/kg/h and was not different in men (1.66 ± 0.67 L/kg/h) and women (1.88 ± 0.81 L/kg/h). The mean value for terminal half-life was found to be 1.78 ± 1.0 hour.	"Using the results from this study coupled with future findings from a dose-response efficacy trial, investigators should be able to adjust infusion rates of progesterone to achieve optimal steady-state concentrations."	Pharmacokinetic Study. No outcomes data.

Wright 2007 (Score = 6.5)	Progesterone	RCT, double-blind	Sponsored by the National Institute for Neurological Disorders and Stroke, National Institutes of Health, and the General Clinical Research Center at Emory University and Grady Memorial Hospital. No mention of COI.	N = 100 with blunt trauma. Patients arrived within 11 hours of injury with a Glasgow Coma Scale score of 4 to 12.	Mean age 35.8 (15.0) years.	Intravenous progesterone group (N = 77) vs. Placebo group (N = 23).	Follow-up for day 1, 2, 3, 4, and 30.	At day 3, the progesterone group had a lower increase in temperature vs. control group [slope= –0.0055 (95% CI: –0.010 to –0.001)]. Severe TBI patients in the progesterone group remained in a longer comma vs. the placebo group (10.1 days [95% CI: 7.7 to 12.5 days] vs. 3.9 [95% CI: 2.5 to 5.4]). 7 patients (30.4%) in the placebo group died within 30 days of the injury. Patients who enrolled with GCS score of 9 – 12, 10 of 18 (55.6%) patients in the progesterone group had a moderate good recovery vs. none of 7 in the placebo group (p = 0.0202).	"In this small study, progesterone caused no discernible harm and showed possible signs of benefit."	Phase 2 trial. Some baseline differences. Higher death in 30d with placebo (30 vs. 13%).

Shakeri 2013 (Score = 3.5)	Progesterone	RCT	Sponsored by Research Deputy of Tabriz University of Medical Sciences. No COI.	N =76 with diffuse axonal injury. Patients had Glasgow Coma Score ≤8. Patients were admitted to the hospital within 8 hours after head trauma. Mean age was 33.97 ± 12.48 years in the case group and 34.68 ± 12.87 years in the control group.		Progesterone (case) group: Medroxyprogesterone tablets (every 12 hours) (N = 38) vs. Control group (N = 38).	Follow-up for 3 months.	29 patients died during hospitalization, 12 (31.6%) out of case group and 17 (44.7%) out of control group. The recovery rate was higher in the case group [10 (26.3)] vs. the control group [6 (15.8)]. The GOS score was 50% higher in the case group vs. the control group (29%). Patients with 5 ≤ GCS ≤ 8 in the case group had significantly higher rates of GOS score vs. the control group (p = 0.03).	"The use of progesterone may significantly improve neurologic outcome of patients suffering severe TBI up to 3 months after injury, especially those with 5 ≤ GCS ≤ 8, providing a potential benefit to the treatment of acute severe TBI patients. Considering this drug had no significant side effects, so progesterone could be used in patients with severe TBI as a neuro-protective drug."	Data suggest modest efficacy but sparse methodological details.

Evidence for the Use of Bromocriptine

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Whyte 2008 (score = 5.0)	Bromocriptine vs Placebo	RCT/Crossover	Sponsored by the National Institute on Neurological Diseases and Stroke, the National Center for Medical Rehabilitation Research, and the National Institute on Child Health and Human Development. No mention of COI.	N = 22 participants with a history of TBI of at least moderate severity for at least 3 months before the study. Participants need to be able to perform tasks for 10-15 minutes semi independently.	Mean age 35.75 years.	Bromocriptine (with upward titration starting at 1.25 mg twice a day to the target dose of 5 mg twice a day during the first 3 days and then tapered for 1 week after 3 weeks of data collection)/placebo (for 3 days before data collection started for 3 weeks) (N=6) Vs. Placebo (titration of placebo to match other group with 3 weeks of data collection)/bromocriptine (titrated and tapered) (N=6) for 8 consecutive weeks with the first 4 weeks dedicated to the first treatment and the second 4 weeks dedicated to the second treatment.	Follow-up for 8 weeks	There was no significant difference between groups.	"[W]e failed to find evidence of positive effects of bromocriptine (5 mg, twice a day) on a range of measures of attentional function after moderate and severe TBI."	Moderate to severe TBI crossover. Data suggest lack of efficacy on attentional skills.

McDowell 1998 (score = 5.0)	Bromocriptine vs Placebo	RCT/Crossover	Sponsored by NIH, the McDonnell-Pew Program in Cognitive Neuroscience, and the Moss Rehabilitation Research Institute. No mention of COI.	N = 24 patients who had suffered a TBI causing concussion with a loss of consciousness more than 4 weeks before testing.	Median age 32.5 years.	2.5 mg bromocriptine followed by cognitive testing 90 minutes after pill administration Vs. Placebo followed by cognitive testing 90 minutes after pill administration. There was a separate control group from a different study that was not taking medication.	Follow-up 90-120 minutes post pill administration.	Mean dual task: counting in msec: placebo 198 v. drug 96, (p=0.028). Mean dual task: digit span in msec: placebo 539 v. drug 400, (p=0.016). Mean trail making test: 83s v. 64s, (p=0.013). Mean stroop interference test: 23s v. 38s, (p=0.05). Mean FAS test (words produced): 23 v. 31, (p=0.02). Mean Wisconsin card sorting: 2.9 v. 1.7, (p=0.041). NS between treatments for spatial delayed response task, reading span, dual task: baseline, stroop color control, trail making A, and letter cancellation test.	"[O]ur empirical findings have shown that dopamine appears to modulate executive processes which are impaired after damage to the prefrontal cortex."	Crossover. Experimental study of executive function with single dose suggests some cognition efficacy.

McAllister 2011 (score = 4.5)	Bromocriptine vs Placebo	RCT, Prospective, double-blind, crossover	Sponsored by NIDRR and NIH. No mention of COI.	N = 26 with mild TBI and N = 31 healthy controls (HC).	The mean age was 31.8 (9.7) years in the HC group and 28.3 (11.3) years in the mTBI group.	Healthy controls (N = 31) Vs. MTBI (N = 26) 1 month after surgery, patients received bromocriptine or placebo.	Follow-up for 1, 2, 3, and 4 hours after medication ingestion.	MTBI group showed poorer 0-back (p = 0.004), 3-back (p = 0.047), and mean-back (p = 0.009) performance on bromocriptine vs. placebo. A main effect of drug was found on 0-back (p = 0.039). Drug effect both HCs and MTBI patients showing improved performance on bromocriptine (p = 0.027).	"[T]he current results remain most consistent with the conclusion that MTBI is associated with subtle dysregulation of frontal dopaminergic systems in the first 4–6 weeks after injury and that simple augmentation strategies with a dopamine agonist that affects predominantly D2 receptors may not improve cognitive functioning"	Crossover trial. Suggests bromocriptine 30days post mild TBI ineffective in improving working memory.

Evidence for the Use of Cyclosporine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hatton 2008 (score = 7.0)	Cyclosporine	RCT	Supported by National Institutes of Health Grant No. R01 NS41239-02, General Clinical Research Center US Public Health Service Grant No. M01RR02602, and Kentucky Spinal Cord and Head Injury Research Trust Grant No. 1R01NS 41239-01 (all to Drs. Young and Hatton). No COI.	N = 40 with acute severe non-penetrating TBI admitted to the Medical Center.	Mean Age was 29.5 years. 80% male.	4 Cyclosporine groups of (N = 8) vs. Placebo (N = 8). Any cyclosporine value of > 300 ng/ml in cohorts I to III and 750 ng/ml in cohort IV. Including, 50% increase in serum creatinine concentration and 50% reduction in dose for the next dosing day.	Follow-up for 6 months .	No significant difference in the mortality rate between cyclosporine-treated patients (18.8% of 32 patients) and placebo-treated patients (25% of 8 patients). Outcome scores improved in 7% patients from poor to good at the 6-months assessment with no improvement in the placebo group, (p = 0.15).	"In patients with acute TBI who received cyclosporine at doses up to 5 mg/kg/day, administered intravenously, with treatment initiated within 8 hours of injury, the rate of mortality or other adverse events was not significantly different from that of the placebo group."	Severe TBI. No differences in deaths but trend to better improvement in status with cyclosporine (p=0.15).
Empey 2006 (score = 5.0)	Cyclosporine	RCT	Supported by NIH 5R01NS041239, NIH M01 RR02602, and the Kentucky Spinal Cord and Head Injury Research Trust 1R01NS41239-01. No COI.	N= 30 patients with traumatic brain injury with a Glasgow score between 4 and 8.	Age was between 16-65 years.	Group 1- 0.625 mg/kg/dose of cyclosporine and identical amount for placebo. (N=8 CsA, 2 placebo) Group 2- 1.25 mg/kg/dose of cyclosporine and identical amount for placebo (N= 8 CsA, 2 placebo) Vs. Group 3- 2.5 mg/kg/dose of	Follow-up for 72 h.	Whole blood level concentration increased as a function of dose. Mean AUC (h* µg/L) was significantly higher in cohort 3 vs. 1 and 2; 32500 vs. 9840 and 18300 ($p<0.05$). The predicted maximum concentration (µg/L) of whole blood was also significantly higher in group 3 vs. group 1 and 2; 1300	"These data show patients with acute severe TBI demonstrate a more rapid clearance and a larger distribution volume of CsA. Pharmacokinetic parameters derived from this study will guide dosing strategies for future prospective clinical trials	Severe TBI. Small samples. Pharmacokinetic study. Patients not well described. No outcomes data.

						cyclosporine and identical amount for placebo (N=8 CsA and 2 placebo). All doses administered for 2 h bouts at 12 h intervals for 72 h		vs. 398 and 645 ($p<0.05$).	evaluating CsA therapy following acute TBI."	
Mazzeo 2009 (score = 4.5)	Cyclosporine	RCT	Supported by the NIH-NINDS as part of project grant no. NS12587 to M.R.B. (the primary investigator), and by the Lind-Lawrence Foundation and the Reynolds Foundation. No COI.	N = 50 after traumatic injury (TBI). Mean age was 32.7 years.		Within 12 h of the injury patients received either: Cyclosporine A (CsA) 5 mg/kg over 24 h as a slow continuous infusion diluted in 250 mL of 5% dextrose (N = 37) vs. Placebo was 250 mL of 5% dextrose alone (N = 13).	Follow-up over 22-month period.	There is no statistical significance between the groups in total alkaline or bilirubin phosphatase levels. Significance difference was seen in WBC counts only at 24 h, ($p = 0.02$). Fisher's exact test demonstrated that the differences between two groups was not statistically significant, at 3 and 6 months, ($p = 0.7$ and 0.3), respectively.	"This study demonstrates the good safety and tolerability profile of CsA when it is administered early after severe TBI with the goal of neuroprotection. "	Some baseline differences with worse GCS in cyclosporine A group. Data suggest no difference in deaths.
Brophy 2013 (score = 4.5)	Cyclosporine	RCT	Supported by NIH NINDS grant N. P50 NS 12587-27. No COI.	N= 50 patients with traumatic brain injury and a Glasgow score of 3-8. Mean age was 34 years.		Cyclosporine group- 5 mg/kg cyclosporine diluted in 250 mL DW for a 24 h continuous infusion (N=37) Vs. Control group-matching placebo with 250 mL of DW (N=10)	Follow-up for 72 hours.	Results of this study were only reported for cyclosporine group. The exposure characteristics were Cerebrospinal Fluid (CSF) and Extracellular fluid (ECF). CSF exposure achieved 0.37% of whole blood AUC, whereas ECF exposure achieved	"The exposure characteristics of CsA in TBI patients in this study were as expected based on its biochemical properties. The total blood clearance reflects that of a low extraction ratio	Secondary report of Mazzeo 2009. Severe TBI. Study of adverse effects and does not have comparative outcomes data.

								0.04% if ECF. There was correlation between ECF and CSF of (r2= 0.651).	drug, as previously reported in the literature."	
Aminmansour 2014 (score = 3.0)	Cyclosporine	RCT	No mention of sponsorship. No COI.	N = 100 patients with diffuse axonal injury after traumatic brain injury; Mean age was 30.5 years.		Intervention Group- 5 mg/kg.24 h cyclosporine as solution in 250 mL of dextrose water. Administered 8 h after injury. (N=50) Vs. Control Group- received placebo as 250 ml DW started at the same time and continued for 24 h. (N=50)	Follow-up at 3 and 6 months .	The Glasgow outcome scale was used to assess neural improvement at follow-up. No significant differences between groups for Glasgow scores at 3 or 6 months (p>0.05). All participants showed MMSE results in either the moderate (10-19) or severe (0-9) ranges. No significant differences between groups for MMSE scores at either time point. Complete blood results showed significantly higher white blood cells in the cyclosporine group at 12 h (p<0.001).	"Our results suggest that CsA administration to patients with DAI during first 8 h after damage with the dose of 5 mg/kg for 24 h is safe and no clinically important side-effect may ensue. However, it may not bring about desired effects in terms of neuroprotection and cognitive outcome."	Study described as RCT but methods describe matched prospective case control. Data suggest lack of efficacy.

Evidence for the Use of Donepezil

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zhang 2004 (score = 6.5)	Donepezil	RCT	Sponsored by the University of Pennsylvania School of Medicine and Texas Health Science Center at San Antonio. No COI.	N = 20 with TBI mean 4mo previously to examine effect of donepezil on short-term memory and sustained attention in post-acute patients using Wechsler Memory-Scale-III (WMS-III), Paced Auditory Serial Addition Test (PASAT), Auditory or Visual Immediate Index (VII or AII).	Mean (±SD) age 33 (±2) for Group A and 31 (±2) for Group B.	Group A received donepezil 5mg/d for 2 and 10mg/d for 8 weeks by mouth for the first 10 weeks, plus washout period of 4 weeks. (N = 10) vs. Group B received placebo visually identical tables, in the first 10 weeks, plus washout period, plus donepezil (N = 10).	Follow-up for 24-weeks, cross-over at 10-week.	At baseline, no significant statistical difference was observed in scores of neuropsychological testing. Patients with donepezil in group A after all treatments for AII and VII, p = 0.002 and p < 0.000. In group B, scores increased after receiving donepezil treatment. No statistically significant difference between the two groups at the week-24 assessment on either the AII or VII, p = 0.588 or 0.397.	"Donepezil increased neuropsychological testing scores in short-term memory and sustained attention in post-acute TBI patients."	Post-acute TBI (subacute-chronic), mean 4mo out. Crossover trial. Data suggest modest efficacy.
Tenovuo 2005 (score = 4.5)	Rivastigmine vs Galantamine vs Donepezil	RCT	No mention of sponsorship or COI.	N=111 with clinically definitive TBI (Kay et al., 1993) with chronic sequels; fairly stable phase after trauma, at least one of the four target symptoms (fatigue, poor memory,	Mean age 40±1.3 years	Donepezil started at 5 mg od in the morning (N=27) vs. Galantamine started at 4 mg bid morning and afternoon (N=30) vs.	No mention of study duration or follow-up time.	Mean maintenance dose: 7.2 mg od donepezil, 5.0 mg bid galantamine, 2.3 mg bid for rivastigmine. Positive response (%); 41% donepezil, 60%	"CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences between the	Quasi-RandomizationData suggest comparable efficacy between all 3 drug groups.

				diminished attention).		Rivastigmine started at 1.5 mg bid morning and afternoon (N=54). Doses raised after 1 week if no therapeutic response with good tolerability or if there was partial response and good tolerability.		galantamine, 59% rivastigmine. No differences between these drugs were found.	three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed."	

Evidence for the Use of Methylphenidate

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Willmott 2009 (score = 8.5)	Methylphenidate vs Placebo	RCT/ Crossover	Sponsored by the Victorian Neurotrauma Initiative and the Wenkart Foundation. No COI.	N = 40 with moderate to severe TBI,	between the ages of 16 and 60. Mean age 26.33±9.14 years.	Methylphenidate 0.3 mg/kg pills twice daily at 8 am and noon Vs. Placebo pills. 6 sessions over 2 weeks. Sessions were blocked in 3s. One session of each block was assigned methylphenidate and the other placebo.	Follow-up for 2 weeks	Speed measures (mean±SD) 2 & 7 automatic speed raw score (ASRS): methylphenidate 134.80±41.76 v. placebo 131.05±42.34, p=0.003. Selection attention task (SAT) reaction time (RT) simple selective attention task RT (SSAT): methylphenidate 762.18±176.33 v. placebo 800.07±200.08, (p=0.001). Four choice reaction time task (4CRT RT) dissimilar compatible RT (DC): methylphenidate 838.70±174.06 v. placebo 881.45±202.77, (p=0.003). 4CRT RT dissimilar incompatible RT (DI): methylphenidate 934.26±223.16 v. placebo 959.17±238.95, p=0.034. 4CRT RT	"[T]his study has clearly demonstrated the efficacy of methylphenidate in facilitating speed of information processing in TBI rehabilitation inpatients."	Crossover trial. Mean 68 days since injury. Data suggest methylphenidate associated with better information processing speed. No long term results.

								similar compatible RT (SC): methylphenidate 864.55±193.79 v. placebo 911.50±231.72, (p=0.002). Symbol digit modalities task (SDMT) no correct: methylphenidate 51.80±13.45 v. placebo 50.18±12.69, (p=0.017). NS between groups for all other measures and outcomes.		
Whyte 2004 (score = 7.5)	Methylphenidate vs Placebo	RCT/ Crossover	Sponsored in part, by grant R01NS39163 from the National Institute on Neurological Diseases and Stroke, National Institutes of Health, and grant R24HD39621 from the National Center for Medical Rehabilitation Research, National Institute on Child Health	N = 39 with a history of TBI for at least 3 months	between the ages of 16 and 60. Mean age 37 years.	Methylphenidate (MP) 0.3 mg/kg/dose twice a day (8:30 am and noon) Monday through Saturday with Sunday being a washout day before crossover followed by placebo alternating weekly MPPMPPMPP, (N = 18) vs Placebo followed by MP (PMPPMPPMP, 5 days a week for 6 weeks (N = 21).	Follow-up for 6 weeks.	Initial speed – perceptually simple visual go/no-go (50% targets) median reaction time (RT), first 32 trials: p=0.03. Initial response bias – perceptually simple visual go/no-go (50% targets) response rate, first 32 trials: p=0.04. Family ratings – cognitive failures questionnaire total score: p=0.04. NS for all other measures.	"MP, in a dose of 0.3 mg/kg twice a day, seems to have clear and consistent positive effects on speed of processing and caregiver ratings of attentiveness in a highly selected sample of individuals with moderate to severe TBI."	Repeated crossover trial. Subjects complained of attention problems. Most results negative but efficacy for cognitive processing and attention is suggested.

			and Human Development, National Institutes of Health. No mention of COI.							
Willmott 2013 (score = 7.5)	Methylphenidate vs Placebo	RCT/ Crossover	Sponsored by the Victorian Neurotrauma Initiative Pty Ltd and the Wenkart Foundation. No COI.	N = 32 moderate-to-severe TBI and N = 40 healthy controls.	Aged between16–60 years.	Methylphenidate (MP) trial at 0.3 mg/kg twice daily for six sessions (N = 32) Vs. Placebo controls for six sessions (N = 40)	Follow-up for 2 weeks.	TBI participants performed more poorly on: SDMT / 2&7 ASRS / 2&7 CSRS / DC RT / and SI RT: ($p < 0.0005$ / $p = 0.001$ / $p < 0.0005$ / $p = 0.005$ / and $p = 0.002$). Performances of Val allele homozygotes: TBI performed more poorly on 7/8 measures: LNS / SDMT / 2&7 ASRS / 2&7 CSRS / SSAT RT / DC RT / and SI RT; ($p = 0.044$ / $p < 0.001$ / $p < 0.001$/ $p = 0.002$ / $p = 0.030$ / $p < 0.001$ / and $p = 0.004$).	"COMT allele status was not strongly associated with attentional performance or response to MP in the TBI sample."	Crossover RCT. Experimental study. Median 47 days since injury. Genetic influences appear minor.
Kim 2006 (score = 6.5)	Methylphenidate vs Placebo	RCT	Sponsored by a grant to YHK from the Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and	N = 18 with chronic TBI, mild cognitive impairment (MMSE score 20-29), and no previous brain disorders.	Mean age 34 years.	Methylphenidate 20 mg (N=9) Vs. Placebo (N=9). Assessments at baseline, 2 hours after treatment was administered and follow-up 2 days later which was also the washout	Follow-up for 2 days.	Improvement ratio for reaction time (%) for working memory task: post drug administration test methylphenidate 13.74±13.22 v placebo 4.02±9.48 ($p<0.05$); post drug washout test, NS between groups.	"[M]ethylphenidate was beneficial for improving cognitive performance in patients with chronic TBI even with a single dose, as was shown from the results of this study."	Experimental with single dose. Small sample. Chronic TBI. Data suggest efficacy though no long term data.

			Technology of Republic of Korea. No mention of COI.			period for the drugs.		Improvement ratio for accuracy (%) for working memory task: NS between groups. Improvement ratio for reaction time (%) for visuospatial attention task: NS between groups. Improvement ratio for accuracy (%) for visuospatial attention task: NS between groups.		
Alban 2004 (score = 6.0)	Methylphenidate vs Placebo	RCT/ Cross over	Sponsored in part, by grant from the National Institute on Neurological Diseases and Stroke. No mention of COI.	N = 36 with a history of traumatic brain injury for at least 3 months before enrollment between the ages of 16-60 years with a GCS score of less than N = 12 and posttraumatic amnesia for more than 1 hour.	Mean age 36 years.	Methylphenidate (MPH) (M) and placebo (P) in alternating weeks, (MPMPMP) or (PMPMPM) for 6 weeks. MPH BID at 0.3 mg/kg/dose rounded to nearest 2.5 mg. Both MPH and placebo were given orally. MPH or placebo for 6 days/week with one day (Sundays) used as washout day. All also attended an activity program 5 d/wk, Monday through Friday.	Follow-up for 6 weeks.	NS between MPH and placebo for adverse effects. Mean arterial pressure (mean±SD): MPH 95.12±10.14 v. placebo 92.63±9.411 (p=0.046). Systolic pressure: MPH 122.81±16.16 v. placebo 119.14±14.59 (p=0.024). Diastolic pressure: NS. Pulse: MPH 83.22±14.11 v. placebo 76.23±12.16 (p<0.001).	"Our findings show MPH to have few adverse effects, although our sample size of 34 participants cannot rule out uncommon adverse effects or small differences in common adverse effects between MPH and placebo."	Methylphenidate associated with increased blood pressure and pulse. One subject discharged for hypertension.

Speech 1993 (score = 6.0)	Methylphenidate vs Placebo	RCT/ Crossover	No mention of sponsorship or COI.	N = 12 ambulatory patients with moderate to severe TBI, at least 21 years of age, high school graduate, no history of learning problems, no history of sensitivity to methylphenidate, and no history of treatment for psychiatric or neurological disorders.	Mean age 27.6 year	Methylphenidate 0.3 mg/kg bid. (8 am and noon) for 1 week followed by placebo for 1 week Vs. Placebo followed by treatment.	Follow-up at the end of the first and second weeks.	Neuropsychological test of attention / learning / cognitive processing speed and social/personality/ functioning: no statistical significance, and none of the drug/placebo comparisons approached significance, (p = NS).	"[W]hile stimulant medications are relatively safe with regard to side-effects and are well tolerated by patients, our results do not provide support for the clinical use of stimulant medications to treat the chronic neurobehavioural sequelae of closed head injury."	Crossover trial. All early post TBI. Data suggest no significant improvements on cognitive tests.
Gualtieri 1988 (score = 4.5)	Methylphenidate vs Placebo	RCT/ Crossover	No mention of sponsorship or COI.	N = 15 closed head injury (CHI) patients with a GCS <8 past the initial recovery phase.	Mean age 24.1±9.41 years.	Methylphenidate (MPH) 0.15 mg/kg bid. 8 am and noon v. MPH 0.30 mg/kg b.i.d.8 am and noon vs. Placebo.	Patients spent 2 weeks in each condition with a 2 day washout period between conditions. MPH responders continued on the drug and had follow-ups monthly. Those that made it to 1 year on MPH (n=3)	Selective reminding test (SRT) CLTR (least square means): placebo 0.25 v. low dose MPH 0.50, p<0.024. SRT Delay CLTR: placebo 1.4 v. low dose MPH 4.8, p<0.03. SRT Sum recall: NS. SRT intrusions: placebo 9.38 v. low dose MPH 3.7, p<0.0044. SRT average trial sum: placebo 6.05 v. low dose MPH 7.17, p<0.024. SRT sum slope: placebo 0.13 v. low dose MPH	"There is some evidence, then, for short-term stimulant effects on the behavioural symptoms and cognitive deficits that occur in many CHI patients."	Crossover. Mean 47 months since injury. Data suggest most patients with favorable results, but not long term differences.

							enrolled in a reversal study.	0.38, p<0.035. SRT sums Ss linear: placebo 1.38 v. low dose MPH 4.26, p<0.029. Verbal fluency test (VFT) Persev err A & B: placebo 3.2 v. 0.7, p<0.026. VFT Persev err B: placebo 2.89 v. low dose MPH -0.19, p<0.0004. VFT Total correct B: NS. Continuous performance test (CPT) Omission errors: NS.		
Lee 2005 (score = 4.0)	Methylphenidate vs Sertraline vs Placebo	RCT	No mention of sponsorship or COI.	N = 30 with TBI for 2 weeks to 1 year	between the ages of 18-55.	Methylphenidate or MPD, started at 5 mg/day and increased by 2.5 mg every day until it reached 20 mg/day (N = 10) Vs. Sertraline or SER, started at 25 mg/day and was increased by 25 mg every 2 days until it reached 100 mg/day (N = 10) Vs. Placebo for 4 weeks (N = 10).	Follow-up for 4 weeks.	Hamilton Rating Scale for Depression (HAM-D) score (baseline/4 week): MPD 25.2/15.7 v. SER 27.6/20.0 v. placebo 25.7/22.3, post hoc MPD>placebo, (p=0.005), SER>placebo, (p=0.050). Recognition reaction time (ms) baseline/4 week: MPD 399.2/340.2 v. SER 405.8/389.5 v. placebo 443.8/377.3, post hoc MPD >SER, (p=0.045), placebo >SER, (p=0.026). Adverse events	"[I]t is concluded that in patients with mild to moderate TBI, both methylphenidate and sertraline had significant effects on the depressive symptoms compared with the placebo, while methylphenidate seemed to have more beneficial effects on cognitive function and daytime alertness than sertraline, at least in the 4 week treatment	Mild to moderate TBI. Dropouts unclear. Data suggest methylphenidate outperformed sertraline for attention and cognition. Both medications comparable for depression and

								were higher in the SER group compared to the MPD group, (p = 0.010).	of patients with TBI."	superior to placebo.
Moein 2006 (score = 4.0)	Methylphenidate vs Placebo	RCT	Sponsored by a grant from Isfahan University of Medical Sciences, Department of Research. No mention of COI.	N = 40 with severe TBI (GCS 5-8) and 40 moderately TBI patients (GCS 9-12).	Mean age for treatment and control groups: 35 (17.9) / 33.7 (13.1).	Methylphenidate 0.3 mg/kg per dose (max 20 mg per dose) twice a day orally on the second day of admissions (N = 46) Vs. Control who received placebo starch pills orally twice daily (N = 39).	Follow-up with the mean hospital stay up to 13.72 days in control vs 11.12 days in treatment group.	Severe head injury ICU stay (days±SD): treatment 9.85±4.66 v. control 12.95±7.59, (p=0.06). Hospital stay (days±SD): treatment 14.1±5.99 v. control 18.35±7.75, (p=0.029). GCS on discharge: NS. Moderate head injury ICU stays: treatment 4.09±1.34 v. control 5.58±3.81, (p=0.05). Hospital stay: NS. GCS on discharge: NS. Total ICU stay: treatment 6.90±4.44 v. control 9.36±7.04, (p=0.031). Hospital stay: treatment 11.12±5.43 v. control 13.72+7.83, (p=0.043). GCS on discharge: NS.	"Methylphenidate was associated with reductions in ICU and hospital length of stay by 23% in severely TBI patients (P=0.06 for ICU and P=0.029 for hospital stay time). However, in the moderately TBI patients who received methylphenidate, there was 26% fall (p=0.05) only in ICU length of stay."	Quasi-randomized (MRN) replaced unknown number of dropouts. Data trended towards shorter ICU stay, but significantly shorter hospital stays.
Mooney 1993 (score = 4.0)	Methylphenidate vs Placebo	RCT	No mention of sponsorship or COI.	N = 38 adult males with severe TBI that were 6	Mean age 29.45 years.	Methylphenidate building up over the first 4 weeks of the study to	Follow-up for 6 weeks.	Repeated measure univariate ANOVA (MS between/ MS within): KAS	"[T]reatment with methylphenidate was found to	Mean 27 months post injury. Some

				months or further out from their injury.		30 mg per day for the last 2 weeks (N = 19) vs. Placebo for 6 weeks total (N = 19).		Belligerence 17.05/1.86, (p=0.005); STAS Trait Anger 666.12/28.96, (p=0.000); STAS State Anger 76.00/20.22, (p=0.06); POMS Anger-Hostility 320.21/24.03, (p=0.001). Mean scores on general psychopathology outcome measures pre/post treatment with methylphenidate [pre915]: OSSI-P placebo 262.91±101.76/258.94±93.28 v. treatment 331.53±101.88/260.74±106.61; OSSI-I placebo 306.81±78.50/305.19±80.09 v. treatment 342.63±85.86/269.26±70.97; KAS-General Psychopathology placebo 41.69±9.57/41.38±8.76 v. treatment 46.37±7.88/38.05±3.95. Repeated measures univariate ANOVA for each general psychopathology	significantly reduce anger in brain-injured men as reflected by changes in scores on the anger outcome measures used in the study."	baseline differences. Data suggest improvement in memory but not attention or anger.

								outcome measure (MS between/MS within): OSSI-P 81664.79/2268.47, (p=0.003); OSSI-I 76125.79/2114.61, (p=0.001); KAS-General Psychopathology 278.17/17.08, (p=0.000).		
Plenger 1996 (score = 4.0)	Methylphenidate vs Placebo	RCT	Sponsored by the Centers for Disease Control grant. No COI.	N = 23 with moderate to moderately severe TBI or complicated mild TBI,	between the ages of 16 to 65.	Methylphenidate 30 mg/kg daily at 8 am and noon (N = 10 acute phase, N = 6 30-day and N = 5 at 90-day) vs. Placebo for 30 days with follow-up 90 days after first day of drug treatment. (N = 13 / 6 / and 4).	Follow-up at 30 and 90 days.	Disability rating scale: 30 days, (p<0.007); 90 day, NS. Continuous performance test (CPT) (Hits and Del): 30 days, (p<0.038); 90 days, NS. CPT (commissions): NS. Attention (CPT + paced auditory serial addition test (PASAT) + 2&7 + Attn/Conc from Wms-R): 30 days, (p<0.03); 90 days, NS. Declarative memory (VSR + WMS-R, Del., Gen., Vis. & Ver.): NS. Motor performance and memory (Porteus Mazes &Pursuit Rotor): 30 days, (p<0.050; 90 days, (p=0.07).	"[A]lthough early treatment of moderately severe traumatic brain injury with methylphenidate appears to hold promise, specific parameters regarding treatment need to be further identified to validate this as a viable clinical treatment."	High dropout rate.
Whyte 1997 (score = 4.0)	Methylphenidate vs Placebo	RCT/ Crossover	No mention of sponsorship or COI.	N = 19 with TBI,	with a mean of 30.8 years	Methylphenidate or MP 0.25 mg/kg, 2 doses	Follow-up for 6 days.	Performance decrement (mean±SD): MP -	"These data suggest that MP can be a useful	Repeated crossover trial.

						per day vs. Placebo 90 minutes before task performance for 6 tasks on 6 different days.		0.07±0.56 v. placebo -0.51±0.48, (p=0.01). Baseline: reaction time (RT): MP 634±249 v. placebo 700±279, (p=0.00). Slope of speed function: MP 94±59 v. placebo 136±71, (p=0.01). Sorting productivity (items sorted): 426±218 v. 399±205, (p=0.00). Optimal warning (ms): NS. Vigilance decrement yes rate: 0.01±0.02 v. 0.03±0.03, (p=0.01). Vigilance level RT: NS. Duration of each off-task behavior (s): 2.19±1.69 v. 3.40±2.96, (p=0.05). Minimum score RT: 540±246 v. 570±217, (p=0.05). All other performance measures: NS.	medication in TBI, by acting primarily to increase mental processing speed."	Appears possibly related to Alban 2004, but N=19 vs. 35.
Johansson 2017 (score = 3.5)	Methylphenidate	Randomized (not placebo cont	No COI. No mention of industry sponsorship.	N= 30 participants, who suffered from long-term post-concussion	Mean age: 39.7 years; 18 females, 12 males	Participants were randomized into 3 groups: No medication (methylphenidate) Vs.	Follow up at 6 months	After six-month follow-up, effects on Mental Fatigue Scale (MFS), depression, anxiety, and cognitive	"Individuals suffering from prolonged symptoms after TBI reported reduced mental fatigue and	Small sample, not placebo controlled. Data suggest long-term

		rolled)		symptoms after a mild TBI or moderate TBI		Low dose (5mg x 3/day) Vs. Normal dose(20 mg x 3/day) Data not given on number of participants.		function (processing speed, attention, working memory) were significantly improved compared to baseline data (P < 0.001, respectively). Heart rate was significantly increased (P = 0.01), while blood pressure was not changed.	improved cognitive functions with long-term methylphenidate treatment. It is suggested that methylphenidate can be a treatment option for long-term mental fatigue and cognitive impairment after a TBI, but further randomized control research is warranted."	methylphenidate use may improve post TBI fatigue but working ability did not change from baseline to 6 months post intervention.
Johansson 2013 (score = 2.5)	Methylphenidate	RCT	No mention of sponsorship. No COI.	N = 29 with a mild TBI and with TBI and also with pain in the neck, shoulders. Physically-well rehabilitated TBI.	Mean age for study patients was 38.6 ± 11.1.	Methylphenidate no medication, Vs. Low dose (5mg x 3) Week 1: 5mg x 1; week 2: 5mg x 2; weeks 3 5mg x 3 Vs. Normal dose (20mg x3) Week 1: 10 mg x 2; week 2: 20 mg + 10 mg + 10 mg; week 3: 20 mg + 20 mg + 10 mg and week 4: 20 mg x 3 Vs. No medication	Follow-up for 4 weeks.	Treatment significantly improved mental fatigue measured by the MFS (F = 21.7, p < 0.001). CPRS depression (F = 8.6, p = 0.001) and anxiety (F = 4.9, p = 0.010) scales also improved significantly. Pain was not significantly changed due to treatment (F = 0.127, p = 0.881).	"Methylphenidate was well-tolerated by TBI subjects. No major adverse effects and no cardiovascular effects were detected in the present study."	Open label. Data suggest less mental fatigue with higher dose.

						short-acting Ritalin®.				

Evidence for the Use of Modafinil (Provigil), Armodafinil

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kaiser 2010 (score = 7.0)	Modafinil vs Placebo	RCT-Pilot Study	No sponsorship. No mention of COI	N=20 patients with TBI who had fatigue or EDS or both.	Ages, 37 ± 9 for treatment group and 43±19 for placebo group	Modafinil group Received 1 oral capsule (100 mg per day) (N=10) Vs. Placebo (N=10)	Follow-up for every 2 weeks, and after 6 weeks.	After 6 weeks, the decrease in ESS scores was higher in the modafinil group (_2.3 ± 2.3 compared with 0.7 ± 1.8 placebo group, p = 0.005 The objective measurement of the ability to remain awake at daytime under nonstimulating conditions revealed Significant increase in the ability to remain awake at daytime compared with baseline of	"[M]odafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue".	Pilot study with placebo group. Posttraumatic fatigue not improved with modafinil but EDS improved as well as ability to stay awake.

								the mean sleep latency on MWT in the treatment group (8.4±9.6 minutes) compared with the placebo group (0.4 ± 6.2 minutes) (p=0.04) Patients treated with modafinil had no change in sleep latencies compared with baseline (2.7 ± 14.7 minutes), and decreased sleep pressure compared with the placebo group (p =0.03).		
Jha 2008 (score = 7.0)	Modafinil vs Placebo	RCT/Crossover	Sponsored by the US Department of Education, Office of Special Education and	N=51 who received inpatient rehabilitation	Mean age 38.25±12.20 years.	Modafinil 100 mg 1 tablet QD at noon for 3 days	Follow-up for at least 24 weeks.	Before crossover mean±SD baseline/w	"In this randomized controlled study of	Crossover trial showed comparable efficacy between

			Rehabilitation Services, National Institute on Disability and rehabilitation Research, and Cephalon. No mention of COI.	for TBI and at least 1 year post injury.		then increased to 1 tablet BID for 11 days followed by maintenance dose of 2 tabs QAM and 2 tabs at noon for 8 weeks. Four wk washout, then crossover to placebo on same schedule (N=27) vs. placebo tabs then modafinil (n=24). All offered 4 week open label period of modafinil.		eek 4 ImPACT visual motor speed composite: modafinil 23.92±5.52/23.49±5.36 vs. placebo 21.44±8.93/25.22±7.19 (p=0.0354). After crossover mean±SD baseline/week 4 Modified Fatigue Impact: baseline/week 4 modafinil 39.73±20.82/28.91±19.06 vs. placebo 36.27±17.67/37.74±17.51, -10.9±15.93 (p=0.0323). After crossover mean±SD baseline/week 4/week 10	fatigue in individuals with moderate to severe TBI, there was no significant difference between treatment with modafinil and placebo over a 10-week period."	Modafinil to placebo. Baseline comparability differences.

								ImPACT Verbal Memory Composite: modafinil 80.26±12.95/76.58±18.18/77.41±16.52 vs. placebo 78.07±11.96/85.36±11/84/87.09±12.01 (p=0.0057 week 4, p=0.0038 week 10).		
Menn 2014 (score = 4.0)	Modafinil, (Armodafinil) vs Placebo	RCT	Sponsored by Teva Pharmaceutical Industries Ltd. COI, Menn received research funding from Teva Pharmaceutical Industries Ltd; Yang is employee of Cephalon/Teva Pharmaceutical Industries Ltd; Lankford has received research funding from Actelion, Apnicure, Arena, Cephalon, Evotec, Fisher Paykel, GlaxoSmith- Kline, Lilly, Merck, Neurim, Neurocrine, Neurogen, Organon, Pfizer, Respironics, Sanofi-Aventis, Schering-Plough, Sepracor, Somaxon, Sunovion,	N=117 with a history of mild or moderate closed TBI (Glasgow Coma Scale score >8) in the last 1-10 years and complaint of excessive sleepiness for ≥3 months within 12 months of TBI.	Mean age 31.3±10.54 years.	Armodafinil 50 mg/day (N=30) Vs. Armodafinil 150 mg/day (N=29) Vs. Armodafinil 250 mg/day (N=29) Vs. Placebo (N=29) 12 week study.	Follow-up at weeks 2, 4, 8, and 12. There was an optional 12 month open-label extension with 150 or 250 mg/day armodafinil.	Mean sleep latency baseline to final visit: armodafinil 50 mg 2.6±4.35, 150 mg 5.0±4.95, 250 mg 7.2±6.35 min vs. placebo (p=0.0010, 250 mg vs. placebo). Clinical Global Impression of Change (CHI-C): week 4 150 mg	"Significant objective improvement in sleep latency was demonstrated for patients receiving armodafinil 250 mg/day in patients with mostly mild closed TBI."	Sponsor terminated study early due to low enrollment. Study terminated early. Poor compliance and high dropout rate (>50%).

			Takeda, Transcept, UBC, Ventus, and Vanda; Lankford is a consultant for Actelion, Apnicure, Cephalon, Cereve, Pfizer, and Somaxon and has participated in speaking engagements for Jazz Pharmaceuticals, Purdue, Sanofi-Aventis, and Somaxon. Manuscript preparation was provided by Teva Pharmaceutical Industries Ltd.					50% responders vs. 250 mg 50% vs. placebo 22% (p=0.0350, and 0.0469 respectively).		

Evidence for the Use of Muscle Relaxants (not including Botox)

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Brown 1996 (score = 5.5)	Suxamethonium vs Saline	Double Blind Crossover	No mention of sponsorship or COI.	N=11 patients who obtained a severe head injury and had a Glasgow Coma score less than 8.	Mean Age 36 (17-70) years	Group 1 Received injection i.v. with 1 mg/kg of suxamethonium at a concentration of 50 mg/mL Vs. Group 2 Received injection i.v. with normal saline 0.02 ml/kg.	Follow-Up time baseline, 1, 2, 4, 6, 8, and 10 minutes after injection.	No statistical significance comparing baseline Intracranial Pressure as well as Cerebral Perfusion Pressure.	"[O]n average the administration of suxamethonium to head injured patients who are sedated with propofol and morphine infusions and are being hyperventilated does not cause an increase in ICP or a fall in CPP."	Small sample cross-over. Data suggest suxamethonium did not lead to increased intracranial pressure or cerebral perfusion pressure compared to NS control.

Meythaler 2001 (score = 5.5)	Tizanidine vs Placebo	RCT/Cross over	Sponsored by Elan Pharmaceuticals, under and investigational drug treatment protocol. No COI.	N=17 with acquired brain injury either from stroke (N=9) or from Traumatic Brain Injury (N=8);	Mean Age 44 (19-67)	N=17 All patients received 6 weeks of either tizanidine or placebo administered orally every 3 to 4 days slightly increasing the dose until they reached 36 mg/day. After the first trial they allowed 1 week for medication tapering then the second arm would start the other medication.	Follow-up at Baseline, 2, 4, 6, 8 weeks.	Tizanidine Phase: Lower Extremity Ashworth score baseline vs week 4; 2.3 ± 1.4 to 1.7 ± 1.1 (p<0.0001). Spasm score baseline vs week 4; 1.0 ± 0.9 to 0.5 ± 0.8 (p=0.0464). Muscle tone vs Placebo at week 6 (p=0.0006). Upper extremity Ashworth score baseline vs week 4; 1.9 ± 1.1 to 1.5 ± 0.9 (p<0.001). motor tone at week 6; 1.8 ± 1.2 increase (p<0.0.117). Motor Strength baseline vs week 6; 3.55 ± 1.3 to 3.73 ± 1.3 (p=0.0089). Placebo Phase: Lower Extremity motor tone baseline vs week 4; 2.6 ± 1.5 to 2.1 ± 1.4 (p=0.0007). Upper extremity motor tone baseline vs 4 weeks; 2.2 ± 1.3 to 1.9 ± 1.3 (p=0.0038). Motor strength baseline vs week 6; 3.55 ± 1.3 to	"[T]izanidine was effective in decreasing the spastic hyper-tonia associated with acquired brain injury relative to placebo. Due to side effects related to drowsiness and somnolence, there were limitations on the therapeutic dosage levels attainable in the study."	Small sample, crossover trial. Mistake on Motor Strength Statistics p values don't line up. Data suggest tizanidine superior to placebo for spasticity/hypertonia. Increases drowsiness.

								3.74 ± 1.3 (p=0.0246)		
Bourgoin 2005 (score = 4.5)	Sufentanil vs Ketamine	RCT, Prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age 29 ± 12 years in the Sufentanil group and 29 ± 11 years in the Ketamine group.	Sufentanil group (N = 15) vs Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was 17.7 ± 6.5 mm Hg in sufentanil group vs. 16.2 ± 6.4 mm Hg in ketamine group. VMCAM value was higher in sufentanil group (77 ± 21 cm/sec) vs. ketamine group (60 ± 33 cm/sec, p = 0.03). At 6, 7, and 13 min, there was difference in BIS value between groups (p < 0.05).	"The present study shows that the increase in sufentanil or ketamine plasma concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients."	Small sample. Data suggest doubling sufentanil or ketamine showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.
Kolenda 1996 (score = 1.5)	Ketamine/Midazolam vs Fentanyl/Midazolam	RCT	No mention of sponsorship and COI.	N=35 patients who suffered a moderate or severe	Mean Age: Group 1 38 (18-72) yrs.; Group 2	Group 1 Received analgosedative therapy with 6.5 mg/kg and 65 mg/kg	Follow-Up baseline and day 14 (final dosage) and day 1, 3, and 7 after	Tube feeding, group 1 vs group 2, 14 day average: 824 mL/day vs 579 mL/day statistical	"We conclude that on the one hand ketamine/midazolam analgosedation	High dropout rate due to multiple complications. Baseline differences in treatment

				head injury;	29 (16-59) yrs.	ketamine per day Vs. Group 2 Received analgosedative therapy with 6.5 mg/kg and 65 mg/kg fentanyl per day.	termination of the analgosedative therapy.	difference at day 3, 4, 5; ($p<0.05$). Mean Arterial pressure (MAP) group 1 vs Group 2, day 3 and 7: 91 (76-107) vs 81 (73-107) and 95 (88-107) vs 77 (76-90); ($p<0.05$). Mean pulse rate group 1 vs group 2, day 2, 3, and 7: 80 (64-104) vs 56 (44-92), 74 (62-104) vs 62 (48-80), 84 (68-96) vs 68 (64-76), respectively; ($p<0.005$). Intracranial Pressure, group 1 vs group 2, day 8 and 10: 16 (14-22) vs 11 (6-18), 18 (14-22) vs 10 (6-22); ($p<0.05$).	in head-injured patients is more expensive than a comparable anaesthetic therapy using fentanyl/midazolam, and this disadvantage is not countered by the earlier restitution of consciousness in the ketamine group. But with regard to risk patients for intensive therapy such as those presenting severe cardiovascular, pulmonary or gastro-intestinal problems requiring intensive medication, ketamine offers an alternative anaesthetic concept [13, 18, 30, and 34]. Its bronchodilating action as well as its stabilizing effect on circulation and gastro-intestinal motility may be of great	groups. Data suggest comparable (in) efficacy.

									beneficial value for these patients.”	

Evidence for the Use of Antiseizure Prophylaxis

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Temkin 1999 (score = 7.0)	Seizure(Prophylaxis Phenytoin vs Valproic Acid	RCT	No mention of sponsorship or COI.	N = 379 patients admitted to a hospital with traumatic brain injury within 24 hours of injury.	Mean age; 37.3 years	1-Week course of Phenytoin (20 mg/kg) (N = 132) Vs. 1-month course of Valproate (20 mg/kg) (N = 120) Vs. 6-month course of Valproate (20 mg/kg) (N=127)	Follow-up for two years.	Levels of ALT were significantly higher in the Phenytoin group compared to either Valproate group at 1 month follow-up ($p<0.02$). There was no significant difference between groups for early seizures ($p=0.14$), however, the valproate groups showed a larger risk ratio (RR=2.9). There was also no significant differences for late seizures ($p=0.27$). The RR for mortality over 2 years was higher the valproate group, and it approached significance;	"Valproate therapy shows no benefit over short-term phenytoin therapy for prevention of early seizures and neither treatment prevents late seizures. There was a trend toward a higher mortality rate among valproate-treated patients."	Data suggest comparable efficacy to prevent early seizures, though no placebo group. Valproate trended towards greater mortality (13.4% vs. 7.2%, $p=0.07$).

								2.0 (0.9-4.1) (p=0.07).		
Temkin 1990 (score = 6.5)	Seizure Prophylaxis Phenytoin vs Placebo	RCT	Sponsored by a grant from the National Institutes of Health (RO1-NS-19643) and the Warner-Lambert/Parke-Davis. No mention of COI.	N = 404 with a severe head injury admitted to a level I trauma center with a diagnosis of cortical contusion, subdural, epidural, or intracerebral hematoma, depressed skull fracture, penetrating head wound, seizure within 24 hours of injury, or a GCS ≤ 10;	Mean (±SD) age 34 (±18) for phenytoin group and 34 (±17) for placebo group.	Phenytoin (20 mg per kg of body weight intravenously initially, but switched to oral administration ranging from 200mg to 1200mg) group (N=208) Vs. Placebo group (N=196); Both groups received allocated treatment within 24 hours of injury.	Follow-up 1, 3, 6, 9, 12 and 24 months.	Phenytoin group had a significantly lower cumulative seizure rate (± SE) at the end of the first week compared to placebo group: 3.6%±1.3% vs. 14.2%±2.6%, (p<0.001). No significant differences reported between groups for late seizures occurring between day 8 and 2 years.	"[P]henytoin reduces the incidence of seizures in the first week after injury, but not thereafter."	Data suggest phenytoin may prevent seizures only in first week after severe head injury.
McQueen 1983 (score=6.5)	Seizure Prophylaxis	RCT	No mention of COI. Sponsored by	N = 164 with a head injury	Total patients in each age range: 5-15 years – 43, 16-29 years – 67, 30-49 years – 34, 50-65 years – 20; 130 males, 34 females	Phenytoin group: received either 50 or 100 mg phenytoin on day of admission to trial, then children (5-15 years) recievd 5 mg/kg body weight, adults received 300 mg/day either in one or two doses (n=84) vs Placebo: matched with same amount as phenytoin subjects (n=80)	2 weeks, 6, 12, 15, 18, and 24 months	Only half of patients entering the trial continued medication usage for one full year. 7 patients died during this study. 11 developed post-traumatic epilepsy within one year (6 taking phenytoin, 5	"These results imply that all randomised clinical trials of prophylaxis of late onset post-traumatic epilepsy conducted to date are too small (by a factor of at least six).	Data suggest low incidence of late post-traumatic seizures following TBI but study may be underpowered to observe effects.

								taking placebo). Four patients developed seizures between 1-2 year post-injury.		
Haltiner, 1999 (score=5.5)	Seizure Prophylaxis	RCT	No COI. Sponsored by National Institutes of Health (NIH) Grant, an NIH training grant, a Clinician Investigator Development Award, and NIH Program project in head injury grant. Parke-Davis Coorporation provided partial funding to complete original study.	N=404 patients with early or late posttraumatic seizures	Age and Gender not provided.	Phenytoin Group: (n=208) received 20 mg/kg of body weight of phenytoin vs Placebo Group: (n=196) received same dose as phenytoin group with placebo	2 weeks, 2 years	Overall incidence for delayed early seizures lower in phenytoin group compared to placebo (3.6±1.3% vs. 14.2±2.6%, p<0.001). Incidence of late seizures (seizures occurring after 7 days post-treatment) did not differ between phenytoin and placebo groups (27.5±4%, 21.1±3.7%, p>0.2)	"The results of this study indicate that the incidence of early posttraumatic seizure can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in drug-related side effects. Reduction in posttraumatic seizure during the 1st week, however, was not associated with a reduction in the mortality rate."	Short follow-up time. Data suggest phenytoin prophylaxis reduced early seizures but did not decrease mortality.
Dikmen 2000 (score = 5.0)	Phenytoin vs Valproic Acid	RCT	No mention of sponsorship or COI.	N = 279 adult subjects who were admitted to a hospital	Mean age was 36.5 years.	1 month of Valproate (40 to 100 mg/mL) (VPA) followed by 5 months of placebo	Follow-up for 12 months	Trend for higher mortality rate in VPA groups vs. phenytoin	"Valproate (VPA) appears to have a benign neuropsycholo	No true placebo arm. Intention-to-treat was secondary analysis. Analyses

				within 24 hours of traumatic brain injury.		(N= 94) Vs. 6 months of VPA (N=91) Vs. 1 week of phenytoin (10 to 20 mg/mL) - followed by 6 months of placebo. (N=94)		group (p=0.07). No significant differences for drug effect for motor functions, attention/concentration and memory (p>0.05). The COWAT verbal skills test did show a significantly higher odds ratio (95% CI) for the drug effect; 4 (1, 8) (p=0.02). There were no other significant adverse or neuropsychological effects of VPA compared to phenytoin.	gical side effects profile, making it a cognitively safe antiepileptic drug to use for controlling established seizures or stabilizing mood."	suggest no difference between treatments.
Manaka, 1992 (score=4.5)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N = 191 Patients with fresh head injuries.	Mean age: 38 ± 19.9 years for group I, 29.3 ± 19.6 years for group II; Gender not specified.	Group I: Severe head injury (N = 126) (Group IA: anticonvulsant administered (N = 50) vs group IB: control (N = 76)) vs group II: mild head injury (N = 65)	Follow-up for a duration of 5 years. Follow-up data reported at first month after injury and annually.	12.7% of group I, broken into 16% for group IA and 10.5% for group IB, and 0% of group II developed epileptic attacks. Statistically significant risk factors for epilepsy: disturbance of consciousness	"1. Phenobarbital does not have a prophylactic effect on posttraumatic epilepsy. 2. Severity of cerebral injury is proportional to incidence for posttraumatic epilepsy. 3. Consciousness,	Data suggest (in) efficacy of phenobarbital for seizure prophylaxis.

								(Relative risk or RR = 5.36, p < 0.01), neurological sign (RR = 4.79, p < 0.01), abnormal CT findings (p < 0.05), intracerebral hematoma (RR = 3.74, p < 0.05)	abnormal CT finding, neurological sequelae and/or intracerebral hematoma were potential factors for attack and, above all, multiplicity of risks was an important risk for posttraumatic epilepsy."	
Dikmen 1991 (score=4.0)	Seizure Prophylaxis	RCT	Sponsored by the National Institutes of Health, Bethesda, MD, the National Center for Health Services Research Office of the Assistant Secretary of Health, Rockville, MD, and Warner-Lamber/Parke-Davis, Morris Plains, NJ. Warner-Lamber/Parke-Davis provided the drug treatments used.	N = 244 with moderate to severe head injuries	Mean age: 30.9 for phenytoin group, 32.9 for placebo group; 152 males, 92 females.	Phenytoin group: received phenytoin for one year, 15% received <3 µmol/L, 36% received 3-6 µmol/L, and 48% received >6 µmol/L (n=208) vs Placebo group: received placebo for one year (n=196)	1, 12, and 24 months	Phenytoin group performed more poorly placebo group across most neuropsychological Measures (Overall rank-sum-type test, p<0.05) at 1 month.	"Our findings do not negate phenytoin's proven efficacy in controlling established seizures nor do they indicate that its cognitive effects are worse than other anticonvulsant drugs."	Data suggest cessation of phenytoin resulted in improved cognition in all groups and prevented posttraumatic seizures in severe TBI patients but moderate and mild TBI patients had unclear benefit from phenytoin.

Murri, 1980 (score=4.0)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N=90 patients with seizures from serious head injury	Mean age: 63 years; 64 males, 26 females	Group 1: (n=) received 0.5-1.5 mg/kg/day of phenobarbitalvs Group 2: (n=) received 1.6-2.5 mg/kg/day of phenobarbital	Baseline, and every 6 months for 2 years	Lower incidence of PTE in participants showed efficient prophylactic effect. Lower dosage of PB showed a favorable effect with only 2 patients having seizures. Twenty-three percent of 88 patients that did not develop seizures showed anomalies even 2 years after trauma.	"In conclusion, our data support the validity for of PB prophylaxis for PTE. However our follow-up was limited to 2 years and it is known that in this period seizures may occur in 70-80~ of patients [3, 10, 18]. Thus, the possibility observed of a delayed onset of epilepsy in these patients, and observed in one subject, cannot be excluded."	Data difficult to interpret due to the variable doses of phenobarbital administered. However, there appears to be some benefit from phenytoin prophylaxis 2 years post injury.
Bertch, 1985 (score=3.5)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N = 267 head injury patients.	Mean Age: Not specified, age range from 18 months to 81 years; Gender not specified.	Phenytion (N = 151) vs placebo (N = 116)	Follow up at baseline, 1 week, 1,3,6,9, 12,15,18,21, and 24 months.	Difference in serum calcium levels statistically significant at visit 8 (p = 0.04) and visit 9 (p = 0.02) for control vs phenytoin patients. No significant difference for phosphorus or folate levels.	"Further studies considering the effects of longterm phenytoin therapy on laboratory indices are suggested."	Data suggest phenytoin infusion for seizure prophylaxis does not negatively impact laboratory values.

Young 1983 (score = 3.0)	Phenytoin vs Phenobarbital	RCT	No mention of sponsorship or COI.	N=214 patients with traumatic brain injury.	Mean age; 25.1 years.	Phenytoin Group (10 to 20 µg/ml) (N=98) Vs. Phenobarbital Group-If patients did not react well with phenytoin they were switched to this group (N=21) Vs. Placebo Group (N=95)	Follow-up for 18 months.	No significant difference between phenytoin and phenobarbital groups for patients having late seizures (p=0.48). Drug group as a whole did not show lower risk for late seizures vs. placebo (p=0.75). Median time to death was 16 days in drug group and 14.5 days in placebo group, (p=0.30).	"It cannot be concluded that higher phenytoin plasma concentrations and higher compliance rates than obtained in this study would not have significantly decreased the occurrence of late post-traumatic epilepsy."	Sparse methods. Data suggest phenytoin not effective compared with placebo to prevent seizures.

Evidence for the Use of Antidepressants

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Rappoport 2010 (score = 7.0)	Citalopram vs Placebo	Double Blind RCT	Sponsored by Ontario Neurotrauma Foundation and Ontario Mental Health Foundation.	N=21 subjects were randomized after completing an open label citalopram treatment for major depression from TBI;	Mean Age 46.67 ± 19.9	Group 1 (N=10) patients who were given the active drug citalopram Vs. Group 2 (N=11) patients who were given placebo treatment	Follow-up every month for 40 weeks.	Group 1 vs 2, relapse rates during 40 week intervention: 5 (50%) vs 6 (54.5%) no significant difference between groups. No significant difference between groups for time of relapse.	"This study highlights the relatively high risk of relapse within depression after TBI and raises questions about the effectiveness and potential limitations of citalopram continuing treatment in preventing relapse of major depression."	Similar relapse rates between citalopram vs. placebo, suggesting lack of efficacy.
Ashman 2009 (score = 6.5)	Sertraline vs Placebo	Double Blind RCT	Sponsored by the National Institute of Disability and Rehabilitation Research, United States Department of Education, and Pfizer Pharmaceutical Company. No COI.	N = 41 6 month post injury TBI patients also diagnosed with depression;	Mean Age 49.1 ± 10.9	Group 1 (N =22) patients who were given Sertraline. Dosage determined by physicians vs. Group 2 (N =19) patients given a placebo.	Follow-up at wk 2, 4, 6, 8, and 10.	Group 1 vs 2, Depression prevalence after 10 wk intervention: 18% vs 37%. Group 1 vs 2, percent of treatment respondents (HAM-D score decrease by 50%): 59% vs 32% (p=0.15). Group 1 and 2, pre vs post intervention, Depression: 26.4 ± 7.5 vs 14.9 ± 9.6 (p<0.001). Anxiety: 21.9 ± 14.9 vs 11.9 ± 11.6 (p<0.001). Quality of Life (QOL): 2.8 ± 0.9 vs 5.7 ± 6.7 (p<0.01).	"Both groups showed improvements in mood, anxiety, and QOL, with 59% of the experimental group and 32% of the placebo group responding to the treatment, defined as a reduction of a person's HAM-D score by 50%.	High drop-out rate. Both groups showed improvements in mood and QOL. Trend toward better HAM-D response than placebo (50% reductions 59% vs. 32%), but not

								Group 1 vs 2, HAM-D scores (HamGScale): 8.16 ± 0.48 vs 9.62 ± 0.52 (p=0.04).		significant (p=0.08).
Novack 2009 (score = 5.0)	Sertraline vs Placebo	Double Blinded RCT	Sponsored by the national institute of Disability and Rehabilitation Research Grant. No COI.	N=99 patients who had TBI and GCS score below 12;	Mean Age: Group 1 35.3 ± 16.7; Group 2 34.5 ± 15.6	Group 1 (N=49) Treatment group Sertraline 50mg QD Vs. Group 2 (N=50) Placebo group	Follow-up on phone weekly for 3 months, monthly after for another 9 months. In hospital visits at 3, 6, and 12 months.	Group 1 vs 2, diagnosis of depression during 90 day intervention: o new cases vs 5 (10%) new cases X2=5.16, (p=0.023). No significant difference in depression diagnosis throughout the year between groups. Group 1 vs 2, Hamilton Depression Rating Scale (HDRS) >6 prevalence: 6.7% vs 25% X2=4.1, (p=0.04). Group 1 vs 2, Neurobehavioral Functioning Inventory, 3 months: 89.0 ± 11.4 vs 96.0 ± 14.0 (p<0.05).	"Sertraline is effective in diminishing depressive symptoms even among those not clinically depressed while the medication is being taken. However, the results do not support the idea that administration early in recovery diminishes the expression of depressive symptoms after the drug is stopped. There is no basis from this study to assume that sertraline administered early in recovery after TBI, when neurotransmitter functioning is often altered, has ongoing effects on the serotonin system after sertraline is discontinued."	Data suggest lack of efficacy between groups.

Banos 2010 (score = 4.5)	Sertraline vs Placebo	Double Blind RCT	Sponsored by the national Institute on Disability and Rehabilitation Research Grant.	N=99 patients with moderate to severe TBI; Mean Age: Group 1 35.3 ± 16.7; Group 2 34.5 ± 15.6		Group 1 (N=49) Sertraline 50 mg QD. Vs. Group 2 (N=50) given placebo.	Follow-up at 3, 6, and 12 months.	Group 1 vs Group 2, Wisconsin Card Sorting Test-64 results at month 3: 78.25 ± 18.7 vs 92.7 ± 15.4 ($p<0.006$). No other significant differences between sertraline and placebo group throughout study.	"Sertraline does not appear to prevent development of cognitive and behavioral problems following TBI, although this does not negate evidence for the treatment (as opposed to prophylactic) role of sertraline to address emotional and neurobehavioral problems in individuals with TBI."	High drop outs in sertraline group. Data suggest early administration of sertraline does not prevent cognitive and behavioral problems for moderate to severe TBI in the first year post-injury.
Wroblewski 1996 (score = 4.0)	Desipramine vs Placebo	RCT	No mention of sponsorship or COI.	N=10 patients with severe traumatic brain injury who were suspected of having depression; Mean Age: Group 1 30; Group 2 33		Group 1 (N=6) Desipramine Vs. Group 2 (N=4) patients treated for placebo for 1 month, if no improvement, they crossed over to desipramine.	Follow-up at 1 month and 2 months.	6 patients (60%) showed a complete resolution from depression after 1 month of desipramine. Group 1 vs 2, improvement over time: Group 1 recovered faster ($p=0.001$). Side effects: 1 patient had a seizure, 1 had mania, and 2 had minor seizures that were resolved by lowering the dosage.	"Results … demonstrate the clinically significant effectiveness of desipramine in treating long-standing depression in a series of patients with severe traumatic brain injury, as rated with DSM-III-R criteria; show statistically significant improvement on affect/mood scale data, favoring the treated versus	Very small samples. Data suggest desipramine may be of modest benefit for longstanding depression associated with TBI.

									untreated(Placebo lead-in) group."	
Lee 2005 (score = 4.0)	Sertraline vs Methylphenidate vs Placebo	Double Blind RCT	No mention of sponsorship or COI.	N=30 patients with mild to moderate TBI; Mean Age: Group 1 35.3 ± 8.0; Group 2 33.6 ± 12.3; Group 3 35.5 ± 7.2		Group 1 (N=10) patients that were given 5 mg/day Methylphenidate (MPD), increase to 20 mg/day after 1 week; Group 2 (N=10) Patients that were given Sertraline (SER) (25mg/day increased to 100 mg/day); Group 3 (N=10) patients that were given placebo treatment	Follow-up at baseline and 4 weeks.	Significant improvement in all groups for HAM-D, Beck Depression Inventory (BDI) and Quality of Life scale, ($p<0.05$). Group 1 vs 2 vs 3, Rivermead Postconcussion Symptoms Questionnaire (RPQ) baseline/4 weeks: 38.0 ± 7.8/24.8 ± 10.0 ($p<0.001$) vs 32.0 ± 10.2/30.3 ± 9.4 (NS) vs 39.4 ± 8.8/30.4 ± 10.7 ($p<0.05$). Group 1 vs Group 3, post hoc analysis group x time of Hamilton Rating scale for Depression (HAM-D): ($p=0.005$). Group 2 vs Group 3, post hoc analyses group x time HAM-D: ($p=0.05$). Group 1 vs Group 2, adverse effects: 6 vs 13 ($p<0.01$). Cognitive function tests revealed Group 1 and 3 were superior to group 2. ($p<0.045$). Group 1 vs 2 vs 3, Recognition	"At the present stage, it is concluded that in patients with mild to moderate TBI, both methylphenidate and sertraline had significant effects on the depressive symptoms compared with the placebo, while methylphenidate seemed to have more beneficial effects on cognitive function and daytime alertness than sertraline, at least in the 4 week treatment of patients with TBI."	Mild to mod. TBI. Dropouts unclear. Data suggest MP outperformed sertraline for attention and cognition.

								Reaction Time (RRT) baseline/4 wks.: 399.2 ± 51.2/340.2 ± 34.5 vs 405.8 ± 56.7/389.5 ± 61.3 vs 443.8 ± 60.7/377.3 ± 37.3 ($p<0.021$) group x time effect.		
Meythaler 2000 (score = 2.0)	Sertraline vs Placebo	Prospective Cross-Over RCT	Sponsored by grants from the UAB Injury Control and Research Center and Pfizer.	N=9 subjects with GCS score less than 7 after TBI injury (motor vehicle accident induced TBI); Mean Age N/A (14-65)		Group 1 (N=6) patients who were given the active drug Sertraline (50 mg/day increased to 100 mg/day). Vs. Group 2 (N=3) patients who were given placebo treatment.	Follow-up after 2 weeks.	Group 1 vs 2, Orientation Log score, baseline/2 wks.: 8.6/12.2 vs 7.7/21.7 placebo group recovered faster ($p<0.0042$). Agitated behavior Scale did not significantly improve for either group. No significant difference in improvement for Galveston orientation and amnesia test [252].	"This pilot study fails to establish whether the early use of sertraline may improve alertness, decrease agitation or improve cognitive recall of material. This may be due to the small size of the study group, the brief duration of treatment or by a skewed placebo group. Larger studies will be required to prove any efficacy. There were no complications with its use and sertraline did not demonstrate a detrimental effect on recovery. This indicates that sertraline may be safe to use in the treatment of psychiatric or behavioral	Small sample, pilot study. Most subjects could not be followed for cross over so it was analyzed with regard to rate of recovery. Data suggest sertraline did not improve arousal/alertness.

									complications attributable to TBI."	
Saran 1985 (score = 2.0)	Amytryptyline vs Phenelzine	Prospective RCT	No mention of sponsorship or COI.	N=22 patients who either had secondary or primary depression; Mean Age: Group 1 42 (36-58); Group 2 44.2 (26-58)		Group 1 (N=10) patients who had secondary depression due to a minor traumatic brain injury Vs. Group 2 (N=12) control group whom had depression primarily and did not acquire a closed head injury	Follow-up Patients were evaluated every week for 8 weeks. First four weeks amitriptyline was given, if no improvement then patients were given phenelzine.	Group 1 vs 2, Dexamethasone suppression Test failure rate: 10% vs 91% (p<0.001). Group 1 vs Group 2, Hamilton Depression rating Scale (HAM-D) during amitriptyline: Group 2 improved, none of Group 1 did not (p<0.001). Group 1 and 2, Phenelzine treatment, wk 1-4 HAM-D score change: Not significant.	"In summary, our results suggest that DST nonsuppression may be useful biologic marker in disguising primary depression with melancholia from depression with melancholia after closed head injury, and amitriptyline and phenelzine have limited use in patients with depression after minor closed head injury."	No placebo comparison. Small sample sizes. Data suggest both amitriptyline and phenytoin have limited benefit in depression with melancholia post TBI and not different between them.

Evidence for the Use of Benzodiazepines

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Ghori 2007 (score = 4.5)	Midazolam vs Propofol	RCT	Sponsored by the Dept. of Anaesthesia and Intensive Care Medicine, Cork University Hospital. COI, George D Shorten	N = 28 TBI patients with GCS score < 9;	Age range 18-65 years.	Midazolam 0.1–0.3mg/kg/h (N = 15); Propofol 1.5–5mg/Kg/h (N = 13); Both groups received morphine sulfate (0.1–0.2mg/kg/h)	Follow-up at baseline, day 1-5, and month 3.	Midazolam vs propofol Serum s100β concentrations (Mean, [SD]); Day 1, (0.99 ± 0.81]) vs (0.41 ± 0.4)µg/L; Day 2, (0.80 ± 0.81) vs (0.41 ± 0.24) µg/L; Day 3, (0.52 ± 0.55) vs	"Plasma concentrations of neurological injury markers were similar in patients who received midazolam and propofol. Patients with poor neurological outcomes had	Methodological details sparse. Small sample size. Many medications given.

			employed by Dept. of Anaesthesia and Intensive Care Medicine at Cork University.					(0.24 ± 0.25) µg/L; and Day 4, (0.54 ± 0.43) vs (0.24 ± 0.35) µg/L; ($p < 0.05$)	consistently higher serum s100β."	
Tanguy 2012 (score = 3.5)	Midazolam vs Propofol	RCT	Sponsored by Programme Hospitalier de Recherche Clinique (PHRC) of Rennes. No COI.	N = 36 with severe TBI.	Mean age 35 – 18 years.	Propofol (N = 15) vs. Midazolam (N = 14)	Follow-up for 72 hours and 12 months.	No difference between propofol and midazolam in the cerebral L: P ratio (time effect $p = 0.201$, treatment effect $p = 0.401$, time x treatment interaction $p = 0.101$).	"[The] results indicate that there is no difference between the effects of propofol and midazolam sedation on the cerebral metabolic profile during the acute phase of severe TBI. Accordingly, the use of propofol as a sedative agent in TBI and its neuroprotective effects warrant further investigation."	Small sample size. Methodological details sparse. Relatively invasive monitoring using cerebral microdialysis catheter. High complication rate.
Sanchez-Izquierdo-Riera 1998 (score = 3.0)	Midazolam vs Propofol vs Combination	RCT	No mention of sponsorship or COI	N = 100 with TBI requiring mechanical ventilation for at least 48 hours;	mean age 35.4 ± 16.6 years.	Group A midazolam 0.1 mg/kg/ hr with max. dose of 0.35 mg/kg/hr. (N = 34); Group B propofol 1.5 mg/kg/hr with max. dose 6 mg/kg/hr. (N	Follow-up at baseline, hour 3, 6, 12, and 24 after sedation stoppage.	Wake-up time significantly increased in Pf groups. Group A (660 ± 400 min) vs Group B (110 ± 50 min) vs. Group C (190 ± 200 min), ($p < 0.01$).	"…Mz and Pf, used alone or in combination, are safe and effective in the sedation of critically ill trauma patients.	Methodological details sparse. Large number of therapeutic failures.

						= 33); Group C combination of midazolam and propofol in doses similar to above groups. (N = 33)				

Evidence for the Use of Corticosteroids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Roberts 2004 (score = 7.5)	Methyprednisolone vs Placebo	RCT	Sponsored by the UK Medical Research Council, Pharmacia and Upjohn. No COI.	N= 10,008 Adults with head injury a Glasgow coma score (GCS) of 14 or less within 8 h of injury	Mean age= 37 years (SD 17)	48 h infusion of corticosteroids (methylprednisolone) (N=5007) Vs. Placebo (N=5001)	Follow up period was 6 months. Primary outcomes were death within 2 weeks of injury and death or disability at 6 months.	Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21·1%] vs 893 [17·9%] deaths; relative risk 1·18 [95% CI 1·09–1·27]; p=0·0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0·22) or time since injury (p=0·05).	"[O]ur results show there is no reduction in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear."	Data suggest IV corticosteroids did not reduce mortality 2 wks.after TBI.
Braakman 1983 (score = 6.0)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N = 161 patients after a non-missile-related head injury.	Mean age not reported.	High-dose dexamethasone phosphate group (N =81) Vs. Placebo group (N =80) The regimen for administration of dexamethasone* in adults was as follows: initial dose: 100 mg	Follow-up for 6 months.	A sequential test was used for analyses, using survival at 1 month as basic effectiveness criterion. No difference in 1-month survival rate or in distribution of outcome after 6 months, either within group as whole, or in subgroups with varying severity of brain damage on admission.	"[D]examethasone in high doses has no statistically significant effect on morbidity or mortality in head-injured patients who are comatose on admission."	Patients all comatose. Data suggest lack of efficacy.

						intravenously; Days 1 to 4:100 mg/day IV; Days 5 to 7:16 mg/day IV or IM; and Days 8, 9, and 10:12 mg, 8 mg, and 4 mg/day, respectively, IV or IM. Children 10-14 years were given half adult dose, and those <10 years received 25% of adult dose.				
Cooper 1979 (score = 5.5)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N= 76 patients with severe head injuries.	Mean Age= 25.6 years.	Low-dose dexamethasone (16 mg/day) (N=25) Vs. High-dose dexamethasone (96mg/day) (N=24) Vs. Placebo (N=27)	Follow up period was 6 months following injury.	Of the 76 patients available for analysis, a good outcome was achieved in 37% of placebo-treated patients, 44% of low-dose-treated patients, and 29% of high-dose-treated patients. These differences are not statistically significant. Similarly dexamethasone administration had no statistically significant effect on	"[N]o previous study has shown a significant improvement in outcome following severe head injury as a result of treatment with corticosteroids. A decrease in mortality rate achieved by increasing the number of vegetative survivors is not a desirable result. Our results show no difference	Sparse methods. Data suggest neither low nor high dose dexamethasone affected morbidity of mortality in severe TBI patients.

								intracranial pressure patterns or serial neurological examinations during hospitalization. Gastrointestinal bleeding occurred in only one patient. Good outcome was associated with age under 10 years, lighter depth of coma on admission, and the preservation of brain-stem reflexes upon admission.	in outcome when either higher low-dose corticosteroid treatment is compared with placebo. This series shows that most patients do not survive because of "diffuse injuries" and other causes of death not amenable to steroid treatment".	
Dearden 1986 (score = 4.5)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N=130 patients with severe head injuries admitted to intensive care during a 3-year period.	Age range (yrs.): for steroid group 7-79 and for placebo group 2-74.	Dexamethasone (50mg, intravenously) (N=68) Vs. Placebo group (N=62). Adults in the steroid group received dexamethasone as a bolus on admission to the neurosurgical unit, then 100 mg on Days 1, 2, and 3, 50 mg on Day 4, and 25 mg on Day 5 on	Follow-up for 6 months.	Outcome appeared worse in the steroid-treated group, with 33 (49%) patients dead or vegetative compared to 22 (35.5%) in the placebo group, although this difference did not reach statistical significance.	"[I]n the light of these two studies, the administration of glucocorticoids in the treatment of severe head injury is no longer indicated and, based on the observations of this study, may even be contraindicated in the presence of an elevated ICP."	Sparse methods. High dropouts due to mortality. Data suggest lack of efficacy at 6mo.

						continuous intravenous infusion. Children received proportionate intravenous dosages calculated on a weight basis.				
Saul 1981 (score = 4.0)	Methylprednisolone vs Placebo	RCT	No mention of industry sponsorship or COI.	N= 100 patients with severe craniocerebral trauma, hospital admittance within 6 hours of injury, GCS ≤7;	Mean age 32 for steroid group and 30 for nonsteroid group.	Steroid group receiving 250mg methylprednisolone intravenously, followed by 125mg every 6 hours (N=50) Vs. Nonsteroid control group (N=50)	Follow up at 6 months.	No statistically significant differences reported between groups for clinical outcome.	"The variable response to steroids observed in different patient groups may partially account for the differences in steroid efficacy reported previously. In order to establish the efficacy of steroids in head injuries, one must conduct studies in which the patient's ongoing response to the entire regimen can be precisely assessed. Based on the data, our regimen for steroid therapy in patients with severe head injuries is as follows: we begin steroid treatment in all such patients (either dexamethasone 1 mg/kg/day, or	Data suggest lack of efficacy at 6mo.

									methylprednisolone 5 mg/kg/day); on the 3rd day, we evaluate the patient's overall response as determined by our "neuro index;" if the patient has improved, we continue steroids for 7 to 10 days; if there has been no improvement, we discontinue the steroids abruptly. Further studies from multiple centers and with larger numbers of patients are warranted to confirm or disprove these concepts."	

Evidence for the Use of Excitatory Amino Acid Inhibitors

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*

Lepeintre 2004 (score = 6.5)	Gacyclidine vs Placebo	RCT, multicenter, prospective, double-blind	Sponsored by BEAUFOUR-IPSEN PHARMA. No mention of COI.	N =48 with acute TBI (GCS 4 – 8).	Age range 18 – 64 years.	Four parallel groups: placebo (N = 12), gacyclidine 0.01mg/kg (N = 11), 0.02mg/kg (N = 13), or 0.04mg/kg (N = 12). The first dose was given within 2 hours following the injury, and the second dose 4 hours after the first.	Follow-up for day 1, 3, 7, 14, 21, 30, 90, 180 and 365.	20 patients died before 1 year, which were no related to the treatment. During the study, 44 patients (91.7%) experienced at least one adverse effect. No significant differences between groups in the GOS scale at any follow-up.	"[B]ased on the available evidence, noncompetitive NMDA receptor antagonits i.e. gacyclidine, appear to be an essential component in their elaboration. Data obtained in this clinical trial appear sufficient to warrant a European multicenter study using the same evaluation criteria."	Pilot study. Small sample with 4 groups. Data suggest gacyclidine may be beneficial esp. at highest dose (0.04mg/kg) for TBI vs. placebo. However, requires a full trial.

Yurkewicz 2005 (score = 5.5)	Traxoprodil vs Placebo	RCT, multi-center, double-blind	No mention of sponsorship or COI	N = 404 with severe TBI (GCS 4–8). Patients were injured within 8 hours of treatment.	Age range 16–66 years.	Traxoprodil (CP-101,606) group: 72 hours intravenous infusion (N = 198) vs. Placebo group (N = 206)	Follow-up for 1, 3, and 6 months.	39 (19.7%) patients died in traxoprodil group vs. 55 (26.7%) in placebo group. Primary outcome: traxoprodil group (41.2%) had more favorable outcomes on dGOS vs. placebo (35.7%) at 6 months (p = 0.21, OR 95% CI: [0.85, 2.06]).	"Traxoprodil was well tolerated. Although these results are intriguing, no definitive claim of efficacy can be made for traxoprodil for the treatment of severe TBI."	Data suggest lack of efficacy. Weak trend favored traxoprodil for Glascow score (p=0.21).

Morris 1999 (score=5.0)	Selfotel vs Placebo	RCT prospective	No mention of industry sponsorship or COI	693 patients with severe head injury in two multicenter double-blind studies done simultaneously (one in Europe, Canada, Australia and Argentina and one in U.S.) 99 medical centers participated in study	Mean age = 32 for Selfotel group and 31 for Placebo group with 77.5% male and 22.5% female.	Selfotel IV 5mg/kg qd for 4 days (N=339) vs. Placebo: 5 mg/kg qd for 4 days (N=354)	Follow-up at 1, 3 and 6 months.	A favorable outcome was defined as "good" or "moderate" score on Glasgow outcome scale (GOS). At 6 mos., favorable outcomes in 185/338 (55%) in Selfotel group vs. 204/352 (58%) in placebo group (p>0.25). 74 vs. 68 deaths in Selfotel vs. placebo (p>0.25). No difference in percentage of time in which patients' ICPs were >20 mm Hg between placebo (23%) and Selfotel (20.6%)	"…no statistically significant difference in mortality rates in all cases between the two treatment groups in the head injury trials."	Trial stopped prematurely due to safety concerns over apparent excessive stroke and mortality incidents associated with study drug although both groups showed similar adverse outcomes in the final analyses.
Bourgoin 2005 (score = 4.5)	Sufentanil vs Ketamine	RCT, prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age 29 ± 12 years in the Sufentanil group and	Sufentanil group (N = 15) vs. Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was 17.7 ± 6.5 mm Hg in the sufentanil group vs. 16.2 ± 6.4 mm Hg in	"The present study shows that the increase in sufentanil or ketamine plasma	Small sample. Data suggest doubling sufentanil or ketamine

					29 ± 11 years in the Ketamine group.			the ketamine group. VMCAM value was significantly higher in the sufentanil group (77 ± 21 cm/sec) vs. the ketamine group (60 ± 33 cm/sec, p = 0.03). At 6, 7, and 13 min, there was statistical difference in the BIS value between groups (p < 0.05).	concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients."	showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.
Merchant 1999 (score = 3.0)	CP-101,606 vs Placebo	RCT, double-blind	No mention of sponsorship or COI.	N = 53 with moderate TBI (GCS 13–14) or mild TBI (GCS 9 – 14) (n = 45) or hemorrhagic stroke (n = 8).	Age range 15–78 years.	Patients received CP-101,606 or placebo within 12 hours of injury. First series of patients had drug/placebo dosed IV 0.75 mg/kg/hr. for 2 hours and then stopped (n = 25). For next two series of patients, after 2-hour infusion,	Follow-up for 0, 1, 2, 12, 24, 48, and 96 hours.	There were improvements in the GCS in the patients receiving treatment; however, there were no differences in the speed of the improvement.	"At all three doses tested in this double-blind placebo-controlled study, CP- 101,606 was well-tolerated and there were no clinically significant cardiovascular or hematological abnormalities. … The results of this study suggest that unlike other NMDA receptor antagonists, CP-101,606 had no	Data suggest lack of efficacy of CP-101,606 in mild-moderate TBI patients.

						subjects had their treatment continued at 0.37 mg/kg/hr. for 22 hours (n = 4) or 70 hours (n = 24) for total dosing time of 24 and 72 hours, respectively.			psychotropic effects and was well-tolerated in patients who had sustained either a mild or moderate TBI or an atraumatic hemorrhagic stroke."	

Evidence for the Use of Amantadine

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Giacino 2012 (score = 9.0)	Amantadine vs Placebo	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 184 with non-penetrating traumatic brain injury.	Mean age amantadine 35.5±15.3 years, placebo 37.2±15.4 years.	Amantadine 100 mg 2x/day, then 150 mg 2x/day at 14 days, and 200 mg 2x/day at week 4 (N = 87) vs. Placebo 100 mg 2x/day, then 150 mg 2x/day at 14 days, and 200 mg 2x/day at week 4 (N = 97).	Follow-up at weeks 4 and 6.	Significant recovery time in amantadine group than placebo group at week 4. (p=0.007) at 0.24 points. Overall no significant differences between baseline and week 6 in DRS score. Amantadine was lower in week 2 than placebo at 0.30 points and (p=0.02).	"Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness."	Data suggest amantadine successful for severe TBI at 4-16 weeks out.
Whyte 2013 (score = 9.0)	Amantadine vs Placebo	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No COI.	N = 184 with nonpenetrating TBI enrolled from acute inpatient rehabilitation programs between 4 and 16 weeks post injury.	Age range 16 – 65 years.	Amantadine hydrochloride (200 to 400mg) vs. Placebo. Treatments were administered daily for 4 weeks.	Follow-up for 2 weeks.	During the 6-week trial, 468 adverse events were reported with an average rate of about 0.40 events per week per patient. The median number of medical complications experienced per patient	“Patients with DOCs have a high rate of medical complications early after injury. Many of these complications require brain injury expertise for optimal management. Active medical management appears to contribute to the reduction in new complications. An optimal system of	Large sample. Trial of amantadine but report of all hospital complications. Second report of Giacino 2012.

								was 2 (mean, 2.85), but the rate of complications for individual patients ranged from 0 to 9. 32 (17.4%) patients did not present new medical events, and 152 (82.6%) experienced at least 1 medical complication. There were 135 (29%) mild medical complications, 270 (58%) moderate, and 61 (13%) severe.	care for DOC patients must provide expert medical management in the early weeks after injury."	
Hammond 2014 (score = 7.5)	Amantadine vs Placebo	RCT	Sponsored by US Department of Education, Office of Special Education and Rehabilitative Services, National Institute on Disability and Rehabilitation Research. No COI.	N = 76 with a sustained closed head injury due to trauma at least 6 months prior to enrollment;	Age range 16 – 65 years.	Amantadine hydrochloride 100 mg every morning and noon (N = 38) vs. Placebo (N = 38) for 28 days.	Follow-up for 28 ± 3 days.	Amantadine group improved 80.56% in NPI irritability vs. 44.44% placebo (p = 0.0016). NPI-I mean change in amantadine group was −4.3 vs. −2.6 in placebo (p = 0. 0085). Significant difference	"Amantadine 100 mg every morning and at noon appears an effective and safe means of reducing frequency and severity of irritability and aggression among individuals with TBI and sufficient creatinine clearance.	Data suggest amantadine improved irritability and aggression associated with chronic TBI.

								between groups in mean change in both frequency (p = 0.0156) and severity of irritability (p = 0.0055). Mean change NPI-aggression −4.65 amantadine vs. −2.46 placebo (p = 0.046).		
McMahon 2009 (score = 5.0)	Amantadine vs Placebo	RCT Crossover	Sponsored by the NICHD and NINDS. No mention of COI.	N = 7 with acquired brain injury	Age 5-18	Placebo 4mg/kg/day for 7 days followed by 6 mg/kg/day for 14 days Vs. Amantadine 4 mg/kg/day (or maximum of 300 mg Amantadine) for 7 days followed by 6 mg/kg/day (or maximum of 400 mg of Amantadine) for 14 days.	Follow-up for 8 weeks	No significant results in recovery in arm from coma. Average CNCS scores P=0.24, P=0.28, and P=0.33	"This study suggests that amantadine facilitates recovery of consciousness in pediatric acquired brain injury and provides important information necessary to design future more definitive studies."	Study in children. Pilot. Only 5 completers.
Meythaler 2002 (score = 4.0)	Amantadine vs Placebo	RCT, Double-blind crossover	Sponsored by NIDRR. No mention of COI.	N = 35 with TBI in a transportation accident; age range 16–75 years.		Group 1: amantadine (200 mg) the first 6 weeks after injury (N = 15) vs. Group 2: placebo the	Follow-up for 6 weeks.	At 6 weeks, group 1 had improvement in MMSE scores of 14.3 points from 8.1 ± 10.4 to	“There was a consistent trend toward a more rapid functional improvement regardless of when a patient with DAI-	Crossover. Data suggest no efficacy over natural history.

						first 6 weeks and amantadine the second 6 weeks (N = 20).		22.5 ± 8.4 (p = 0.0185) vs. 2.4 from 22.5 ± 8.4 to 24.8 ± 6.1 points in placebo (p>0.05). Group 1 had improvement in DRS scores of 9.8 points from 15.5 ± SD to 5.7 ± SD 4.2 (p = 0.0022) vs. 0.15 points from 5.7 ± 4.12 to 5.5 ± 4.6 in group 2 (p>0.05). Group 1 had improvement in GOS score of 0.8 points from 3.0 ± 0 to 3.8 ± 0.6 (p = 0.0077) vs. 0.1 points from 3.8 ± 0.6 to 3.9 ± 1.2 in 2nd 6-week period (p>0.05). Group 1 had improvement in FIM-cog scores of 15.1 points from 11.6 ± 8.6 to 26.7 ± 8.7 (p = 0.0033) vs. 11.3 points	associated TBI was started on amantadine in the first 3 months after injury."	

								from 8.4 ± 5.5 to 19.7 ± 12.9 in group 2 (p = 0.0030).		
Schneider 1999 (score = 3.0)	Amantadine vs Placebo	RCT, Crossover	No mention of sponsorship or COI.	N = 10 Age 18-55 with closed head injury		Amantadine 50 mg to 150 mg for 2 weeks followed by 2 week withdrawal followed be 2 week placebo (N = 5) vs. Placebo for 2 weeks followed by 2 week withdrawal followed be 2 week (N= 5) Amantadine 50 mg to 150 mg.	Follow-up for 8 week	No significant results for amantadine P=0.773 verses placebo group P=0.405 for comparable variables.	"[A]lthough patients generally improved, this initial exploratory study found no differences in rate of cognitive improvement between subjects given amantadine versus those given placebo."	Crossover. Small sample (10). Only reports data on 10 after 8 dropouts. Data suggest lack of efficacy.

Evidence for the Use of Cannabinoids

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Maas 2006 (score = 8.5)	Dexanabinol	RCT	Sponsored by Pharmos Corporation. HH, NK, and MM were employed by Pharmos Corporation.	N = 846 with traumatic brain injury. Median age dexanabinol 33 years, placebo 32 years.	Study group age 33 years, Placebo group age 32 years	Dexanabinol group 150mg diluted dissolved into cosolvent mixture of ethanol, Cremophor, and 0.9% sodium chloride single dose within 6	Follow-up at 3 and 6 months.	There were no significant differences between groups.	"The results of this trial show the safety of dexanabinol in the treatment of traumatic brain injury, but do not show efficacy."	Large sample size. Assessed efficacy of one early dose on 6 month outcomes and showed no efficacy.

						hours of surgery (N = 428) vs. Placebo group 150mg of cosolvent mixture single dose within 6 hours of surgery (N = 418).				
Knoller 2002 (score = 7.0)	Dexanabinol	RCT	No mention of sponsorship or COI.	N = 67 with a GCS score of 4-8, phase 1 demonstrated that dexanabinol (HU-211) was safe and well tolerated in healthy volunteers at doses up to 200 mg per subject; phase 2 evaluated the safety of this agent in severe brain injury patients.	Mean age dexanabinol 29±12 years, placebo 31±13 years.	Dexanabinol 150mg, 20 patients; 48mg, 10 patients (study drug). (N = 30) vs. Placebo, 13 with low dose, 24 with high dose (N = 37).	Follow-up for 10 days or until discharge.	Mean percentage time ICP above 25 mm Hg: reduced in dexanabinol group by 67%, 82%, and 97% on first, second ($p<0.02$) and third day ($p<0.005$).	"Dexanabinol was safe and well tolerated in severe head injury. The treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure."	Severe TBI. Modest sample size. Data suggest lower ICP with dexanabinol. Trend to better long term outcomes.
Firsching 2012 (score = 7.0)	Endocannabinoids	RCT	Sponsored by Key Neurotek Pharmaceuticals AG, Magdeburg, Germany. R.F. was the European coordinator, .F. and J.P. were	N = 97 with severe TBI, addressing acute neurodegeneration.	Age groups: 18–58 for high dose / 19–63 low dose / 18–64 and placebo.	High dose high dose: IV infusion of KN38-7271, 80 µm as accelerated infusion (1 hour) þ 920 µm as constant-rate infusion over 23 hours (N =	Follow-up for 1, 3 and 6 months.	Survival rates showed significant difference between either or both KN38-7271-treated groups and placebo (p = 0.026). Highest and	“KN38-7271 appeared beneficial in the acute early phase of the comatose patient after a head injury.”	Phase 2 trial. Data suggest lower ICPs and short term survival but no long term survival advantage and placebo group had more injury, procedure complications raising question of confounding.

			intensively involved in the study design.			31) vs. Low dose IV infusion of KN38-7271, 40 µm as accelerated infusion (1 hour) þ 460 µm as constant-rate infusion over 23 hours (N = 33) vs. Placebo without KN38-7271, given as 1-hr accelerated infusion followed by constant infusion over 23 hours (N = 33).		lowest CPP values recorded were highest in high-dose group and lowest in placebo with, (p = 0.0582, actual highest CPP, days 0 to 7) and 0.0456 (actual lowest CPP, days 2 to 7, not shown).		

Evidence for the Cerebrolysin

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Muresanu 2016 Score = 9.5	Cerebrolysin Vs Placebo	RCT Double blind parallel group study	Sponsored by EVER Neuro Pharma GmbH, Austria. COI, Dr Muresanu is a coordinating investigator of the Cerebrolysin and Recovery After Stroke (CARS) trial and a member of the Cerebrolysin	N=208 ischemic supratentorial strokes with a volume of >4 cm3	Mean age = 64.0, 63.9% male, 36.1% female	30 mL Cerebrolysin (diluted with physiological saline to 100 mL) (n=104) Vs. Placebo (physiological saline (100 mL)) (n=104) administered once daily. (Ed., dose not	Follow-up at 7, 14, and 21 days after baseline and on days 42 and 90 post stroke.	Mean±SD Action Research Arm Test score baseline vs day 90: 10.1±15.9 vs. 40.7±20.2 Cerebrolysin. 10.7±16.5 vs. 26.5±21.0 placebo. Effect size on	"Cerebrolysin had a beneficial effect on function and global outcome in early rehabilitation patients after stroke. Its safety was comparable with that of the placebo, suggesting a	Data suggest cerebrolysin superior to placebo for ARAT score and global outcome after stroke at 90 days. However, results need confirmation

			Asian Pacific Trial in Acute Brain Injury and Neurorecovery (CAPTAIN) trial scientific advisory board. Dr Muresanu reports receipt of grants/research supports from EVER Neuro Pharma.			clearly defined in the study, only volume defined).		the ARAT score on day 90 Cerebrolysin vs. placebo (Mann–Whitney estimator, 0.71; 95% CI: 0.63–0.79; p<0.0001)	favorable benefit/risk ratio. Because this study was exploratory and had a relatively small sample size, the results should be confirmed in a large-scale, randomized clinical trial."	on a larger Phase III trial.
Chen 2013 (score = 7.0)	Cerebrolysin	RCT, Double-Blind Pilot Study	No mention of sponsorship. No COI.	N = 32 with mTBI.	Mean age 44.8 ± 16.36 years (range, 30 – 75 years).	Group A: Cerebrolysin (once daily intravenous infusion of 30 mL Cerebrolysin over a 60-min period for 5 days) (N = 17) vs. Group B: placebo (N = 15). (Ed., dose not clearly defined in the study, only volume defined).	Follow-up for week 1, 4, and 12.	At week 12, the CASI score was greater in group A vs. group B (21.0 ± 20.4 vs. 7.6 ± 1 2.1; p = 0.0461). Group A had greater difference vs. group B in drawing subscale at week 4 (1.79 ± 1.42 vs. 0.20 ± 1.47) and week 12 (2.14 ± 2.54 vs. 0.57 ± 1.74), (p = 0.0066 and p = 0.0472). Group A had greater difference in the long-term memory vs. group B at week 12 (1.79	"[The] results indicated that Cerebrolysin therapy started within 24 h after the onset of MTBI with intracranial contusion haemorrhage can improve patients ' CASI scores; this finding suggests that Cerebrolysin may enhance cognitive recovery after MTBI. We believe that MTBI with intracranial contusion haemorrhage patients can benefit from supplementary treatment with	Phase 2 pilot study. Data suggest cerebrolysin improves cognitive function of MTBI patients at 3rd month post-injury esp. regarding memory and drawing.

								± 3.91 vs. -0.57 ± 1.87), (p = 0.0256).	Cerebrolysin in addition to the usual medical treatment for this condition."	

Evidence for the Use of Tranexamic Acid

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Roberts 2013 (score = 8.5)	Tranexamic Acid vs Placebo	RCT	Sponsored by the London School of Hygiene & Tropical Medicine and the World Health Organization. No COI.	N = 20,211 adult trauma patients with, or at risk of, significant bleeding.	Mean age: 35 years.	Tranexamic acid (TXA) (N = 10,115) vs. Placebo (N = 10,115).	No long-term follow-up.	Death (Any cause) – 1463 (14.5%) TXA vs 1613 (16.0%) Placebo; RR 0.91 (95%CI 0.85-0.97; p=0.0035); Death (vascular occlusion) – 489 (4.9%) TXA vs 575 (5.7%) Placebo; RR 0.69 (95%CI 0.44-1.07; p=0.096). Any vascular occlusive event – 168 (1.7%) TXA vs 201 (2.0%) Placebo; RR 0.84 (95%CI 0.68-1.02; p=0.084). Blood product transfused – 5067 (50.4%) TXA vs 5160 (51.3%) Placebo; RR 0.98 (95%CI 0.96-1.01; p=0.21)	"Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study.	Data suggest TXA reduced risk of death in bleeding trauma patients when given within 3 hours compared with placebo.
Yutthakasemsunt 2013 (score = 8.0)	Tranexamic Acid vs Placebo	RCT	No mention of sponsorship. No COI.	N = 240 patients with moderate to severe TBI.	Mean age: 40 years.	Tranexamic acid (TXA) (N = 120) vs. Placebo (N = 120).	Follow-up not reported.	TXA vs Placebo: Progressive intracranial haemorrhage – Relative Risk (RR) = 0.65 (95%CI 0.40-1.05); Increase in pressure effect – RR	"We have not shown that TXA improves clinical outcomes and this information would be required in order to make any recommendation	Data suggest TXA did not significantly reduce progressive intracranial hemorrhage compared with

								= 0.91 (95%CI 0.42-1.97); Improved GCS motor score – RR = 0.98 (95%CI 0.67-1.44); Death – RR = 0.69 (95%CI 0.35-1.39).	about the use of TXA in clinical practice."	placebo (18% vs. 27%, p= 0.65). Study may be underpowered.
Perel 2011 (score = 6.5)	Tranexamic Acid vs Placebo	RCT	Part of CRASH-2 study (Lancet 2010). Sponsored by the UK Health Technology Assessment Programme. No COI.	N = 270 trauma patients with, or at risk of, significant extracranial bleeding and traumatic brain injury	Mean age: 36+14years Tranexamic Acid group; 37+14years Placebo group.	Tranexamic acid (N = 133) vs. Placebo (N = 137).	Follow-up time uncertain.	Difference in haemorrhage growth (ml) between Tranexamic acid and Placebo patients –All patients (unadjusted): -2.1 (-9.8 to 5.6; p=0.33); All patients (adjusted*): -3.79 (-11.5 to 3.9; p=0.33). Deaths – Tranexamic acid vs. Placebo: 11% vs. 18% (95%CI 0.21 to 1.04; p=0.06). *Adjusted for Glasgow coma score, age, time from injury to the scans, and initial haemorrhage volume.	"The CRASH-2 trial has shown reliably that early administration of tranexamic acid in trauma patients with, or at risk of, significant bleeding reduces the risk of all cause mortality."	Nested placebo-controlled of Crash-2 study. Data suggest comparable efficacy of TXA vs. placebo for bleeding reduction among TBI and TXA trended towards less mortality (p=0.06)

Evidence for the Use of Sedatives, Sedative Hypnotics, Analgesics, & Narcotics

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
James 2012 (score = 5.5)	Dexmedetomidine vs Propofol	RCT Crossover Design	Sponsored by the Hospira Worldwide,	N = 8 with TBI;	Age range ≥ 18	0.54 µg/kg/h of dexmedetomidine administered to patients and	Follow-up at baseline and hours	No significant statistics reported. Differences in cerebral substrates	"[D]exmedetomidine and propofol appear equally effective	Pilot study. Small sample size. Data suggest similar efficacy between

			Inc. and the American Heart Association Scientist Development Grant. COI, Dr. M. L. James serves as a speaking consultant for Hospira Worldwide, Inc.		years old.	25.5 µg/kg/min of propofol administered to patients over a 12 hour crossover design (N = 8)	2, 6, 8, and 12.	(lactate/pyruvate ratio) were noted. DEX group L/P ratio before testing (45.9 ± 39.5, (p = .398)) Post testing (33.8 ± 10.7, (p = .328))	in sedating patients with TBI and neither is associated with adverse physiological effects.	dexmedetomidine vs propofol. Excluded as n<10.
Ghori 2007 (score = 4.5)	Midazolam vs Propofol	RCT	Sponsored by the Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital. COI, George D Shorten employed by the Department of Anaesthesia and Intensive Care Medicine at Cork University.	N = 28 TBI patients with GCS score < 9;	Age range 18-65 years.	Midazolam 0.1–0.3mg/kg/h (N = 15); Propofol 1.5–5mg/Kg/h (N = 13); Both groups received morphine sulfate (0.1–0.2mg/kg/h)	Follow-up at baseline, day 1-5, and month 3.	Midazolam vs propofol Serum s100β concentrations (Mean, [SD]): Day 1, (0.99 ± 0.81]) vs (0.41 ± 0.4)µg/L; Day 2, (0.80 ± 0.81) vs (0.41 ± 0.24) µg/L; Day 3, (0.52 ± 0.55) vs (0.24 ± 0.25) µg/L; and Day 4, (0.54 ± 0.43) vs (0.24 ± 0.35) µg/L; (p < 0.05)	"Plasma concentrations of neurological injury markers were similar in patients who received midazolam and propofol. Patients with poor neurological outcomes had consistently higher serum s100β."	Methodological details sparse. Small sample size. Many medications given.

Bourgoin 2005 (score = 4.5)	NMDA receptor antagonist Sufentanil vs Ketamine	RCT, prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age 29 ± 12 years in the Sufentanil group and 29 ± 11 years in the Ketamine group.	Sufentanil group (N = 15) vs. Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was 17.7 ± 6.5 mm Hg in the sufentanil group vs. 16.2 ± 6.4 mm Hg in the ketamine group. VMCAM value was significantly higher in the sufentanil group (77 ± 21 cm/sec) vs. the ketamine group (60 ± 33 cm/sec, p = 0.03). At 6, 7, and 13 min, there was statistical difference in the BIS value between groups (p < 0.05).	"The present study shows that the increase in sufentanil or ketamine plasma concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients."	Small sample. Data suggest doubling sufentanil or ketamine showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.
Nadal 2000 (score = 3.5)	Fentanyl vs Morphine	RCT, Crossover design	Sponsored by the Fondo de Investigaciones Sanitarias de la Seguridad	N = 30 patients with severe closed-head injury during the	Mean age 30 ± 13 years.	2.0 µg/kg fentanyl was administered intravenously over 1 minute to group 1. 0.2 mg/kg morphine was	Follow-up at baseline, minute 5 and 60, and day 1 and 2.	MABP decreased significantly after 5 minutes; Morphine (p = 0.002); Fentanyl (p = 0.016); ICP increased after 5 minutes: Morphine	"[M]orphine and fentanyl increased intracranial pressure and decreased mean arterial blood pressure and	Small sample size. Methodological details sparse.

			Social, Madrid, Spain and the Marato TV3, Barcelona, Spain. No mention of COI	first 3 days of admission into the ICU;		administered intravenously over 1 minute to the group again 24 hours later. (N = 30)		(p = 0.008) Fentanyl (p = 0.044). Cerebral perfusion pressure at 5 minutes had minimum values of 64 ± 15 mmHg after morphine (p = 0.001) and 65 ± 18 mmHg after fentanyl (p < 0.0001)	cerebral perfusion pressure. No significant effect was shown on arteriovenous oxygen levels and middle cerebral artery mean flow velocity in TBI patients."	
Tanguy 2012 (score = 3.5)	Propofol vs Midazolam	RCT, prospective, single-blind	Sponsored by Programme Hospitalier de Recherche Clinique (PHRC) of Rennes. No COI.	N = 36 with severe TBI.	Mean age 35 – 18 years.	Propofol (N = 15) vs. Midazolam (N = 14)	Follow-up for 72 hours and 12 months.	There was no difference between propofol and midazolam in the cerebral L: P ratio (time effect p = 0.201, treatment effect p = 0.401, time x treatment interaction p = 0.101).	"[The] results indicate that there is no difference between the effects of propofol and midazolam sedation on the cerebral metabolic profile during the acute phase of severe TBI. Accordingly, the use of propofol as a sedative agent in TBI and its neuroprotective effects warrant further investigation.	Small sample size. Methodological details sparse. Relatively invasive monitoring using cerebral microdialysis catheter. High complication rate. Data suggests similar efficacy between propofol and midazolam.
Karabinis 2004 (score = 3.0)	Remifentanil vs Fentanyl vs Morphine	RCT	No mention of sponsorship. COI, Andreas Karabinis, Kostas	N = 161 patients with acute TBI or had undergone	Age range 18-80 years.	Remifentanil was given at 9 µg kg-1 h-1 and increased to a maximum of 18 µg kg-1 h-1 before	Follow-up at baseline and day 1, 3, and 5.	Between-patient variability at the time of neurological assessment was significantly smaller when using remifentanil	"Analgesia-based sedation with remifentanil permitted significantly faster and more	Methodological details sparse. Data suggest remifentanil superior for measured outcomes.

			Mandragos, Spiros Stergiopoulos, Apostolos Komnos, Jens Soukup and Ben Speelberg received payment from Glaxo-SmithKline according to the number of patients recruited. Andrew JT Kirkham is an employee of GlaxoSmith Kline.	intracranial surgery;		administering propofol at 0.5 mg kg-1 h-1 during days 1-3. Midazolam was administered in doses of 0.03 mg kg-1 h-1 during days 4 and 5. (N = 84). vs. Fentanyl & morphine were administered at recommended doses along with the same dosage/timing of propofol and midazolam as seen in group 1. (N = 77).		(remifentanil = 0.44 vs. fentanyl = 0.86 (p = 0.024) vs. morphine = 0.98 (p = 0.006)). Mean neurological assessment times were significantly shorter when using remifentanil (remifentanil = 0.41 hour vs. fentanyl = 0.71 hour (p = 0.001) vs. morphine = 0.82 hour (p <0.001)).	predictable awakening for neurological assessment."	
Sanchez-Izquierdo-Riera 1998 (score = 3.0)	Midazolam (Mz) vs Propofol (Pf) vs Combo Mz-Pf	RCT	No mention of sponsorship or COI	N = 100 with acute TBI requiring mechanical ventilation for at least 48 hours;	Mean age 35.4 ± 16.6 years.	Group A received midazolam at a rate of 0.1 mg / kg-1 / h-l with a maximum dose of 0.35 mg / kg-1 / h-1. (N = 34); Group B received propofol at a rate of 1.5 mg / kg-1 / h-1 with a maximum dose of 6 mg / kg-1 /	Follow-up at baseline, hour 3, 6, 12, and 24 after sedation stoppage.	Wake-up time significantly decreased in Pf groups. Group A (660 ± 400 min) vs Group B (110 ± 50 min) vs. Group C (190 ± 200 min), (p < 0.01).	"In summary, the results indicate that Mz and Pf, used alone or in combination, are safe and effective in the sedation of critically ill trauma patients.	Methodological details sparse. Large number of therapeutic failures. Data suggest propofol either alone or in combination with midazolam resulted in shorter wake-up times.

						h-l. (N = 33); Group C received a combination of midazolam and propofol in doses similar to the previous groups. (N = 33)				
Kolenda 1996 (score = 1.5)	Ketamine/ Midazolam vs Fentanyl/Midazolam	RCT	No mention of sponsorship and COI.	N=35 patients who suffered a moderate or severe head injury;	Mean Age: Group 1 38 (18-72) yrs.; Group 2 29 (16-59) yrs.	Group 1 Received analgosedative therapy with 6.5 mg/kg and 65 mg/kg ketamine per day Vs. Group 2 Received analgosedative therapy with 6.5 mg/kg and 65 mg/kg fentanyl per day.	Follow-Up baseline and day 14 (final dosage) and day 1, 3, and 7 after termination of the analgosedative therapy.	Tube feeding, group 1 vs group 2, 14 day average: 824 mL/day vs 579 mL/day statistical difference at day 3, 4, 5; ($p<0.05$). Mean Arterial pressure (MAP) group 1 vs Group 2, day 3 and 7: 91 (76-107) vs 81 (73-107) and 95 (88-107) vs 77 (76-90); ($p<0.05$). Mean pulse rate group 1 vs group 2, day 2, 3, and 7: 80 (64-104) vs 56 (44-92), 74 (62-104) vs 62 (48-80), 84 (68-96) vs 68 (64-76), respectively; ($p<0.005$). Intracranial Pressure, group 1 vs group 2, day 8 and 10: 16 (14-22) vs 11 (6-18), 18 (14-22) vs 10 (6-22); ($p<0.05$).	"… [K]etamine/midazolam analgosedation in head-injured patients is more expensive than a comparable anaesthetic therapy using fentanyl/midazolam, and this disadvantage is not countered by the earlier restitution of consciousness in the ketamine group. But with regard to risk patients for intensive therapy such as those presenting severe cardiovascular, pulmonary or gastro-intestinal problems requiring intensive medication,	High dropout rate due to multiple complications. Baseline differences in treatment groups. Data suggest comparable (in) efficacy.

									ketamine offers an alternative anaesthetic concept [13, 18, 30, and 34]. Its bronchodilating action as well as its stabilizing effect on circulation and gastro-intestinal motility may be of great beneficial value for these patients."	
Albanese 1999 (score = 1.5)	[Previous table header, if any]	RCT Crossover	No mention of sponsorship or COI	N = 6 males with TBI and GCS score ≤ 8;	Age range 20-45 years.	6-min injection of either sufentanil (1 µg/kg), alfentanil (100 µg/kg), or fentanyl (10 µg/kg) followed by an infusion of 0.005, 0.7, and 0.075 µg/kg/min, for 1 hr. The three opioids were given to each patient at 24-hr intervals. (N = 6)	Follow-up at baseline, 10, 30, and 60 minutes after opioid administration, and at 3, 24 hour intervals.	Significant increases in ICP were associated with infusions. (Minute 3/5/10 in mm Hg) Sufentanil (25 ± 5 / 27 ± 6 / 24 ± 6), fentanyl (21 ± 2 / 25 ± 4 / 21 ± 4), alfentanil (22 ± 7 / 21 ± 5 / 20 ± 6) Overall ICP increase (9 ± 2 mm Hg, 8 ± 2 mm Hg, and 5.5 ± 1.0 mm Hg, ($p < 0.05$).	"[S]ignificant, but transient, equal increases in ICP were observed after bolus injections of alfentanil, sufentanil, and fentanyl in patients with head trauma and increased intracranial pressure."	Small sample size. Methodological details sparse. Study excluded as sample size too small (<10) as well as quality score low.

Evidence for the Use of Barbiturates

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Schwartz 1984 (score = 4.5)	Pentobarbital vs Mannitol	RCT	Sponsored by the Sunnybrook Medical Center grant. No mention of COI.	N = 59 with elevated intracranial pressure from severe head injury. Glasgow Coma Scale scores <8.	Mean age mannitol 30.1 years, pentobarbital 28.9 years.	Mannitol 20% 1g/kg with a serum osmolality of 320mOs/L (N = 31) vs. Pentobarbital IV bolus of 10mg/kg and continuous infusion at 0.5-3mg/kg/hr. (N = 28).	All patients given CT scan.	Scores on the GCS correlated with survival rates at 3 months 16/28 patients had dies in the pentobarbital group and at 1-year 6/12 remained hospitalized. For mannitol 13/31 had died and at 1-year 8/16 were hospitalized. Twice as many patients starting with pentobarbital had to use mannitol as rescue medicine, making pentobarbital not 25% better (p=0.04) than mannitol.	"There is no evidence that pentobarbital is 25 percent better than mannitol, either for the control of raised intracranial pressure or for improving survival in patients with intracranial hypertension due to head injury."	For patients experiencing elevated episodes of ICP they were given rescue medicine, making the study a cross-over, unblinded study. Severe TBI. Data suggest mannitol superior for mortality ()(41% Mannitol vs 77% Pentobarbital)
Eisenberg 1988 (score = 4.5)	Pentobarbital vs Conventional Treatment	RCT	Sponsored by National Institutes of Health. No	N = 73 patients with TBI	Age range between 15-50 years old.	Barbiturate treatment group. 10 mg/kg pentobarbital	Follow-up at baseline, hours 3,	ICP control in barbiturate group had success in 12	"High dose pentobarbital treatment in addition to	Failed conventional treatment, could be

			mention of COI	and a GCS score ≤ 7;		administered over 30 minutes followed by 5 mg/kg/hr. for three hours. A maintenance dose of 1 mg/kg/hr. was used to keep serum levels at 3-4 mg % (N = 37) Vs. Conventional treatment group. 1 mg/hr. morphine administered, hyperventilation, elevation of head, and ≥ .25 g/kg bolus Mannitol administered (N = 36)	12, 24, 48, day 1, and month 6.	(32.4%) patients vs. 6 (16.7%) in the conventional treatment group, (p = 0.12).	conventional treatment can assist in managing elevated ICP in TBI patients."	crossed over to barbiturate treatment. Did not meet enrollment target. Very specific population; generalizability questionable. Control treatment no longer typically used.
Pérez-Bárcena 2008 (score = 3.0)	Pentobarbital vs Thiopental	RCT	Sponsored by the Spanish government's Fondo de Investigación Sanitaria. No COI.	N = 44 with TBI and a GCS score ≤ 8;	age range between 15-76 years old	10 mg/kg of pentobarbital administered over 30 minutes followed by 5 mg/kg per hour for 3 hours (N = 22) Vs. 2 mg/kg bolus thiopental administered over 20 seconds followed by 3 mg/kg per hour. (N = 22).	Follow-up at baseline, day 1, 2, 3, and month 6.	Uncontrollable ICP in 11 cases in thiopental group and 18 cases in pentobarbital group, (p = 0.03). Thiopental ICP control vs pentobarbital, (odds ratio = 5.1) and 95% CI, (1.2 to 21.9) (p = 0.027).	"Thiopental appeared to be more effective than pentobarbital in controlling intracranial hypertension refractory to first-tier measures."	Possible randomization failure. Data suggest thiopental may be superior to pentobarbital for reducing intracranial pressure, but with possible randomization failure, the results are questionable.

Young 1983 (score = 3.0)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N=214 patients with traumatic brain injury.	Mean age; 25.1 years.	Phenytoin Group (10 to 20 µg/ml) (N=98) Vs. Phenobarbital Group-If patients did not react well with phenytoin they were switched to this group (N=21) Vs. Placebo Group(N=95)	Follow-up for 18 months.	No difference between phenytoin and phenobarbital groups for having late seizures (p=0.48). Drug group as whole did not show lower risk for late seizures vs. placebo (p=0.75). Median time to death was 16 days in the drug vs. 14.5 days in placebo, (p=0.30).	"It cannot be concluded that higher phenytoin plasma concentrations and higher compliance rates than obtained in this study would not have significantly decreased the occurrence of late post-traumatic epilepsy."	Sparse methods. Data suggest phenytoin not effective compared with placebo to prevent seizures.
Ward 1985 (score = 3.0)	Pentobarbital	RCT	Sponsored by the National Institutes of Health. No mention of COI	N = 53 with an acute intradural hematoma;	Age range above 12 years old.	Pentobarbital administered at 5-10 mg/kg initially, followed by 1-3 mg/kg per hour. (N = 27) Vs. Control group (N = 26)	Follow-up at baseline, day 4, and weeks 1 and 2.	ICP (mean, SD) of pentobarbital group (19.5 mm Hg, ±13.0 mm Hg) vs control group (18.5 mm Hg, ±12.1 mm Hg) showed no significant difference. Arteriole hypotension occurred in 14% of the treated patients and 7% of the control group.	"Results show the prophylactic use of pentobarbital in TBI patients has no significant effect, thus its use is not recommended."	Methodological details sparse. Many complications in both groups.

Evidence for the Use of Beta Blockers

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Levitt 2001 (score = 7.5)	Beta Blockers (Landiol for intubation vs Lidocaine)	RCT, double blind	No mention of sponsorship or COI.	N = 30 with isolated blunt injury to the head and required intubation.	Mean age 44.1 ± 16.7	Given 0.14 ± 0.06 mg/kg esmolol. (N = 16) vs. Given 0.15 ± 0.11mg/kg lidocaine. (N = 14). Measurements were recorded at one minute intervals for a total of eight minutes.	Follow-up at 8 minutes, not long term.	No difference between groups for changes in HR, (p = 0.68). No difference between groups for changes in DBP, (p = 0.56). No difference between groups for changes in SBP, (p = 0.23).	"Esmolol and lidocaine have similar efficacies to attenuate moderate hemodynamic response to intubation of patients with isolated head trauma."	Small sample. Data suggest comparable efficacy for reducing response to intubation.
Kawaguchi 2010 (score = 7.0)	Beta Blockers (Landiolol vs Placebo)	RCT Multicenter	Supported by the Department of Anesthesiology, Nara medical University, the Department of Anesthesiology – Resuscitology, Yamaguchi University Graduate School of Medicine, and the Department of Anesthesiology, Hachioji medical Center Tokyo Medical University. No mention of COI.	N = 56 with undergoing intracranial aneurysm surgery with tachycardia	Age 20-75.	Landiolol, given a bolus of (50μg/kg) followed by a continuous infusion at (20μ/kg/min) (N = 28) vs. No Landiolol administrated (N = 28).	Follow-up at 24, 72 hours and at 3 months post operation.	No significant differences in BNP and troponin T values at all-time points between the groups. Serum S-100β values 24 hours after operation were significantly lower in the landiolol treated group, (p = 0.0409).	"[C]ontinuous administration of landiolol can be effectively used for the treatment of tachycardia during intracranial aneurysm surgery in patients with SAH without affecting on arterial blood pressure."	Data suggest landiolol reduced serum S-100 β levels 24 hours post-op compared with controls. However, landiolol associated with more bradycardia (57% vs. 18%).

Cruickshank 1987 (score = 4.0)	Beta Blockers (Atenolol vs Placebo)	RCT	No mention of sponsorship or COI.	N = 114 with acute head injury.	Aged 11-70 years.	Atenolol 10 mg every 6 hours for 3 and further 4 days (N = 56) vs. Placebo 10 mg every 6 hours for 3 and 4 more days (N = 58).	7 day follow-up.	There was a significant positive correlation between arterial noradrenaline and creatine kinase. 30% vs 7.4% of atenolol group ($p < 0.05$) showed CKMB levels >3% of total CK.	"Atenolol appeared to reduce significantly the likelihood of supraventricular tachycardia and ST-segment and T-wave changes and prevented cardiac necrosis seen at necropsy."	Data suggest atenolol reduces risk of SVT, ST-segment and T-wave changes. Among those who died, there were fewer cardiac changes at necropsy.
Brooke 1992 (score = 3.5)	Beta Blockers (Propranolol vs Placebo)	RCT	Supported by the National Institute on Disability and Rehabilitation Research grant G00830076, Department of Education, Washington DC and Harborview Injury Prevention and Research Center, Center for Disease control grant CCR49-002570. No mention of COI.	N = 21with severe, traumatic, closed-head injuries with more than one hour unconsciousness less than an 8 on Glasgow Coma Scale upon admission and any agitation severe enough to be scored on the Overt Aggression Scale.	No age reported.	Treated with increasing dose of propranolol beginning with 60mg a day increasing by 60mg every third day to a maximum of 420mg and tapering off after 3 weeks. (N = 11) vs. Given a placebo dose increasing and tapering in pattern with treated group. (N = 10).	Follow up on a weekly basis for seven weeks.	Intensities for agitation by week higher for placebo. ($z = -2.028$, $p < .05$) and patterns of increase and decrease between groups not similar, ($r = 0.491$). Number of agitation episodes by week for placebo not greater ($z = -1.5213$) and decrease patterns for N of episodes was similar ($r = .892$, $p > 0.05$).	"The intensity of agitation was significantly lower in the treatment group although the number of episodes were similar. The use of restraints was also significantly lower in the treatment group."	Small sample with sparse methods. Data suggest propranolol reduced intensity of agitation compared with placebo.

Evidence for the Use of Aminosteroids

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Marshall 1998 (score = NA)	Aminosteroids	RCT	Sponsored by UpJohn Co. No mention of COI.	N = 1120 patients with severe head injury or moderate head injury exhibiting CT scan abnormalities, Glasgow Coma Score (GCS) of 4-8 or 9-12; Eighty-five percent (957) of the patients had suffered a severe head injury (Glasgow Coma Scale [GCS] score 4–8) and 15% (163) had sustained a moderate head injury (GCS score 9–12).	Mean age= 33.6 years.	10 mg/kg tirilazad mesylate group (N =562) vs. 10 mg/kg placebo group (N= 558). Both groups received treatment by intravenous infusion through a central venous line every 6 hours for 5 days.	Follow up at 3 and 6 months.	Six-month outcomes for tirilazad-and placebo groups for Glasgow Outcome Scale categories of both good recovery and death showed no differences. In a subgroup analysis, those with moderate injury at 6mo had lower mortality with tirilazad vs. placebo: 6% vs. 24%, (p=0.042). Among severe head injury group, borderline significance in mortality rates between tirilazad and placebo: 33% vs. 43%, (p=0.071).	"[O]verall efficacy of the use of tirilazad mesylate in patients with moderate and severe head injury could not be demonstrated. A potential positive effect may exist in male patients with traumatic SAH. The reported study emphasizes potential problems occurring within trials of severe head injury."	Appears to be a randomization failure as there were “striking imbalances between baseline prognostic variables”, therefore this study cannot be scored.

Evidence for the Use of Citicoline

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Zafonte 2012 (score = 6.5)	Citicoline	RCT	Sponsored by the National Institute of Child Health and Human Development and Ferrer Grupo. No COI.	N= 1213 receiving an acute inpatient hospitalization at a trauma center for non-penetrating TBI;	Ages 18 to 70 years.	Citicoline (2000 mg/d) group (N=607) Vs. Placebo group (N=606). Both groups received treatment via enteral route for 90 days beginning within 24 hours of injury	Assessments at baseline, every 12 hours for 7 days, 14, 30, 58, 90, 135 and 180 days.	Trial was stopped for futility. Patients with complicated mild TBI in the placebo group did better than those given citicoline (global OR 0.72, 95% CI 0.56-0.91, p=0.004). No other significant differences between groups.	"[T]his large, randomized, blinded study showed that acute and subacute treatment with citicoline did not result in improvement in functional and cognitive status. These findings call into question the use of citicoline for patients with TBI."	Data suggest citicoline comparable to placebo for cognitive status at 90 days out from TBI.
Levin 1991 (score = 5.0)	Citicoline	RCT	No mention of sponsorship or COI.	N =14 hospitalized patients with mild to moderate head injury	Between the ages of 16 to 70; Median age 25 for CDP-choline group and 20 for placebo group.	One gram oral CDP-choline group (n=7) Vs. Placebo group (n=7)	Assessments at baseline and 1 month.	Neuropsychological findings (baseline/follow-up/percent change). Recall of words: CDP-choline (76/111/147), placebo (117/106/8). Recall of locations: CDP-choline (67/94/40), placebo (95/95/-1). Recall of designs: CDP-choline (25/38/104, ($p<0.05$)), placebo (40/45/29, ($p<0.05$)). Verbal fluency: CDP-choline	"[I]t appears that CDP-choline is well tolerated, although the patients who were treated did complain more of gastrointestinal distress at one month than the non-treated patients."	Very small samples. Baseline characteristics sparse. Data from preliminary results suggest improved recognition memory for CDP-choline group.

								(22/41/8), placebo (35/37/13). Designs-free: CDP-choline (18/16/-9), placebo (13/20/25). Designs-fixed: CDP-choline (14/11, p<0.05/0), placebo (13/19, p<0.05/77). CPT (msec): CDP-choline 1527/1225/-9), placebo (1444/1108/-15). PASAT (correct/time): CDP-choline (0.315/0.344/25), placebo (0.398/0.479/27).		
Shokouhi 2014 (score = 3.5)	Citicoline	RCT	Sponsored by Iran's National Elites Foundation and the Neuroscience Research Center. No COI.	N = 58 with diffuse axonal injuries, GCS ≤8, no presence of lesions on the chest, abdomen or focal brain, and who were admitted to affiliated trauma departments;	Mean (±SD) age 30.94 (±8.6) for participants.	Citicoline treatment group receiving 500mg every 6 hours (N =29) vs. Control group (N =29)	Assessments at baseline, 1 day, 6, 12 and 15 days.	On 12th day assessment, Citicoline group exhibited significantly higher Matrix Gla Protein (MGP) values compared with control group; 44.86±21.58 vs. 31.11±17.65, (p=0.01). No statistically significant differences reported between groups for average GCS scores or Fetuin-A levels.	"[C]iticoline, having neutral effects on levels of consciousness, may have a protective role against inflammation and, following vascular calcification, in secondary-TBI through increasing serum levels of fetuin-A and MGP."	Sparse methods. Data suggest citicholine may have protective effect for inflammatory damage and calcification secondary to TBI. But no functional benefit demonstrated.
Maldanado 1991 (score = 3.0)	Citicoline	RCT	No mention of sponsorship or COI.	N =216 with a head injury, initial GCS between 5 and 10;	Mean ages not reported.	CDP-Choline treatment group (receiving 1 g IV Q 6	Assessments at baseline, ICU discharge	Percentage of patients improved at 3 months: headache – NS, dizziness – NS,	"[O]ur results and those of other authors indicate that CDP-choline is effective and safe in	Sparse methods. Data suggest trend in motor, cognitive and psychic improvement in

						hours for 1st and 2nd day, 1 g every 8 hours for 3rd and 4th day. Participants with a phleboclysis got same dose until discharge, and those without received 1g Q 12 hours. After discharge, 200mg Q 8h) (N=115) Vs. Control group (N=101). Both groups received conventional plus allocated treatment.	and 3 months.	motor dysfunction – NS, memory problems – NS, superior neurological dysfunction (SND) – NS, changes in character CDP-choline 91.83 v. control 75, ($p<0.05$). Distribution of patients by GOS score at 3 months: I-CDP-choline 77 v. control 51, ($p<0.05$), II – NS, III – NS, IV – NS, V – NS.	the treatment of patients with moderate or severe head injuries."	CDP-Choline group among severe TBI patients.
Leôn-Carriôn 2000 (score = 2.5)	Citicoline	RCT	Sponsored by the University of Seville and Ferrer Internaciónal. No mention of COI.	N = 7 with severe memory deficits due to traumatic brain injury;	Ages 18 to 40.	CDPc (1 g/d v.o.) (N=X) Vs. Placebo group (N=X)	Both underwent a memory rehabilitation program for 3 months and received treatment concurrently.	Before and after within group results were gathered. Placebo (before/after): attention (95.60±5.73/97.60± 2.19), vigilance (88.40±8.65/96.80± 1.79), verbal fluency (22.40±9.91/23.60± 11.01), Benton visual retention test	"[P]atients who underwent concurrent neuropsychological + CDPc treatment showed significant improvement in memory volume and verbal fluency."	Small sample size and sparse methods.

								– number of errors (8.20±3.63/9.40±6.95), Luria's memory words (62.80±13.24/62.00±11.58). CDPc: attention (82±33.79/90.80±20.57), vigilance (89.60±17.74/98.90±1.79), verbal fluency (24.80±14.65/31.80±9.36, (p<0.05)), Benton visual retention test – number of errors (8.80±5.45/7.20±3.70), Luria's memory words (63.20±17.31/71.00±12.98, (p<0.05)).		

Evidence for the Use of Physostigmine (Eserine)

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Levin 1986 (score = 5.5)	Physostigmine vs Placebo	RCT, Double-blind, placebo-controlled crossover design	Sponsored by the Moody Foundation, the Javits Neuroscience Investigator Award, and the Del Oro Hospital. No COI	N= 16 men undergoing inpatient rehab for TBIs;	Age range 18-38 years	Group 1: oral physotigmine (N = 8) Vs. Group 2: placebo (N = 8) Patients received either 1 mg or 1.5 mg of oral physotigmine or placebo three times a day during two, seven day testing periods. Two 8 g servings of phosphatidylcholine	Follow-up at baseline and day 7, 15, and 21.	Patients showed improvement in sustained attention after receiving physotigmine (p = 0.008). Patients who received oral physotigmine in treatment 1 showed more significant	"Although the results generally indicated no difference in the effects of the physotigmine-lecithin combination as compared to lecithin alone, sustained	Crossover. Data suggest physostigmine of no additive benefit above the placebo (lecithin).

						(lecithin) were administered daily for 21 days.		improvements in the performance testing than patients in treatment 2 (p = 0.02).	attention on the continuous performance test was more efficient under physotigmine than placebo when the drug condition occurred first in the crossover design."	
Cardenas 1994 (score = 5.0)	Physostigmine vs Placebo	RCT, Double-blind, placebo-controlled crossover design	Sponsored by the National Institute on Disability and Rehabilitation Research, Department of Education. No COI.	N = 36 men with at least 3 months post-TBI;	Mean age 29±5	Responders (N = 16) and Non-responders (N =20). Each group received both placebo and physostigmine with scopolamine. 2 treatment phases scopolamine 5 µg/hr. for 8 days by transdermal patch. Subsequent subjects received a transdermal patch behind each ear for 4-12 hours. Initial physotigmine 2.0 mg and then increased to a maximum dose of 4.0 mg over 7 days.	Follow-up at baseline, 8 and 16 days, and 1 month.	16 (44%) of patients who took physotigmine improved in their memory test performances (p = 0.384). Responders who took physotigmine improved their standing time when standing tandem with eyes closed vs. non-responders (p < 0.05).	"Results support the potential benefit of cholinergic agonists on memory after TBI and the need for further research of possible clinical markers for the drug."	Crossover design. Sparse results reported with mostly reporting of data by "responders." Follow-up only short term (8 days)

Evidence for the Use of Rivastigmine (Exelon)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tenovuo 2009 (score = 7.5)	Rivastigmine vs Placebo	RCT Double blind crossover	Sponsored by Novartis Finland. No COI.	N=102 with TBI, at least two of the following target symptoms: fatigue, decreased stress tolerance, difficulties in concentration, decrease of initiative ability, poor short-term memory, cognitive slowness and changes in behaviour or personality.	18 years or older	N=51 Sequence A (rivastigmine–wash-out–placebo) vs. =51 sequence B (placebo–wash-out–rivastigmine for 8 weeks with 4 week wash-out period. Dose raised every 2 weeks. Max dose equaled 12mg rivastigmine.	Follow-up at 8 weeks.	Primary outcome: rivastigmine group had higher right answers in Subtraction test (OR 2.81; 95% CI: 0.22–5.39; p = 0.034) and Vigilance test (OR 0.08; 95% CI: 0.001–0.17; p = 0.048) vs. placebo group.	"A weak trend favouring rivastigmine for chronic symptoms of TBI was observed. The clinical significance of the results and the problems in conducting drug trials for chronic TBI symptoms are discussed"	High dropout rate (32% dropped out due to ADRs). Data suggest weak trend for rivastigmine for chronic TBI symptoms.
Silver 2006 (score = 6.0)	Rivastigmine vs Placebo	Multicenter RCT	Sponsored Novartis Pharmaceuticals Corporation. COI, J. Silver has received honoraria from Novartis. B. Koumaras is an employee of Novartis and owns equity interest. M. Chen is an employee of Novartis. D. Mirski is a former	N = 157 with mild TBI, based on the International Classification of Diseases, Ninth Revision, Clinical Modification 854.0 head injury, and met or exceeded the American Congress of Rehabilitation Medicine criteria.	Aged 18 to 50 years.	Rivastigmine 3 to 6 mg/day (N = 80) Vs. Matching placebo (N = 77).	Follow-up at 12 weeks.	Mean duration of treatment (81.0±23.0 days and 79.6±22.7 days for rivastigmine vs. placebo, respectively; p = 0.712). No differences were found between the groups.	"Rivastigmine was safe and well tolerated in patients with traumatic brain injury with cognitive deficits. Rivastigmine shows promising results in the subgroup of patients with traumatic brain injury	Overall study data do not support efficacy. However, post-hoc analyses of moderate to severe TBI patients suggest rivastigmine may be effective for cognitive function in those more

			employee of Novartis, owns equity interest, and has received honoraria from Novartis. S. Potkin has received grants and honoraria (in excess of $10,000) from Novartis. P. Reyes has received grants (in excess of $10,000) and honoraria (in excess of $10,000) from Novartis. D. Warden has nothing to disclose. P. Harvey has received honoraria from Novartis. D. Arciniegas has received educational grants (in excess of $10,000) and honoraria (in excess of $10,000) from Novartis and has given expert testimony related to the subject of the						with moderate to severe memory deficits. "	severely affected.

			study. D. Katz has nothing to disclose. I. Gunay is an employee of Novartis.							
Tenovuo 2005 (score = 4.5)	Rivastigmine vs Galantamine vs Donepezil	RCT	No mention of sponsorship or COI.	N=111 with clinically definitive TBI (Kay et al., 1993) with chronic sequels; fairly stable phase after trauma, at least one of the four target symptoms (fatigue, poor memory, diminished attention).	Mean age 40±1.3 years	Donepezil started at 5 mg od in the morning (N=27) vs. Galantamine started at 4 mg bid morning and afternoon (N=30) vs. Rivastigmine started at 1.5 mg bid morning and afternoon (N=54). Doses raised after 1 week if no therapeutic response with good tolerability or if there was partial response and good tolerability.	No mention of study duration or follow-up time.	Mean maintenance dose: 7.2 mg od donepezil, 5.0 mg bid galantamine, 2.3 mg bid for rivastigmine. Positive response (%); 41% donepezil, 60% galantamine, 59% rivastigmine. No differences between these drugs were found.	"CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences between the three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed."	Quasi-randomization Data suggest comparable efficacy between all 3 drug groups.
Silver 2009 (score = 4.0) Second report, see	Rivastigmine vs Placebo	Multicenter RCT	Sponsored by Novartis Pharmaceuticals Corporation. COI, B. Koumaras, X. Meng and I. Gunay are all	N=127 ICD-9, Clinical Modification 854.0 head injury criteria (nonpenetrating) and met or exceeded the	Aged 18 to 50 years.	Rivastigmine 3 to 6 mg/day (N=65) vs. matching placebo (N =62).	Follow-up at 38 weeks.	At week 38, differences from baseline (week 0) were seen for the following	"Treatment with rivastigmine for up to 38 weeks was safe in patients with TBI and	Open-label extension study to Silver 2006. 2nd report. Data suggest approximately 40% had

Silver 2006.			employees of Novartis Pharmaceuticals Corporation. Dr. Harvey was compensated by Novartis Pharmaceuticals during the clinical trial for research assistance. He received no compensation for the preparation of this paper.	American Congress of Rehabilitation Medicine criteria for mild TBI. Current cognitive deficits which started to occur at least 12 months earlier.				efficacy measures: CANTAB RVIP A' (P<0.001); CANTAB RVIP mean latency (P<0.001); CANTAB-RT simple reaction time (P=0.002); HVLT total word recall (P<0.001); CANTAB-SWM total errors (P<0.001); COWA-semantic association fluency (P=0.008); Trail A (P<0.001); and Trail B (P<0.001).	cognitive impairment."	significant improvement from baseline in CANTAB RVIPA and HVLT total word recall for ex-placebo subgroup from week 12-38. However, lack of placebo group limits conclusions on efficacy.

Evidence for the Use of Complementary/Alternative Medicine

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Moein 2013 (Score = 5.0)	Complementary/Alternative Medicine	RCT, double-blind, cross-over	Sponsored by Isfahan University of Medical Sciences, Medical	N = 38 with diffuse axonal injury, coma >6hrs.	Age range 15–65 years.	Group A: Placebo (N = 20) vs. Group B: Boswellia Serrata capsules (3 times per day) (N = 18) for 6 weeks	Follow-up for 2, 6, and 12 weeks.	Both groups showed improvements in the DRS (p = 0.15), but there was not statistically	"These results suggest that BS resin does not significantly affect general outcome, but may enhance	Pilot. Crossover. High dropouts. Data suggest treatment may have efficacy and

			School, Isfahan, Iran. No COI.	GCS≤12 within first 24 hrs.		and then switched to the other intervention for another 6 weeks.		difference. After taking Boswellia Serrata capsules, patients had higher improvement on cognitive ability for self-care activities.	the cognitive outcome of patients with DAI."	need full size trials.
Chapman 1999 (Score = 3.0)	Complementary/Alternative Medicine	RCT, double-blind	Sponsored by the National Institutes of Health, Office of Alternative Medicine, Laboratoires Boiron, and the Boiron Research Foundation. No mention of COI.	N = 50 with MTBI (mean 2.93 years since injury, SD 3.1).	Mean age in the treatment group was 42.7 (11.3) years and 43.5 (12.3) in the placebo group.	Treatment group: homeopathic medicines. Each patient received a medication (from 18 homeopathic medicines) according to his/her symptoms. (N = 27) vs. Placebo control (N = 23).	Follow-up for 4 months.	The DSS was statistically improved in the treatment group vs. the placebo group [95% CI: – 0.895 to – 0.15], (p = 0.009). Additionally, the treatment group had greater improvements in the SRS vs. the placebo group [95% CI: – 0.548 to 0.01], which was almost statistically significant (p = 0.058). The treatment group showed significant reduction on the main symptoms in the SRS-10 vs. the placebo group [95% CI – 0.766 to – 0.048)], (p = 0.027).	"This study suggests that homeopathy may have a role in treating persistent MTBI. Our findings require large-scale, independent replication."	Pilot study. Various treatments used. Baseline differences concerning (e.g. alternative med. experiences 17 vs. 41%). DSS was stat. improved in treatment group vs. placebo [95% CI: – 0.895 to – 0.15], (p = 0.009). Treatment group had greater improvements in SRS vs. placebo [95% CI: – 0.548 to 0.01], which was almost significant (p = 0.058). Treatment group showed significant reduction in main symptoms in SRS-10 vs. placebo [95% CI – 0.766 to – 0.048)], (p = 0.027).
Sun 2009 (Score = 2.0)	Complementary /Alternati	RCT	No mention of sponsorship or COI.	N = 80 with traumatic intracranial hematoma	Age range 16 – 64 years.	Trial group: Danhong Injection (herbal TCM product from	Follow-up for day 7, day 14	GCS was statistically significant difference in the	"No obvious adverse reaction occurred during the whole	Sparse details.

	ve Medicine			(TICH). Patients had Glasgow Coma Score (GCS) ≤8.		Radix Salviae miltiorrhizae and Flos Carthami tinctorii) (N = 40) Vs. Control group (N = 40).	and at 3 months.	trial group (11.88 ± 0.97) vs. the control group (11.10±1.15) after treatment ($p < 0.01$). There was a significant difference between groups in the reduction of hematoma volume ($p < 0.05$). The trial group (4.48 ± 1.11) had a superior GOS vs. the control group (4.02 ± 0.91), ($p < 0.05$).	therapeutic course. No abnormal intracranial hematoma expansion or rehemorrhage was detected during the therapeutic course. No abnormality was found in the dynamic observation of the patients' coagulation spectrum, indicating DHI was effective and safe in treatment of TICH, with no possibility of hemorrhage. These results indicate that DHI may be considered as an effective agent in the treatment of TICH."	

Evidence for the Use of Inthrathecal Baclofen (ITB) Pump

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Meythaler 1996 (score = 6.5)	Intrathecal Baclofen vs Placebo	RCT/Crossover	Sponsored in part by grant from the United States Department of Health and Human Services, Centers for Disease Control and Prevention – National Center for Injury Prevention and Control to the University of Alabama Injury Control Research Center. No COI.	N=11 adults who had an acquired brain injury (9 Motor vehicle crash (MVC) 1 Gunshot wound (GSW) and 1 Anoxic episode; Mean	Age 25 (20-37)	N=11 All patients were randomized to receive a bolus injection of either intrathecal, preservative-free normal saline or 50 ug of baclofen diluted with preservative saline. Crossover phase at 48 hours.	Follow-up for baseline 1, 2, 4, and 6 hours post injection.	Lower extremity (LE) Ashworth baseline vs 4 hours; 4.2 ± 0.8 vs 2.2 ± 0.6 (p=0.0033). LE Ashworth score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 (p=0.0084) hr. 6 (p=0.0163). LE spasm score baseline vs 4 hours; 3.1 ± 1.0 vs 1.0 ± 0.7 (p=0.0032). LE Muscle spasm score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 (p=0.0073) hr. 6 (p=0.0049). LE reflex score baseline vs 4 hours; 3.2 ± 0.5 vs 1.0 ± 1.3 (p=0.0033). LE Reflex score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 (p=0.0086) hr. 6 (p=0.0085). Upper extremity (UE) Ashworth score baseline vs 4 hours; 3.3 ± 1.3 vs	"Intrathecal baclofen has the potential for improving, significantly, The quality of life in patients with acquired BI. The issue is whether there is a reduction in tone, and whether the dosage required to produce this change in spastic hypertonia may negatively affect the patient's cognitive function or have other untoward effects. Particular attention must be given to evaluating patients for cognitive changes and functional improvements, as well as the long-term costs of the system."	Small sample crossover trial. Intrathecal baclofen associated with reduced spastic hypertonia compared with placebo.

								1.9 ± 0.8 (p=0.0033). UE spasm score baseline vs 4 hours; 1.8 ± 1.3 vs 0.6 ± 1.0 (p=0.007). UE biceps reflex score baseline vs 4 hours; 2.7 ± 0.5 vs 1.7 ± 0.6 (p=0.0111).		
Meythaler 1999 (score = 3.5)	Intrathecal Baclofen vs Placebo	RCT	Sponsored by Medtronics, Inc. Commercial party with a direct financial interest in the results of the research supporting this article has conferred or will confer a financial benefit upon one or more of the authors.	N = 17 patients with TBI and intractable spasticity and dystonia for more than 6 months' duration recruited in a consecutive manner.	Mean age: 29± ll yrs.)	Patients were randomized to receive a bolus intrathecal injection of either preservative-free normal saline (N=not mentioned) Vs. 50 µg of baclofen. (N=not mentioned) A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 cc was injected.	Follow-up for data collection every 1 month, 3 months, 6 months, 9 months, and 1 year after pump placement.	After 1 year of continuous ITB treatment the average LE Ashworth score decreased from 3.5 ±1.3 (SD) to 1.7 ± 0.9 (p < .0001), spasm score from 1.8 to 1.3 to 0.2 ± 0.5 (p < .0001), and reflex score from 2.5 ± 1.1 to 0.1 ±0.3 (p < .0001). The average UE Ashworth score decreased from 2.9 ± 1.5 to 1.6 ± 1.0 (p < .0001), spasm score from 1.2 ± 1.5 to 0.2 ± 0.6 (p < .000l), and reflex score from 2.2 ± 0.5 to 1.0 ±0.8 (p < .0001). The average ITB dose required to attain these effects at 1 year was 302pg continuously infused per day.	"Continuous intrathecal infusion of baclofen is capable of maintaining a reduction in spasticity and dystonia in both the upper and lower extremities of TBI patients."	Small sample size. Data suggest that at one year, continuous infusion of Baclofen reduces spasticity and dystonia in both the upper and lower extremities.

Evidence for the Use of Occipital Nerve Blocks

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Naja, 2006 (8.0)	Occipital Nerve Block	RCT	Sponsored by the Makassed General Hospital and the suggestions of the peer-reviewers in the preparation of this article. No mention of COI.	N = 50 patients with cervicogenic headache.	The mean age of the block group is 46.44 years. 3 males, 19 females. The mean age of the placebo group is 47.36 years. 7 males, 18 females.	Block Group (N =25): received either both GON and LON blocks, or GON and LON with facial nerve blockade, depending on the extension of the headache. Vs. Placebo Group (N =25): received injections of an equivalent volume of preservative-free normal saline.	Two weeks.	At the two-week follow up the Block and Placebo group depicted the following data, respectively. Duration of pain relief (days): 3.67, 1.52, p=0.0001. Frequency of headaches/2 weeks: 5.50, 7.04, p=0.026. Number of analgesics consumed/2 weeks: Paracetamol (tablet 500mg) – 48, 70.96, p=0.0001; Dextropropoxyphene (capsule 30mg) – 18.33, 40.17, p=0.0001; Tramadol hydrochloride (tablet 50 mg) – 2.33, 5.56, p=0.006; Ketoprofen (tablet 100 mg) – 0.50, 4.30, p=0.01. Total Pain Index: 194.25, 329.96, p=0.0001.	"In conclusion, the nerve stimulator-guided occipital nerve blockade is a treatment that provides relief of CGH and accompanying symptoms for up to two weeks. This simple technique merits further investigation for patients suffering from CGH."	Some also injected with facial nerve blocks. Data suggest at 2 weeks post injection, block group had sig. reduction in cervicogenic headache and symptoms c/w controls. However, only 3.67 days vs. 1.52 days relief from NS injection. Analgesic use also decreased and return to functional activities better in block group.

Dilli 2015 (8.0)	ONB	RCT	Sponsored by CTSA grant number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). No COI.	N = 70 with ICHD (International Classification of Headache Disorders, second edition) II defined episodic	Aged 18 and 75 years; 20 females and 55 females.	Active intervention, 2.5 ml 0.5% bupivacaine plus 0.5 ml 20 mg methylprednisolone over the ipsilateral (N = 35) vs Placebo intervention, bilateral (bilateral headache) occipital nerve or 2.75 ml normal saline plus 0.25 ml 1% lidocaine without epinephrine (N = 35).	About 15-days	Those with at least 50% reduction in the frequency of moderate or severe migraine headache was 30% for both groups; 10/33 vs 9/30, Δ 0.00, 95% CI –0.22 to 0.23. Mean frequency of at least moderate (mean 9.8 versus 9.5) and severe (3.6 versus 4.3) migraine days / acute medication days (7.9 versus 10.0) not different at baseline.	"Greater ONB does not reduce the frequency of moderate to severe migraine days in patients with episodic or chronic migraine compared to placebo."	Data suggest occipital nerve blocks did not decrease frequency of moderate to severe headache days in patients with either episodic or chronic migraines c/w placebo.
Lauretti 2014 (7.5)	Occipital Nerve Block	RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache	Mean age: 43 years. 8 males, 20 females.	Group 5: GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic	2 and 24 weeks	Significant decrease in VAS ($p < 0.01$) was ovserved in all subcompartmental roups during 24 weeks compared to only 2 weeks of effective analgesia after classic GON technique ($p < 0.01$).	"[T]he suboccipital compartmental GON technique resulted in at least 24 compared to 2 weeks of analgesia when the same dosage of dexamethasone and	No placebo control. Randomization only involved an evaluation of different volumes of injectate (5, 10 or 15mL).

						iodine contrast and saline, 5 mL final volume) (N = 10) vs Group 10 GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic iodine contrast and saline, 10 mL final volume (N = 10) vs VS Group 15 GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic iodine contrast and saline 15 mL final volume		Rescue analgesics were reduced during first 2 weeks under GON and for at least 24 weeks for all groups. Analgesic effect persisted similarly for all 3 groups regardless of final volume.	lidocaine was applied by the classical technique, suggesting that the administration of the drugs near to the dorsal ganglion was more efficacious to counteract CH."	Data suggest no differences. All groups reported sig. pain reductions last 24 wks, although pain levels gradually rose.

						(N = 10).				
Cuadrado 2016 (7.5)	Occipital Nerve Block	RCT	No sponsorship or COI.	N = 36 women with chronic migraines (CM).	Mean age: 35.8 ±11.1 years.	Occipital nerve (GON) blocks with bupivacaine 0.5% (N = 18) vs Sham procedure with saline (N = 18).	At 1 hour, 1 week after and 1 week following treatment .	The GON block had significant results compared to the placebo in decreasing the amount of days per week with moderate-or-severe headache (MANOVA; p= 0.027), or any headache (p= 0.04). Pressure pain thresholds (PPT) differences at baseline (T=0) compared to treatment (T1) and follow up (T2) among groups were statistically significant for the supraorbital (T0–T1, p= 0.022; T0–T2, p= 0.031) and infraorbital sites (T0–T1, p= 0.013; T0– T2, p= 0.005).	"GON anaesthetic blocks appear to be effective in the short term in CM, as measured by a reduction in the number of days with moderate-to-severe headache or any headache during the week following injection."	Data suggest greater occip. nerve blocks had short term efficacy for chronic migraine attributed to decrease in moderate to severe headache days. Blocks also resulted in increase in pressure pain thresholds.
Inan 2015 (7.5)	ONB	RCT	No mention of sponsorship. No COI.	N = 84 with chronic migraine (CM).	Mean age 37.0 ± 9.1 group A and 37.3 ± 8.8 group B; 7 males, 65 females.	Group A, injections of bupivacaine GON blockade (N = 37)	4-weeks	1st month; Post-treatment values group B, ($p < 0.001$) vs placebo, ($p = 0.223$).	"[G]ON blockade with bupivacaine was superior to placebo and was found to be effective,	Data suggest greater occip. nerve blocks plus bupivacaine superior to placebo for decreasing number,

						vs Group B, injections of placebo GON blockade (N = 37).		2nd month; Headache duration for group A vs B; p < 0.001 vs p < 0.05. Both group's values 2nd and 3rd month values, (p < 0.001). Headache durations, at all follow-up periods, (p > 0.005).	safe, and cost-effective for the treatment of CM."	duration and severity of headache pain.
Gabrhelik 2011 (4.0)	ONB	Pilot RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache.	Mean age 45.90 (12.8) group A and 43.60 (9.2) group B; 13 males and 17 females.	Group A, greater occipital nerve block with steroid (N = 15) vs Pulsed radiofrequency treatment (N = 15).	Evaluated parameters were recorded before the procedures, and at 3 and 9 months after the treatment.	Median VAS before treatment; 5.5 in group A vs 5.9 group B. At 9-months; VAS of 4.3, (p < 0.05) in group A vs 3.1 group B, (p < 0.001). Before treatment / and 3 months after treatment; the median index MQS – III. 9.2 in both groups / 4.8 in group A vs 3.2 in group B, (p < 0.001).	"Greater occipital nerve blockade with a mixture of local anaesthetic and steroid and pulsed radiofrequency to the greater occipital nerve are both effective intervention techniques in the treatment of refractory cervicogenic headaches."	Pilot study. Claims blind, but likelihood seems low as one arm was an injection. Data suggest comparable results, with improved pain at 3mo, but then worsening pain at 9mo.

Evidence for Occipital Nerve Stimulation (ONS)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Gabrhelik 2011 (4.0)	ONB	Pilot RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache.	Mean age 45.90 (12.8) group A and 43.60 (9.2) group B; 13 males and 17 females.	Group A, greater occipital nerve block with steroid (N = 15) vs Pulsed radiofrequency treatment (N = 15).		Median VAS before treatment; 5.5 in group A vs 5.9 group B. At 9-months; VAS of 4.3, ($p < 0.05$) in group A vs 3.1 group B, ($p < 0.001$). Before treatment / and 3 months after treatment; the median index MQS – III. 9.2 in both groups / 4.8 in group A vs 3.2 in group B, ($p < 0.001$).	"Greater occipital nerve blockade with a mixture of local anaesthetic and steroid and pulsed radiofrequency to the greater occipital nerve are both effective intervention techniques in the treatment of refractory cervicogenic headaches."	Pilot study. Claims blind, but likelihood seems low as one arm was an injection. Data suggest comparable results, with improved pain at 3mo, but then worsening pain at 9mo.

Evidence for the Use of Occipital Nerve Blocks (ONS)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Silberstein 2012 (9.0)	ONS	RCT	Sponsored by St. Jude medical Neuromodulator Division.	N = 157 With Chronic Migraine.	Mean age 44.6(±12) 32 males, 124 females.	(N = 105) Received implantation of peripheral nerve stimulation (PNS)	12 weeks	Percentage of responders in the active compared with the control group. (95% lower confidence bound (LCB) of -0.06; p=0.55). patients that	"Study failed to meet its primary endpoint, this is the first large-scale study of PNS of the occipital nerves in CM patients that showed significant	Data suggest lack of efficacy. As well, only 17% vs. 13% considered responders.

			No conflict of interest for authors, SN, KR, JV, JO, JG, NM and PW. For all other authors there was COI.			device. The device was St Jude Medical Neuromodulation. Connected to the implantable pulse generator(IPG). These patients received programing for appropriate stimulation. vs (N = 52) Received implantation of peripheral nerve stimulation (PNS) device. The device was St Jude Medical Neuromodulation. Connected to the implantable pulse generator(IPG). Connected to a sham and did not receive stimulation programming.		achieved a 30 % reduction (p = 0.01). Active compared to control reduction of headache days (Active = 6.1), baseline = 22.4, Control = 3.0, Baseline = 20.1 (p = 0.008). reduction in migrated related disability (p = 0.001). direct report of pain relief (p = 0.001).	reductions in pain, headache days, and migraine-related disability."	
Slotty 2014	ONS	RCT	No sponsorship. JV and PJS are	N = 8 with ONS.	Ages 18 or older,	Group 1, effective Stimulation	Unknown	At baseline, group differences; VAS and MPQ, p < 0.0001 and	"ONS delivers consistent and reproducible results in the	Sample too small for reliable conclusions (n=8). Data suggest

(5.5)			consultants for SJM, receiving payment for preparing and giving educational presentations, as well as reimbursement for travel expenses. CW and SS are consultants for SJM and Spinal Modulation Inc, receiving payment for preparing and giving educational presentations, as well as reimbursement for		gender not specified.	(N = 8) vs Group 2, subthreshold Stimulation (N = 8) vs Group 3, no Stimulation (N = 8).		SF-36, p = 0.012. Subthreshold stimulation (Group 2) vs with no stimulation (Group 3), with a VAS score of 5.65 ± 2.11 and 8.45 ± 0.99, (p = 0.0031). Difference observed between pre-study and Group 1, (p = 0.091).	treatment of distinct medically intractable migraine.”	paresthesia not needed for pain reduction but supra threshold stimulation led to better results.

			travel expenses. AG is a consultant for Allergan, MSD, Bayer, Teva, Pfizer, Weber und Weber.							
Dodick, 2015 (5.0)	ONS	RCT	Drs Mekhail, Vaisman, Reed, Trentman, Goldstein, Narouze and Ordia, report no conflicts of interest, all other authors report a COI.	N= 157 patients with chronic migraines.	Mean age: 44.6 ±10.3 years. 91 females, 66 males.	All participants were implanted with a neurostimulation system. For 52 weeks the active group (N= 105) received appropriate stimulation of their implantable pulse generator (IPG). Control group (N= 52) had a sham program with no IPG stimulation. Control group received stimulation for 12 weeks, then received	Follow-up at 12, 24, and 52 weeks.	Significant results in reduction of headache days by 6.7 (±8.4) in the Intent-to-treat (ITT) group ($p<0.001$), and by 7.7 (±8.7) days in the intractable chronic migraine (ICM) group ($p<0.001$). Significant results in both migraine disability assessment (MIDAS) and Zung Pain and Distress (PAD) in both ITT and ICM groups at 24 and 52 weeks ($p<0.001$).	"Our results support the 12-month efficacy of PNS [peripheral nerve stimulation] of the occipital nerves for headache pain and disability associated with chronic migraine."	Open label phase, then DB-RCT. Data suggest peripheral nerve stimulation at 12mo decreased HA pain and intensity but sig. adverse events. High rates of adverse events and explanation within 12 mo.

						appropriate IPG stimulation for 40 weeks.				
Saper, 2010 (4.5)	ONS	RCT	Sponsored by GlaxoSmithKline (GSK), Johnson & Johnson, Eli Lilly, Merck, St. Jude Medical, Map Pharma, Nupathe, Zogenix, Neura Axon and Boston Scientific and Medtronic, Advanced Neuromodulation Systems, St. Jude Medical, the National	N=66 patients with intractable chronic migraine.	Mean age: 43±10.6 years. 13 males, 53 females.	AS Group: (n=28) adjustable stimulation VS PS Group: (n=16) preset stimulation VS MM Group: (n=17) medical management VS Ancillary Group: (n=5)	1 and 3 months	For AS group headache days per month reduced by 27.0±44.8%, 8.8±28.6% for PS, 4.4±19.1% for MM, and 39.9±51.0% for ancillary group. Actual headache days reduction corresponds to 6.7±10 for AS, 1.5±4.6 for PS, 1.0±4.2 for MM, and 9.1±12.3 for ancillary group. Pain reduction was 1.5±1.6 for AS, 0.5±1.3 for PS, 0.6±1 for MM, and 1.9±3.5 for ancillary group. Responder rate was 39% for AS group, 6% for PS group, 0% in the MM group. These differences are significant.	"The results of this feasibility study offer promise and should prompt further controlled studies of ONS in CM."	Feasibliity study, which is underpowered. Data not sig., but trend towards reduced pain in adjustable stim group.

			Institute of Neurological Disorders and Stroke and Mayo Clinic. SDS has consulted for Novartis. No mention of COI.							
Bono 2014 (4.0)	ONS	RCT	No sponsorship or COI.	N = 160 with chronic migraines or chronic tension-type headache.	Mean age: 41±12 years. 33 males, 127 females.	Real occipital transcutaneous electrical stimulation or OTES, pulse width 250 ms, frequency 40 Hz, intensity 20 mA (N = 108) vs Sham OTES, pulse width 250 ms, frequency 40 Hz, intensity 20 mA (N = 52).	3 months	% of responders in the real OTES vs with sham OTES, ($p < 0.001$). Multivariate analysis; CA / OTES treatment / and CA and OTES interaction; $p = 0.00016$ / $p = 0.003$ / and $p = 0.004$. Anxiety and mood between real vs sham, ($p = 0.6$ and 0.21).	"Severe CA is associated with decreased response to treatment with OTES in patients with CM and CTTH."	Data suggest the Occiptial transcutaneous electric simtulation group had sig. more responders than sham. But severe cutaneous allodynia associated with reduced response to the stimulation treatment in chronic migraine and chronic tension-type headache patients.

Serra, 2012 (3.5)	ONS	RCT	No sponsorship or COI.	N=34 patients with chronic migraines.	The mean age is 46 years. Author reported 76% women, 34% men.	Internal Neurostimulator On – Arm A: Vs. Internal Neurostimulator Off – Arm B: patients could switch stimulation on if their headache attacks increased in severity or frequency by 30% or more.	1 month, 3 month, 6 month, and 12 month follow ups.	Migraine Disability Assessment (MIDAS) at baseline, 1-month FU, 3-month FU, 6-month FU, and 12-month FU for Arm A are 70, 25, 20, 19, 14, p<0.001; Arm B scores are 8, 6, 6, 6 , 5, p<0.001 respectively.	"According to the results obtained, ONS appears to be a safe and effective treatment for carefully selected CM and MOH patients."	Crossover. But trial apparently unblinded as one arm of the trial could turn device on, and did so on average 4.9 days. Variable lengths of followup. Data suggest occipital nerve stimulation for chronic migraine and medication overuse headache may be of benefit for decreasing intensity and frequency of HAs and improving quality of life and reducing medication use at 1yr.

Evidence for the Use of Botulinum Toxin

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Barnes 2010 (7.0)	Neurotoxin vs Neurotoxin	RCT	Sponsored by Merz Pharmaceuticals GmbH, Germany Authors received lecture fees and honoraria for serving on advisory boards	N=192 adults who had suffered a stroke, brain injury, multiple sclerosis or cerebral palsy wrist	Mean Age 55.4 ± 14.3 with 81 females and 111 males	Group 1 (N=96) Was given NT 201 injection of a more dilute concentration (20 U/ml) with a maximum dose of 400 units at investigators discretion. Vs Group 2 (N=96) Patients were given the	Follow-up at baseline, 4 and 12 weeks. Safety follow up at 20 weeks.	Treatment response at week 4; 95 of the pre-protocol patients (57.6%; n=165). 20 U/ml group: 51 (63%) 50 U/ml group 44 patients (52.4%). Week 12	"[T]he administration of one set of NT 201 injections resulted in substantial improvements in functional disability and	88% of sample stroke patients. Data suggest NT201 whether 20 u/ml had similar

			for the sponsor, Compensation for the conduct of the study and honoraria for serving on advisory boards for the sponsor, compensation for the conduct of the study, some are employees of the study sponsor.	focal wrist ad elbow flexor spasticity;		same treatment and duration of treatment with a more concentrated NT 201 solution (50 U/ml).		Pre-protocol response: 44.6% Full Analysis Set difference between responds from Group 1 vs 2 at 4 weeks; 11.2% (95% Confidence interval (CI): -2.9, 24.6). Week 4 Ashworth 1-point improvement prevalence; 62.2% Week 12 Responses in all muscle group prevalence; 44%-56.8% Global Assessment of Treatment response (GATR) at week 4 improvement prevalence in both groups; patients 80.2% investigators 89.0%	muscle tone. This study supports the treatment of upper limb spasticity with NT 201 regardless of etiology."	efficacy for improving functional disability and muscle tone in a diverse population of patients with upper limb spasticity at 4 weeks after injection.
Simpson 2009 (6.0)	Botulinum neurotoxin vs Placebo vs Combination	RCT	Sponsored by Mount Sinai School of Medicine, and unrestricted grants by Allergen Inc. No COI.	N=60 adults who had a prior stroke (N=49) or traumatic brain injury (N=11);	Mean Age: Group 1 52.4 ± 14.5, Group 2 51.9 ± 17.3, Group 3 51.3 ± 14.7. There are 33 men and 27 women in	Group 1 (N= 20) Botulinum neurotoxin (BoNT) IM 100 units of BoNT-A, 0.5 mg human albumin, and 0.9 mg sodium chloride with oral placebo Vs. Group 2 (N=21) Placebo IM plus oral dose of Tizanidine (TZD) 4 mg tablets. Dose were taken twice per day and initiated at 2 mg/day to a maximum of 36 mg/day. Vs. Group 3 (N=19) Received both intramuscular injection	Follow-up at baseline, week 3, 6, 12, 18, 22.	Modified Ashworth Score (MAS) reduction in wrist flexor tone baseline minus week 3 - score (Mean change from baseline MAS); Group 1: -1.55 (1.19) Group 2: -0.25(0.64) Group 3: -0.67(0.91); (p=0.001). At week 6 - score (Mean change from baseline MAS);	"[I]njections of BoNT alone to treat focal or multifocal spasticity decrease muscle tone with few systemic effects and should be considered as the primary treatment before oral medications."	High dropout rate. Study suggests Botulinum more effective than tizanidine or placebo in reducing muscle tone in upper extremity from stroke or TBI.

					this study.	and oral placebo. Study duration was 22-24 weeks.		Group 1: -1.32 (0.89), Group 2: -0.22(0.88), Group 3: -0.68(1.00); (p=0.01). MAS reduction in finger flexor tone baseline minus week 3 - score (Mean change from baseline MAS); Group 1: -1.45(1.19), Group 2: -0.65(0.75), Group 3: -0.17(0.71); (p=0.001). At week 6 - score (Mean change from baseline MAS); Group 1: -1.37(1.46), Group 2: -0.39(0.98), Group 3: -0.26(0.93); (p<0.02). Finger Flexor tone in varying doses of BoNT vs all groups at week 3 and week 6 – improvement (MAS change from baseline); Any dose: 1.63(1.20) and 1.53(1.41) 100 unit dose improvement: 2.00 wk 3, (p=0.001 vs group 2 and p<0.001 vs Group 3), 1.62 (p=0.01 vs Group 2 and p<0.02		

								vs Group 3). 200 unit MAS reduction: 2.75 wk 3 (p=0.03 vs Group 2, p=0.01 vs Group 3), 2.75 wk 6 (p<0.02 vs Group 3). Adverse events BoNT vs TZD throughout trial – number (percentage); 8(40% vs 19 (90.5%) (p=0.0007).		
Verplancke 2004 (6.0)	Botulinum Toxin vs Saline	RCT	Sponsored by Allergen Inc. No COI.	N=35 Patients who had acquired an acute sever brain injury (N=20 for TBI) and (N=15 for neurosurgery /anoxia);	Mean Age N/A (17-70) with 10 women and 25 male patients.	Group 1 N=11 Control group that underwent standard program of physiotherapy. Vs Group 2 N=12 Received injections of saline as well as casting. Vs Group 3 N=12 Received injections of botulinum as well as casting.	Follow-up at baseline and 12 weeks.	Modified Ashworth Scale scores baseline vs 12 weeks, Group 2; 2.2 ± 1.056 vs 1.0 ± 1.297 (p<0.03). Group 3; 2.3 ± 0.77 vs 1.3 ± 1.619 (p=0.04). Range of Motion increase (Dorsal Ankle Flexion), baseline vs 12 weeks -Mean (Range), Group 1; 4.59º (-18º to +26º). Group 2; 11.65º (-22º to +28º). Group 3; 13.56º (-22º to 30º).	"[T]his study has shown that early active intervention is not only safe but probably has value. Active intervention with casting with and without botulinum toxin A is valuable for patients who are losing range of ankle movement following severe brain injury."	Blinding unclear between groups. Data suggest physiotherapy comparable to botulinum and both superior to placebo.
Smith 2000 (5.5)	Botulinum Toxin	RCT	This study was supported by an educational grant from Ipsen Limited UK who supplied the	N=21 hemiplegic patients with troublesome upper limb spasticity. N=19 with stroke and	Mean age placebo: 45 years, 500Mu 39 years, 1000 Mu 67 years,	Placebo injection (N=6) vs. 500 Mu (N=6) vs. 1500 Mu (N=6) vs. 1000 Mu (N=7) dose of botulinum toxin.	Assessments at baseline (week 0) and at 2, 6 and 12 weeks post dosing.	Mean (SD) modified Ashworth (median range) for the fingers: Changes at 6 weeks: placebo 2 (–3,3), 500Mu –3 (–4,–1), 1000Mu 0 (–3,1), 1500Mu –1 (–	"Botulinum toxin produced beneficial effects in spasticity and passive range of movement in the hemiplegic upper	Baseline comparability dissimilar re. ages (45 vs. 39 vs. 67 vs. 54yrs). at 6 weeks, data suggest

			botulinum toxin used in this study.	two with head injury.	1500 Mu 54 years. 10 males, 15 females.			4,–1), Combined dose–2 (–4,1)***; p<0.01.	limb. Increasing the dose increased the magnitude of response for impairments in some muscle groups but had little effect on duration of response."	botulinum associated with improved passive ROM in hemiplegic upper limb and reduced spasticity and dose increases increased response but not response durations.
Francisco 2002 (5.0)	High volume Botox vs low volume Botox	RCT-Pilot Study	Sponsored by grant from the national Institution on disability and Rehabilitation Research, U.S Dept. of Education, Washington, DC. No COI.	N = 13 adults whom had modified Ashworth scale scores of 3 both wrist and finger flexors;	Mean Age 44.5 (27-70) with 9 males and 4 female patients.	Group 1 (N = 6) (N= 1 for TBI, 5 for Stroke) Group received High-Volume Botulinum Toxin-A (BTX-A) solution of 50 units per 1 ml of preservative saline. Vs Group 2 (N = 7) (N=2 for TBI 5 for Stroke) Group received Low-Volumes BTX-A solution containing 100 units per 1 ml of preservative free saline.	Follow-up for 4, 8, and 12 weeks.	Modified Ashworth score (MAS) baseline vs.4 weeks, 8 weeks, and 12 weeks. Group 1 decreased 1.8 ± 0.7, 1.9 ± 0.9, and 1.7 ± 1.2 at 4, 8, and 12 weeks respectively vs group 2 decreased 1.3 ± 0.4, 1.4 ± 0.7. and 0.9 ± 0.6 as same post injection periods. (p<0.05) decrease for all groups and follows ups. MAS wrist flexor score 4 weeks vs 12 week significantly higher for both groups at 12 weeks (p=0.045) (weakening of treatment) Group 1	"At the doses used in this study, wrist and flexor spasticity secondary to stroke or traumatic brain injury was significantly reduced, as demonstrated by decreases of at least one point in the MAS. This improvement was maintained up to 12 wk after BTX-A administration. The decrease in MAS scores was also consistent with the perceived clinical improvement by	Study methods sparse. No placebo control.

								vs group 2 Global Rating Scale (patient) at 8 weeks, 2.0 ± 0.6 vs 3.3 ± 1.1 (p=0.041) Group 1 vs Group 2 Global Ratings Score (investigator scores) at 8 weeks; 1.7 ± 0.8 vs 3.9 ± 0.7 (p=0.003) at 12 weeks; 3.0 ± 1.3 vs 4.6 ± 1.0 (p=0.045)	the patient (or caregiver) and by a blinded investigator. When two different volume preparations of the same BTX-A dose were compared, there was a trend in favor of the high-volume preparation, although this difference did not reach statistical Significance."	

Evidence for the Use of Meniett Device

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Gates 2004 (7.0)	TBI	RCT	Sponsored by Medtronic Xomed as an unrestricted grant to each of the 4 study centers. No mention of COI.	N = 77 with clinical diagnosis of active, definite, unilateral cochleovestibular Meniere's disease causing disruptive levels of vertigo.	Aged 33 to 71 years; 35males and 42 females.	Treatment group, with an active Meniett device (N = 34) vs Control group, an identical device to treatment group that did not generate pressure (N = 33).	4-months	During 2 weeks; median proportion of vertigo days was 0.13 (0.07-0.36) for pre-tube placement vs 0.21 (0.07-0.36) for post-tube placement, (p = 0.34). Vertigo score per month as the dependent variable and treatment group and treatment month as the predictor variables was (p = 0.03 for treatment group vs treatment	"The Meniett device is a minimally invasive, safe, and efficacious intermediate treatment for people with substantial vertigo uncontrolled by medical therapy."	Data suggest Meniett device appears helpful for controlling vertigo.

								month (p = 0.053).		
Gates 2006 (4.5)	Meniett Device	RCT	Supported by an unrestricted grant from Medtronic Xomed, Inc. No COI.	N = 58 with active, unilateral cochleovestibular disease.	Mean Age: 48.9 ± 9.3 years. 20 males, 38 females.	Meniett Device Group: (N =29) low sodium diet using meniett device 3 times per day and maintain tympanostomy tube in affected ear vs Placebo Group (N =29) low sodium diet, placebo meniett device	2 years	Thirty-nine of 58 patients had remission or greatly improved results, 14 dropped to receive surgery. Of the 43 patients with active vertigo, 20 went in remission. On average, achieved remission in 2.8±3.7 months. Of remaining participants, 8 improved and 2 worsened. Only 7 of 35 had relapse with Me´nière's disease.	"Use of the Meniett device was associated with a significant reduction in vertigo frequency in about two thirds of the participants, and this improvement was maintained long term."	2-year follow-up of Gates 2004. Suggest Meniett device associated with reduction in vertiginous symptoms.
Ödkvist, 2000 (4.5)	Meniett Device	RCT	No mention of sponsorship or COI.	N = 56 patients with Meniere's disease.	Age range 20-65. No mention of sex.	Treatment group (N =31) received 2 weeks of treatment consisting of repeated pressure pulses applied to the middle of the ear via ear canal. vs Placebo group (N =25) was set up to a similar device, but did not	2 weeks from baseline	Hearing threshold levels before and after treatment with active Meniett were significantly different from 0 at the frequencies 500 Hz ($p<0.03$) and 1 kHz ($p<0.01$) A significant improvement in frequency and intensity of vertigo, dizziness, aural pressure and tinnitus was found in the active group	"The study showed an improvement in the inner ear symptoms after Meniett treatment."	Data suggest improvement at 500Hz and 1000Hz for pure tone audiometry in Meniett group.

						receive any stimulation.				

Evidence for the Use of Transcranial Direct Current Stimulation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Ulam 2015 (4.5)	TDCS	RCT	No sponsorship or COI.	N = 26 recovering from TBI.	Mean age of 33.52 years; 22 males and 4 females.	Active tDCS group, 20 minutes session of 1mA anodal stimulation to the left dorsolateral prefrontal cortex, on 10 consecutive days (N = 13) vs Sham TDCS group, electrodes place in the same locations as treatment (N = 13)	10-day treatment	Delta yielded a significant difference between active and sham TDCS groups at F3, (p = 0.043). Decreases in delta were correlated with improved performance on neuropsychological tests for the active group.	"Results suggest that 10 anodal TDCS sessions may beneficially modulate regulation of cortical excitability for patients with TBI."	Data suggest TDCS may modulate cortical excitability in TBI patients. No meaningful clinical measures, as the study was about potential mechanisms.
Yoon 2014 (3.0)	TDCS	Sham-controlled trial. Non-RCT	Sponsored by National Research Foundation of Korea and SNUBH Research Fund. No COI.	N = 16with chronic neuropathic pain.	Mean age of 27.5 years; 12 males and 4 females.	Active TDCS (N = 10) vs Sham TDCS (N = 6)	No mention of follow up.	There was significant decrease in NRS for pain in the active TDCS group (P = 0.016) but not the sham group (P = 0.102). The active TDCS group alleviated pain interference with daily life while there was no effect on pain interference with mood or sleep (P = 0.380, P = 0.135). Also, TDCS efficacy in the active group was found to correlate with metabolic changes in the cerebellum and left medulla.	"[F]indings suggest that, similar to invasive MCS, noninvasive TDCS has a potential role in alleviating neuropathic pain."	Data suggest increased metabolism in the medulla and decreased metabolism in the left DLPFC post TDCS compared to sham.

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:
Zhao, 2015 (8.0)	Functional Electrical Stimulation	RCT	Sponsored by the Science Foundation on Traditional Chinese Medicine (TCM)/Integrative Medicine of the Tianjin Administration of TCM (grant no. 11031). No COI.	N=60 patients with muscle spasticity after brain injury.	The mean age for the 100 Hz group was 62 years. 15 males, 5 females. The mean age for the 2 Hz group was 63.5 years. 16 males, 4 females. The mean age for the Sham group was 62.45 years. 15 males, 5 females.	100 Hz group – received 100 Hz transcutaneous electrical acupoint stimulation (TEAS). N=20. Vs. 2 Hz group – received 2 Hz transcutaneous electrical acupoint stimulation. N=20. Vs. Sham group – received 0 Hz transcutaneous electrical acupoint stimulation. N=20.	After 1 month and 2 months.	The MAS score for the wrist at Week 2, 3, 4, and Month 1 depicts a significant difference between the 100 Hz and sham, $p<0.05$. Week 2 depicted a significant difference between the 100 Hz and 2 Hz, $p<0.05$. Week 4 depicted a significant difference between the 2Hz and the sham. The MAS scores for the elbow, shoulder, knee, and ankle were changed with 100 Hz or 2 Hz treatments.	"TEAS appears to be a safe and effective therapy to relieve muscle spasticity after brain injury, although large-scale studies are required to further verify the findings."	Data suggest that at one month post intervention muscle spasticity was significantly decreased in the TEAS 100 Hz group compared to both the TEAS 2 Hz and control groups.
Jonas 2016 (7.0)	Acupuncture	RCT	Funded by a grant from the Department of Defense Telemedicine and Advanced Technology	N=43	40 males, 5 females; Mean age 34.	(N=15) Auricular Acupuncture (AA). (N=14) Traditional Chinese Acupuncture [1196]. (N=14) Usual Care (UC)	Week 6, 12	Headache Impact test (HIT) improved in TCA and AA but not UC. AA, -10.2% [-6.4	"In this small exploratory study, AA and TCA acupuncture improved headache-	Data suggest both AA and TCA decreased headache scores via

			Research Center. No COI.			for 6 weeks than 6 weeks AA treatment.		points]; TCA, -4.6% [-2.9 points]; UC, +0.8% [+0.6 points]. AA significantly improved vs UC, (p=0.0079). Global pain score decreased substantially in both TCA and AA vs UC, (p=0.0036, p=0.0155, respectively). Usual pain decreased more in TCA group vs UC (p=0.0008). TCS & AA vs UC in Numerical rating scale (NRS), Pain now (p=0.0021), Pain Usual (p=0.0153), Pain Best (p=0.0004).	related QoL more than UC in Service members with TBI and resulted in only a few minor adverse effects."	HIT when compared to UC.
Zolloman 2012 (3.5)	Acupuncture	Randomized Pilot Study	Work supported by US Army Medical Research and Material Command (CDMRP). No COI.	N=24	Group 1: 7 males, 5 females; Mean age 44.5±15.2. Group 2: 2 males, 6 females; Mean age 43.5±16.1.	Group 1: control group received no acupuncture, only described medical history and prescribed sleep aid by study physician. Group 2: received same treatment but also 20 minutes of acupuncture twice weekly.	Follow up at baseline and twice weekly for 5 weeks.	Baseline vs post treatment: group 2 showed improvement (Z=-3.07, p<0.01), same decrease from baseline line to 1 month. Group 1 did not improve significantly post-treatment	"This pilot intervention study, although not conclusive, supports the contention that acupuncture has a beneficial effect on perception of	Dropouts before study enrollment /completion results in substantially unequal groups (n=8 v 12) and trends towards many

								(Z=-1.75, p=0.08), and baseline vs 1 month (Z=-1.41, p=0.16). Repeatable battery for the Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Test (PASAT) improved in group 1 but not group 2, RBANS: Z=-2.81, p<0.01 vs Z=-0.52, p=0.60. PASAT: Z=-2.50, p=0.01 vs Z=-1.47, p=0.14. Depression improved in group 1 (Z=-2.68, p<0.01) not in group 2.	sleep or sleep quality and on cognition in patients with TBI."	baseline differences. Educational control group may have been equivalent to placebo-control.

Evidence for the Use of Functional Electrical Stimulation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*

Leung, 2014 (7.0)	Functional Electrical Stimulation	RCT	Sponsored by The Rehabilitation and Disability Research Grants of the Royal Rehabilitation Centre Sydney, and the Research Infrastructure Block Grants of the University of Sydney. No COI.	N=36 patients with severe traumatic brain injury and ankle plantarflexion contractures.	Experimental Group mean age was 38 years. 14 males, 3 females. Control group mean age was 38 years. 15 males, 3 females.	Experimental Group - tilt table standing, electrical stimulation and ankle Splinting. N=17. Vs. Control Group - tilt table standing only. N=18.	Week 10.	Passive Ankle Dorsiflexion (PAD) for experimental minus control group for week 6 minus week 0 and week 10 minus week 0, respectively at 12 Nm (deg) was –3(–8 to 2) and –1(–6 to 4). At 9 Nm (deg) was –1(–5 to 3) and –1(–6 to 4). At 7 Nm (deg) 1(–3 to 5) and 0(–5 to 5). At 5 Nm (deg) was 2(–2 to 6) and 1(–3 to 6). At 3 Nm (deg) was 2(–3 to 7) and 0(–6 to 5).	"Contrary to expectations, the present study showed that 6 weeks of regular standing on a tilt table combined with electrical stimulation and ankle splinting did not provide added benefits when compared to a less-intensive program of tilt table standing alone, for people with severe traumatic brain injury and ankle contractures."	Experimental study without clinical outcomes. Baseline differences between groups for time from injury to baseline assessment. Data suggest similar efficacy between groups.
Lairamore, 2014 (6.0)	Functional Electrical Stimulation	RCT	No mention of sponsorship or COI.	N=32 patients with stroke or brain injury.	The mean age for the experimental group was 54.8 year. 10 males, 3 females. The mean age for the control group was 47.8 years. 6 males, 7 females.	Experimental Group – received Functional Electrical Stimulation. N= 13. vs. Control Group – received sensory stimulation. N=13	No follow up mentioned.	Differences between the experimental and control group have a p values of p=0.83 in change in gait speed, p=0.77 FIM locomotion scores, p=0.79 EMG activity of the TA muscle during the swing phase of gait, and p=0.71 in loading phase of gait.	"The current results with this small sample suggest a low dose of gait training with single channel FES did not augment gait nor EMG activity beyond gait training with sensory stimulation; therefore, clinicians will likely be better served using a larger dose of FES or multichannel FES in this clinical population."	Data suggest lack of efficacy of functional ES on gait recovery post-neurological injury.

Peri, 2001 (6.0)	Functional Electrical Stimulation	RCT	No mention of sponsorship or COI.	N=10 coma patients	The mean age of the patients was 40 years. 8 males, 2 females.	ES – received 300 µs pulses at 40 Hz electrical stimulation to the median nerve via 'Respond Select' by EMPI. N=6. Vs. Control - received a "sham" stimulation. N=4.	3 months.	The ES treatment group emerged from coma an average of 2 days earlier than the control group, p=0.31. The FIM/FAM results depict that the ES patients had a better functional status with a mean score 114 than the control patients with a mean score of 64.5. The difference is not statistically significant.	"These data show an interesting trend, although statistical power was limited in this small pilot study, suggesting the need for a larger trial."	Small sample. Pilot Study. Data suggest a trend towards ES group awakening from coma 2 days sooner than controls.

Evidence for the Use of Neuromuscular Electrical Stimulation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Terre, 2015 (7.0)	Neuromuscular Electrical Stimulation	Allied Health	Sponsored by a grant of the FUNDACIÓN MAPFRE. No COI.	N=20. 14 stroke patients and 6 patients with severe traumatic brain injury.	The mean age of patients in the NMES group is 46 years. 6 males, 4 females. The mean age of the patients in the SES group is 51 years. 6 males, 4 females.	NMES group - Patients underwent NMES and conventional swallowing therapy. N=10. Vs. SES group - patients underwent sham electrical stimulation (SES) and conventional swallowing therapy. N=10.	3 months.	The Functional Oral Intake Scale (FOIS) score prior treatment for the NMES group was 2, SES group was 2.1. After treatment score was 4.9 NMES group and 3.1 SES group. The difference is p=0.0005. At 3-month follow-up, FOIS score is 5.3 NMES and 4.6 in SES group. Not	"Neuromuscular electrical stimulation significantly accelerated swallowing function improvement in patients with orophary	Data suggest NMES therapy accelerate the swallowing function in patients with oropharyngeal dysphagia resulting from an acquired

								statistically significant.	ngeal dysphagia secondary to acquired brain injury."	brain injury.
Beom, 2015 (5.0)	Neuromuscular Electrical Stimulation	Allied Health	Sponsored by Cyber-medic Corp., Iksan, Republic of Korea. No COI.	N=132	The mean age of the SM group was 64.4 years. 33 males, 33 females. The mean age of the SI group was 59.8 years. 42 males, 22 females.	SM group - received hyolaryngeal NMES of the suprahyoid muscles only with Stimplus. N=66. Vs. SI group - received electrical stimulation of the suprahyoid muscle with one pair of electrodes and of the infrahyoid muscle with another pair of them. N=66.	No follow-up.	The Functional Dysphagia Scale score report a decrease in scores 42.0 ± 19.1 to 32.3 ± 17.8 in the SM group and from 44.8 ± 17.4 to 32.9 ± 18.8 in the SI group, after electrical stimulation, $p<0.001$, respectively. The Swallow Function Score increased from 3.3 ± 1.8 to 4.2 ± 1.6 in the SM group and from 2.8 ± 1.8 to 4.0 ± 1.8 in the SI group, after electrical stimulation, $p<0.001$, respectively.	"In conclusion, electrical stimulation of the suprahyoid muscle showed no significant differences in FDS scores and SFSs from that of the infrahyoid muscle. The results of this study suggest that both SM and SI therapies induced	Data suggest similar efficacy between groups. (ES to suprahyoid muscles similar to ES to infrahyoid muscles) Significant number of dropouts in both groups.

									similar improvements in swallowing function in brain-injured patients.”	
Alon, 1998 (3.5)	Neuromuscular Electrical Stimulation	Allied Health	No mention of sponsorship or COI.	N=20. 13 patients who survived a cerebrovascular accident and 7 with TBI.	The mean age of the patients is 51.65 years. 14 males, 6 females.	No comparison group.	No follow-up.	ANOVA test scores from flexion at rest to flexion immediately after a 10-meter walk for the elbow are 14.3 ± 3.5 to 15.5 ± 0.5, respectively. P<.001. For the wrist are 11.5 ± 3.1 to 8.6 ± 0.9, respectively, p<.001. Active wrist extension and flexion increased by 12.7 ± 0.5 and 9.0 ± 3.3 degrees, respectively. P<0.01.	“Application of the NESS system for three to four hours daily improves selected impairments and may help to restore partial hand functions of patients with chronic stroke or head injury.”	Small sample. Data suggest use of NESS improved some functions in TBI and stroke patients as 80% [16385] patients were able to hold a 1 kg weight with an active NESS system vs only 3 patients without active NESS.

Evidence for the Use of Behavioral Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*

McDonald 2008 (6.0)	Behavioral Programs	RCT	Sponsored by the Australian National Health and Medical Research Council. McDonald is an author of The Awareness of Social Inference Test, which is used as an outcome measure in this study, and receives royalties for its sale. No COI.	N = 51 with traumatic brain injury and social skills deficits.	Mean age for Skills training / Social / and Waitlist groups: 36.3 ± 10.7 / 33.1 ± 11.7 / and 35.2 ± 11.3 years, 40 males and 11 females.	Social skills training program of 12 weekly 3-hour group sessions with therapist plus 1 weekly individual session with clinical psychologist (N = 18) vs Social group program of 12 weekly sessions focused on group activities for companionship (N = 17) vs Waitlist group (N = 16).	12-weeks	No sig. difference between groups in any of the outcomes variables assessed, except on Partner Directed Behavioral Skill (PDBS) scores improved significantly across all three groups (p=0.004).	"[D]espite the small numbers and the severe, chronic nature of disability experienced by the participants, improvements in social behavior were apparent especially in a reduction in self-centered behavior and greater effort to involve the conversational partner."	Data suggests limited positive effects from social skills training in patients with severe or chronic brain injuries.
McLaughlin 2013 (5.0)	Behavioral Programs	RCT	Sponsored the National Institute of Child Health and Human Development. No COI.	N = 201 with TBI.	Age range 18 – 61 years, 140 males and 62 females.	Intervention, an online screening tool on the BIAUSA Web site (N = 97) vs Controls used the Web site for a minimum of 30 minutes (N = 104). Outcome measures: caregiver knowledge, skill application, behavioral intention, and overall life satisfaction.	3-months	(51%) had 1 visit to the program Web site, 24% 2 visits, 18% 3 or more visits, and 7% did not visit the Web site. The knowledge item posttest change score, (r = 0.24, p = 0.016).	"This study demonstrated the effectiveness of a Web-based intervention in teaching effective skills to caregivers advocating for a family member with brain injury."	Data suggest use of a web-based training intervention may be of benefit to teach the necessary skills to caregivers caring for TBI family members.
Brown 2015 (5.0)	Behavioral Programs	RCT	Sponsored by the Department of Education, National	N = 257 with moderate–severe TBI 1 or more	18 years of age or older, 97 males and 160 females.	Curriculum group, 6-hour sessions, consistent with the design of	4-months	Between groups, ABRS scores increased after	"Curriculum-based advocacy training was not superior to a self-directed approach in	Data suggest equal in efficacy.

			Institute on Disability and Rehabilitation Research, Mayo Clinic TBI Model System Center Grant. No COI.	years post-injury.		a community-based practical behavioral trial and REAIMS framework (N = 129) vs Allocated to Usual Care group (N = 128). Outcome measure; advocacy Behaviour Rating Scale (ABRS).		intervention in both groups, p = 0.4447 and 0.1282. ABRS ratings significantly greater after an intervention for both letters, (p < 50.001) and videos (p < 50.001).	improving ABRS scores."	
Hanks 2012 (4.0)	Behavioral Programs	RCT	Sponsored by the U.S. Department of Education-National Institute of Disability Research and Rehabilitation—The Traumatic Brain Injury Model Systems Project. No COI.	N = 199 with TBI.	Mean age for control and mentoring group: 40.90 ± 17.33 / 38.46 ± 17.60 years, 136 males and 22 females.	Mentoring (N = 96) vs No mentoring (N = 62). Outcome measures: Peer Mentoring Questionnaire; Brief Symptom Inventory-18; Family Assessment Device (FAD); Coping Inventory for Stressful Situations; Short Michigan Alcohol Screening Test; Medical Outcomes Study 12-Item Short-Form Health Survey; and Community Integration Measure.	2 years	Differences in subjective perception of community integration and levels of depression or anxiety, (p = 0.35). 88% in the mentoring group reported positive experience. Those who received mentoring had better behavioral control and less chaos in the living environment	"Mentoring can be an effective way to benefit mood and healthy coping after TBI, and it can help to prevent maladaptive behaviors, such as substance abuse and behavioral dyscontrol, in the living situation."	Data suggest mentoring may increase coping post TBI.

								/ lower alcohol use / less emotion-focused / avoiding coping / and good physical quality of life: p = 0.04 / 0.01 / 0.04 / 0.03 / and 0.4.		
Carnevale 2006 (4.0)	Behavioral Programs	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research, U.S. Department of Education and the Henry H. Kessler Foundation. No COI.	N = 47 with a diagnosis of TBI.	Mean age 40.5 ± 12.2, 56 males and 18 females.	Control group, no education (N = 17) vs Education only: full education from the Natural Setting Behavior Management (NSBM) staff (N = 14) vs Full NSBM: personalized education from NSBM staff (N = 16).	Follow-ups were at 7, 16, and 30 weeks.	No significant differences in ANOVA at 7 and 16 weeks, and at 30 weeks (F = 3.32, p = 0.05). The NSBM and the education only groups (Tukey honestly significant difference, P < 0.04). Average frequency at baseline correlated with frequency at 7, 16, and 30 weeks post baseline (r =	"A program of caregiver education and individualized behavior management in natural settings can decrease the frequency of disruptive behavioral challenges."	Data suggest the rate of disrupture behavior in the NSBM group declined.

								0.81, r = 0.76, r = 0.75; all P < 0.001). When controlling for baseline emotional exhaustion, treatment effects did not reach significance at 7 and 16 weeks, but did at 30 weeks (F = 4.26, P < 0.03).		

Evidence for the Use of Comprehensive Integrated Inpatient Interdisciplinary Rehabilitation Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Vanderploeg 2008 (4.5)	Comprehensive Integrated Inpatient Interdisciplinary Rehabilitation Programs	RCT	Sponsored by the Defense and Veterans Brain Injury Center, Uniformed Services University of the Health Sciences, Bethesda, MD, the Department of Veterans Affairs, Veterans Health Administration, and a Department of Defense award administered	N = 366 with moderate to severe nonpenetrating TBI within the last 6 months with a Glasgow Coma Scale score of ≤12, in a coma for 12+ hours, PTA for 24+ hours, RLAS cognitive level of 5 to 7, 18 years old or older, active duty military member or veteran, and	Mean age for cognitive and functional rehabilitation groups: 33.2 ± 13.5 / 31.7 ± 12.9, 340 males and 26 females.	Cognitive-didactic treatment targeted 4 cognitive domains impaired by TBI: attention, memory, executive functions, and pragmatic communication; one on one sessions (N = 184) vs Functional-experiential treatment with the use of real-life performance situations and common tasks to	1-year	NS between groups at 1 year for: percent who returned to work or school and percent living independently. Cognitive FIM at end of treatment: cognitive group (27.3±6.2) vs functional group (25.6±6.0), p = 0.01. NS	"The results from this trial, with the largest sample ever treated in a randomized controlled rehabilitation trial of TBI, indicated no difference between cognitive-didactic and functional-experimental approaches to brain injury	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term

			through the Henry Jackson Foundation. No COI.	need of 30 days or more of acute interdisciplinary TBI rehabilitation.		compensate for functional deficits after brain injury; group sessions (N = 182).		between groups for motor FIM and DRS. Memory problems [1274]: cognitive 22.2% v. functional 27.6%, p = 0.05. Those with more education more often lived independently at 1 year in the functional group (69.1%) compared to the cognitive group (47.4%), p < 0.02. Younger participants were more often working at 1 year in the cognitive group (53.3%) compared to the functional group (37.8%, p<0.03).	rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	functional cognition

Evidence for the Use of Multidisciplinary Rehabilitation Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*

Powell J 2001 (7.5)	Multidisciplinary Rehabilitation Programs	RCT	No mention of COI. The research assessor was funded by a grant from the Medical Research Council, and the treatment programme was funded by the Department of Health.	N= 110 Patients who sustained severe TBI between 3 months and 20 years previously, and had no other neurological conditions.	Mean age: 34.5; (Males 71, Females 23)	Outreach group (N=54) vs. Information group (N=56) (No other description of study design and comparison groups)	Follow up for an average of 24.8 months	The outreach participants were significantly more likely to show gains on the BI (Barthel index) and the BICRO-39 (brain injury community rehabilitation outcome-39) total score and self-organization and psychological wellbeing subscales. There were likewise strong trends ($p<0.10$) for BICRO personal care and mobility, and on the FIM+FAM for personal care and cognitive functions. Differential improvements were not seen for indices of socializing, productive employment, anxiety, or depression. Median	This is the first RCT of multidisciplinary community rehabilitation after severe TBI, and suggests that even years after injury it can yield benefits which outlive the active treatment period.	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury occurrence not correlated to amount of gains.

								changes on individual subscales were small, reflecting the diversity of the clinical population; however, 40% of outreach but only 20% of information participants made a clinically significant improvement of 2+ points on at least one BICRO-39 scale. Time since injury was unrelated to the magnitude of gains.		
Cicerone 2008 (7.0)	Multidisciplinary Rehabilitation Programs	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No COI.	N = 68 with traumatic brain injury (TBI) recruited from clinical referrals and the community.	Standard Neurorehabilitation group 34.5 ± 12.4 Intensive cognitive rehabilitation group 38.7± 11.1	Standard neurorehabilitation, includes physical, occupational and speech therapies (N = 34) vs. Intensive Cognitive Rehabilitation, includes communication group, cognitive group and life skills group (N = 34). Both groups received 15 hours of treatment for week for 16 weeks. Primary/Secondary outcomes; Community	6 months	There were no significant main effects for treatment or condition on the CIQ / PQOL / NP scores / Self – efficacy scores. 74% participant after completion of the study required follow - up	"Improvements seen after intensive cognitive rehabilitation may be related to interventions directed at the self-regulation of cognitive and emotional processes and the integrated treatment of cognitive, interpersonal, and functional skills."	Data suggest a comprehensive NP rehab plan post TBI improves self perceived quality of life and community functions.as measured by CIQ and PQOL.

						Gender (M:F) 46:22	integration (CIQ), Life satisfaction (PQOL) / NP functioning, Perceive self-efficacy, community based-employment.		treatment. Participants showed improvement on CIQ scores from post treatment to follow – up (p = 0.04).		

Browne 2013 (4.5)	Multidisciplinary Rehabilitation	RCT	Sponsored by the Australian and New Zealand College Of Anaesthetists and the State Health Research and Advisory Council of Western Australia. No COI.	N = 142 non-severe head injured trauma inpatients.	Mean age of 37 years, 106 male and 36 female.	Intervention Multidisciplinary Intervention or MI (N = 69) vs Control, usual care or UC (N = 73).	1, 3, and 6 months	Intervention group reported significantly greater relief from pain vs the control, ($p < 0.05$). At 6 months, alcohol use predicted a significant 26%, 49%, 56%, and 30% of the variance in pain, depressive, and PTSD severity, and physical mobility, respectively. 24% of the UC group below the cut-off for being at risk of developing PTSD/Depression received new clinical diagnoses at 6 months vs none of the 'not at risk' MI group.	"[T]he multidisciplinary intervention was not superior to usual care in reducing pain and psychological symptom severity, and improving functional outcomes within the first 6 months when overall group outcomes were compared."	Signficiant loss to follow-up for 6 month outcome analysis. Data suggest importance of early multidisciplinary programs to decrease and prevent traumatic injury disability.

Barreca 2003 (4.0)	Multidisciplinary Rehabilitation	RCT	Sponsored by the Ontario Neurotrauma Foundation. No mention of COI.	N = 12 with acquired brain injury.	Mean age 41.3 (1.5) ranging from 17 to 66 years, 10 male and 3 female.	Treatment A received an enriched stimulus environment, collaborative multidisciplinary interventions and additional yes/no response training (N = 7) vs Treatment B received the standard hospital environment and interventions (N = 6).	8 weeks	No order effect AB vs BA, (p = 0.60), but a trend towards statistical significance for increased responsiveness with treatment A, (p = 0.07). Inter-rater reliability (n = 10) ranged from fair-to-good, intra class correlation (ICC) 0.51; 95% (CI) (0.29–0.93). Post-hoc analyses showed statistically significant increased responsiveness for 4 participants with treatment A, (p < 0.001).	"Evidence is provided that enhanced communication strategies can improve responsiveness in a sub-group of participants with severe acquired brain injuries."	Randomized crossover study design. Data suggest enhanced communication may improve responsiveness in acquired brain injury patients.

Evidence for the Use of Home and Community-Based Rehabilitation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Powell 2002 (7.5) RCT	Home and Community Based Program	RCT	Sponsored by the Medical Research Council and Department of Health. No mention of COI.	N = 110 with sustained severe traumatic brain injury (TBI) between 3 months and 20 years previously.	Age 16 – 65.	Information group received assessment and limited treatment, with pursuing referrals to patient services (N = 56) vs Outreach treatment for 2 – 6 hours a week, plus goal planning framework for 27.3 weeks (N = 54). Primary outcomes: Barthel Index, brain injury community rehabilitation outcome-39 scales (BICRO-39). Secondary; functional independence/assessment Measures (FIM+FAM). Outcome measures; Barthel Index, brain injury community rehabilitation outcome-39	24.8-months	Barthel Index (BI) / Functional Independence Assessment Measure (FIM+FAM) / and Brain Injury Community Rehabilitation Outcome-39 (BICRO-39): 35% vs 20%, $p < 0.05$ / median score change on the BICRO-39 were greater for those in the outreach vs the information group for the total score / and mean rank 53.2 vs 40.4, ($p < 0.03$). Clinically significant improvement / high success rates; 71% compared 40% in the outreach group / 2.0 points compared to 1.0 success scores.	"In patients with severe traumatic brain injury, a multidisciplinary community-based outreach rehabilitation program improved social functioning."	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury occurrence not correlated to amount of gains.

Evidence for the Use of Opioid/Chemical Treatment Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Tweedly 2012 (5.5)	TBI	Treatment	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	"There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach statistical significance…. Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population."	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.

Corrigan 2005 (3.0)	TBI	Treatment	Funding for this project was provided by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration , via Grant 5 KD1 TI12013. No mention of COI.	N= 195	138 males, 57 females. Mean age is 36.6 years.	195 participants randomly assigned into 4 groups. [170] Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incetive.	Appoin tments unspeci fied and varied by particip ant prefere nce. Fol low up at 3 and 6 months .	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview (45%) and attention control (45%) groups. Significance indicated through client signing an individualized service plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign (*M* = 22.8 days, *SD* = 14.7), (*M* = 44.0 days, *SD* = 35.8) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	"Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational interview and control groups…. Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman's (1997) conception of how engagement in treatment can affect later retention."	Data suggest financially compensate d and barrier reduction groups were more likely to sign on to a substance abuse treatment program post TBI than the motivationa l interview or attention control groups.
Vungkhanching 2007 (3.0)	TBI	Treatment	Funded by US Department of Education,	N = 117	83 males, 34 females.	Intervention (N = 36) vs Comparison (N = 81)	There were 12	Intervention group participants	A skills-based intervention	Differences in baseline between

			Office of Special Education and Rehabilitation Services, National Institute on Disability and Rehabilitation Research (NIDRR; H133P980014) to A.W.H. No mention of COI.		Mean age is 35 years.		systematic sessions of motivational counseling aimed at alcohol or drug abuse. There was a 3 month and 9 month follow up.	more likely to be employed (89.7% vs 35.1%), abstain from alcohol (24.1% vs 9.4%) than comparison group. A higher proportion of participants remained abstinent of drug use.	provides a promising approach to promoting abstinence from all substances and increasing readiness for employment for adults with traumatic brain injuries in outpatient settings.	groups particularly in GOAT scores and time post injury. Data suggest skills based intervention appears to result in a sig. reduction of drug and alcohol abuse and increased employment likeliness at 9mo.

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:*
Lynch, 2016 (4.5)	Music Therapy	RCT	No mention of COI or sponsorship.	N=14	Mean age: 43.93 years. 9 males, 5 females.	MT group: received music therapy (n=5) Vs. Singing group: (n=5) Vs. Control group: (n=4)	None	One-way ANOVA of the and pre- and posttest group differences showed a trend toward improvement in the Music therapy group over the singing group.	"Feasibility and effect size data support a larger trial of the MEFT protocol."	Small sample. Data suggest a trend towards MEFT group being better than SG group.

Evidence for the Use of Non-Operative Therapeutic Procedures

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Terre, 2015 (7.0)	Vision, Speech, Swallowing, Balance, and Hearing	RCT	Sponsored by a grant of the FUNDACIÓN MAPFRE. No COI.	N=20. 14 stroke patients and 6 patients with severe traumatic brain injury.	The mean age of patients in the NMES group is 46 years. 6 males, 4 females. The mean age of the patients in the SES group is 51 years. 6 males, 4 females.	NMES group - Patients underwent NMES and conventional swallowing therapy. N=10. Vs. SES group - patients underwent sham electrical stimulation (SES) and conventional swallowing therapy. N=10.	3 months.	The Functional Oral Intake Scale (FOIS) score prior treatment for the NMES group was 2, SES group was 2.1. After treatment score was 4.9 NMES group and 3.1 SES group. The difference is p=0.0005. At 3-month follow-up, FOIS score is 5.3 NMES and 4.6 in SES group. Not statistically significant.	"Neuromuscular electrical stimulation significantly accelerated swallowing function improvement in patients with oropharyngeal dysphagia secondary to acquired brain injury."	Data suggest NMES therapy accelerate the swallowing function in patients with oropharyngeal dysphagia resulting from an acquired brain injury.
Dahlberg 2007 (5.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. COI.	N = 52 patients with TBI at least 1 year post-injury who had social communication deficits and received rehabilitation treatment.	Mean age group sessions 42.43, control 39.91. 44 males, 8 females.	Weekly group sessions for 12 weeks (each 1.5 hours) focused on improving communication skills (n = 26) Vs.	3, 6, and 9 months	Analysis of treatment effects via independent t tests showed significant differences between two groups in 7 out of 10 of The Profile of Functional Impairment in	"TBI subjects who received social communication skills training had improved communication skills that were maintained on follow-up. Overall life satisfaction for participants was improved."	Volunteer basis for subjects. Data suggest group sessions improve communication skills within subjects, even during

						Control group receiving no treatment (n = 26)		Communication (p values ranging from .001 - .024). There was also a statistical difference between two groups for the Social Communication Skills Questionnaire -Adapted measurement (p = .005).		the follow-up months.
Thiagarajan 2014 (4.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT crossover	No COI. Supported by U.S. Department of Defense (DoD) grant, the College of Optometrists in Vision Development, and SUNY graduate program.	N = 12 with mild TBI, injury onset of over 1 year, displayed at least one clinical sign of accommodative dysfunction	8 female, 4 male Mean age overall 29 ± 3 years	Oculomotor training (OMT) Vs. Placebo training (P) Each session 60 minutes, two sessions per week, 9 hours for one treatment total	15 weeks	Placebo training produced no significantly different measures (p > 0.05). OMT produced an increase of about 30% in peak velocity for increasing (t(11) = 3.61, p = 0.01) and decrease (t(11) = 3.65, p = 0.01) steps of accommodation.	"These results provide evidence for a significant positive effect of the accommodatively based OMT on accommodative responsivity. Such improvement is suggestive of oculomotor learning, demonstrating considerable residual brain-visual system plasticity in the adult compromised brain.	Small sample, crossover design. Data suggest OMT improved most measures related to accomodation responsivity which may be the result of oculomotor learning.

Evidence for the Use of Anger Management

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Medd 2000 (3.5)	TBI	RCT	No mention of sponsorship or COI.	N = 16 with brain injuries	14 males 2 females, aged 16 to 60 years old. Mean of 35.88 for Treatment and 34.0 for Waiting List	Treatment Group (TREAT) (N = 8) vs Waiting List Group (WAIT) (N = 8)	Follow-up at week 8	The pre-intervention TREAT group had significantly higher levels of AX-O than WAIT group [F(1,14) = 12.18, P = .004]. There was a significant interaction between Group and Time for the variable AX-O [F(1,14) = 10.50, P = .006]. This indicates that TREAT group showed a decrease in AX-O between Pre- and Post-intervention than the WAIT group.	"Repeated-measures analyses for TREAT showed significant improvements between pre-treatment and post-treatment measures (immediate and 2-month follow-up) on the STAXI. No significant generalisation of treatment effects to self-esteem, anxiety, depression, or degree of self-awareness were found."	Baseline differences in time in months post injury (37.3 vs. 74.3) as well as dissimilar number of amnesia days. Data suggest no sig. differences between groups in terms of self-esteem, depression, anxiety or self awareness.

Evidence for the Use of Suicide Prevention

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Simpson 2011 (6.5)	Psychological Therapy	RCT	No COI. Funded by grant from the National Health and Medical Research Council Health	N = 17, sever TBI with posttraumatic amnesia > 1 day, suffered	No gender distribution described. Mean age treatment group	20 hour manualized group cognitive behavior therapy (n = 8) vs wait-listed controls (n = 9)	3 months	Within treatment group, a group-by-time interaction found for Beck Hopelessness Scale (F1,15=13.2, P=0.002). Indicates reduction in mean	"This trial provides initial evidence for the efficacy of a psychological	Small sample. Data suggest treatment gains maintained

			Professional Fellowship.	from moderate to severe hopelessness (Beck Hopelessness Scale [BHS]) and/or suicide ideation	39.41 years, wait-list 44.08 years			score between time 1 and 2 without group or time main effects. At follow-up 75% of treatment group maintained improvement. Suicide ideation, depression, social problem solving, self-esteem, and hopefulness showed no statistically significant group-by time interactions or main effects.	intervention in reducing hopelessness among long-term survivors with severe TBI."	3 months post-intervention for 75% of patients evidenced by reduction in mean Beck Hopelessness Scale.
Ponsford 2016 (5.5)	Psychological Therapy	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))	"Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI."	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54 vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease

										anxiety and depression.
Bombardier 2009 (5.0)	Psychological Therapy	RCT	Supported by a grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 126 with TBI, discharged from inpatient rehabilitation	32 female, 94 male. Mean age 36 years	Motivational Interviewing via phone call at day 1 and again at months 1, 2, 3, 5, 7, and 9 (n = 62) vs Control group (n = 64)	1 year	Brief Symptom Inventory-Depression (BSI-D), Neurobehavioral Function Inventory-Depression subscale (NFI-D), Mental Health Index-5 (MHI-5). Pre-post changes on BSI-D subscale showed significant between group differences (Control 0.45±0.95, Telephone 0.08±0.72, P=0.019). Posttreatment BSI-D score: control 1.03±1.05, telephone 0.44±0.66 (P=0.000). Posttreatment NFI-D score: control 32.3±12.9, telephone 24.0±9.1 (P=0.000). Posttreatment MHI-5 score: control 20.2±5.9, telephone 23.4±4.8 (P=0.002). Pooled difference in treatment outcome via BSI-D score changes did not statistically vary by age, sex, or coma severity (P > 0.15 for all). Significant difference in white vs nonwhite participants, white reporting higher scores (P = 0.002).	"Telephone-based interventions using problem-solving and behavioral activation approaches may be effective in ameliorating depressive symptoms following TBI. Proactive telephone calls, motivational interviewing, and including significant others in the intervention may have contributed to its effectiveness. "	High dropouts Data suggest the use of scheduled telephone interventions utilizing problem solving and behavioral activation techniques may help reduce TBI depressive symptoms.

Tiersky 2005 (4.5)	Psychological Therapy	RCT	No COI. Supported by the National Institute on Disability and Rehabilitation Research and the Henry Kessler Foundation.	N = 20, mild or moderate TBI	11 female, 9 male. Mean age 46.85±10.51 years	Cognitive-behavioral psychotherapy and cognitive remediation (n = 11) vs Control (n = 9), all followed for 11 weeks	11 weeks, 1 and 3 months	Outcome measures at end of treatment: GSI – CBP+CR 0.86±0.41, control 1.74±1.00 (P=0.045), Depression – CBP+CR 1.12±0.45, control 2.11±1.14 (P=0.046), Anxiety subscale – CBP+CR 0.72±0.42, control 1.53±1.02 (P=0.066), PASAT – CBP+CR 135.55±30.71, control 110.88±60.28 (P=0.257), Problem solving – CBP+CR 13.06±2.67, control 12.58±2.21 (P=0.685), Attention Questionnaire CBP+CR 19.42±11.56, control 29.29±9.94 (P=0.082)	"Cognitive behavioral psychotherapy and cognitive remediation appear to diminish psychologic distress and improve cognitive functioning among community-living persons with mild and moderate TBI."	Data suggest TBI patient may benefit from CBT and cognitive remediation in terms of reducing anxiety and depression.
Radice-Neumann 2009 (4.5)	Psychological Therapy	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State University of New York.	N = 19 with acquired brain injury, minimum 1 year post-injury	8 female, 12 male. Mean age 43 years	Facial Affect Recognition "FAR" (n = 10) vs Stories of Emotional Inference "SEI" (n = 9), both treatments given for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (P=.225, P=.312), LEAS-Self (P=.064, P=.732), LEAS-Other (P=.340, P=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, P=.004). DANVA2-AF: Significant performance change found in FAR (P<.001) and SEI (P=.006).	"Training can improve emotion perception in persons with ABI. Although further research is needed, the interventions are clinically practical and show promise for the population with ABI."	Small groups. No sham/placebo. Data suggest specific training may enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improveme

						Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)		DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR P=.584, SEI P=.166). LEAS-Self: Both significant change over time (FAR and SEI both P=0.019). LEAS-Other: Significant change over time for FAR (P=0.004). No change in SEI (P=.579). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (P = .042). No change perceived in SEI (P = .363).		nt in ability to infer how they would feel in a given context.
Ashman 2014 (4.5)	Psychological Therapy	RCT	Sponsored by National Institute for Disability and Rehabilitation research grants H133B040033 and H133B000001. NO COI.	N = 77 individuals with TBI and a diagnosis of depression	Cognitive Behavioral Therapy (CBT) group: 47.1. Supportive psychotherapy (SBT) group: 48.1. Gender (M:F) 32:42	CBT group (N=29) received 16 sessions of treatment focused on cognitive restructuring techniques to challenge and reshape automatic thoughts into more rational self-statements. SPT group (N=26) received 16 sessions of client-centered psychotherapy	3 months	After treatment, 35% of participants in CBT group no longer met criteria for depression vs 17% of participants in SPT group. However, difference in remission rates was not statistically significant (P =.16). Changes in the Beck Depression Inventory-II scores were not significant between CBT group and SPT group. (P=.632)	"Both forms of psychotherapy were efficacious in improving diagnoses of depression and anxiety and reducing depressive symptoms. These findings suggest that in this sample of individuals with TBI, CBT was not more	High dropout rate, substantial intergroup variability. Data suggest comparable efficacy between groups.

						treatment. Treatment focused on improving self-esteem, maximize adaptive capacities, and maintaining the individual's best possible level of functioning.			effective in treating depression than SPT, though further research is needed with larger sample sizes to identify different components of these interventions that may be effective with different TBI populations."	
Ruff 1990 (3.5)	Psychological Therapy	RCT	No mention of COI. Supported by grant from the Robert Wood Johnson Foundation.	N = 24, moderate to severe head injury with at least 1 hour of coma duration	7 females, 17 males. Mean age experimental group 28.3 years, control group 31.1 years	Experimental group – cognitive retraining on attention, visuospatial abilities, learning and memory, and problem solving. Small groups of 2-4, 12 hours per week for 8 weeks, 2 hour of group therapy and 20-30 minute "wrap-up" sessions at the end of the day (n=12) vs. Control group – also received group and "wrap-up" session therapy, training focused	8 weeks after intervention began	Test—re-test correlations in Katz Adjustment Scale (KAS) subset; Social Obstreperousness: Patient rating r=0.87 (P<0.001), Relative rating r=0.88 (P<0.001), Patient vs. Relative rating r=0.01 (P>0.01). Acute Psychoticism: Patient r=0.68 (P<0.001), Relative r=0.76 (P<0.001), Patient vs Relative r=0.45 (P>0.01). Withdrawn Depression: Patient r=0.78 (P<0.001), Relative r=0.65 (P<0.1), Patient vs Relative r= -0.07 (P>0.01). Both groups	"In this study, self-ratings according to the KAS proved to be reliable for both relative and patient ratings. Nonetheless, very little agreement existed between patient and relative ratings, as indicated by zero correlations for global scales of social	

						on psychosocial functioning and activities of daily living (n=12). All participants' relatives also were involved in evaluation.		did not perceive changes in emotional and psychosocial function from interventions (SO: U=58 P>0.10, AP: U=64 P>0.10, WD: U=62.5, P>0.10). Relatives of both groups also did not perceive changes (SO: U=55 P>0,10, AP: U=48.5 P>0.10, WD: U=36, P>0.10).	obstreperousness and withdrawn depression. Furthermore, relatives but not patients reported significant gains."	

Evidence for the Use of Substance Abuse Counseling

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/ Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zatzick 2014 (6.5)	TBI	Treatment	Grants supplied by National Institute on Alcohol Abuse and Alcoholism R01/AA016102 and National Institute of Mental Health K24/MH086814 were given to support this article. No	N=878	208 females, 670 males. Mean age is 36.9.	Intervention sites (n=10, patient n=469). Vs control sites (n=10, patient n=409)	Follow up after baseline at 6 and 12 months post-injury.	In the first year following injury, intervention group participants had a significant 8% reduction in Alcohol Use Disorders Identification Test (AUDIT) hazardous drinking cut-offs compared to control group. Intervention group also had a significant increase in abstinent from drinking days over the next year post-injury (P = 0.02).	"[T]hese findings suggest that a brief trauma center intervention based upon MI (motivational interviewing) principles can yield relevant population level reductions in alcohol consumption and related hazardous drinking outcomes."	Population mixed between TBI and others. Assessment via interviews. Data suggest modest (8%) reduction in problem drinking patients, especially non-TBI patients.

			declaration of interests.							
Tweedly 2012 (5.5)	TBI	Treatment	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	"There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach statistical significance…. Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population."	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.
Sander 2012 (3.5)	TBI	Treatment	This work was supported by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education (grants	N = 104	85 males, 19 females; Mean age is 35.75 years.	Standard of Care (N = 50) Vs. Intervention group (N = 54).	Follow up period of 3 months.	History of alcohol binging was not significant (P=.55). There was an effect on group treatment and control on AEQ-III GP. Treatment vs control (P=.01). Group effect and binge history did not interact (P=.06). Treatment wasn't effected by injury severity, history of binges, attribution or	"Brief intervention can be effective for educating on the negative impact of alcohol use for people with severe TBI who have emerged from posttraumatic amnesia. Attribution of the injury to alcohol use could potentially increase readiness to change in some settings, and might be used to	Brief treatment (10min video) followed up by education and a motivational interview did not show efficacy to improve problem alcohol use or readiness to change.

			H133B031117, H133B090023, H133A070043, and H133A070029). No COI.					site (P=.25). After adjustment there was still no effect (P=.86).	generate discussion about the negative impact of alcohol use."	
Corrigan 2005 (3.0)	TBI	Treatment	Funding for this project was provided by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, via Grant 5 KD1 TI12013. No mention of COI.	N = 195	138 males, 57 females. Mean age is 36.6 years.	195 participants randomly assigned into 4 groups. [170] Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incetive.	Appointments unspecified and varied by participant preference. Follow up at 3 and 6 months.	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview (45%) and attention control (45%) groups. Significance indicated through client signing an individualized service plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign (*M* = 22.8 days, *SD* = 14.7), (*M* = 44.0 days, *SD* = 35.8) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	"Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational interview and control groups…. Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman's (1997) conception of how engagement in treatment can affect later retention."	Data suggest financially compensated and barrier reduction groups were more likely to sign on to a substance abuse treatment program post TBI than the motivational interview or attention control groups.
Vungkhanching 2007 (3.0)	TBI	Treatment	Funded by US Department of Education, Office of Special Education	N = 117	83 males, 34 females. Mean age	Intervention (N = 36) vs Comparison (N = 81)	There were 12 systematic sessions of motivational counseling aimed at alcohol or drug	Intervention group participants more likely to be employed (89.7% vs 35.1%), abstain from alcohol (24.1% vs 9.4%) than comparison group. A higher proportion of	A skills-based intervention provides a promising approach to promoting abstinence from all substances and increasing readiness for	Differences in baseline between groups particularly in GOAT scores and time post injury. Data suggest skills based intervention appears

			and Rehabilitation Services, National Institute on Disability and Rehabilitation Research (NIDRR; H133P980014) to A.W.H. No mention of COI.		is 35 years.		abuse. There was a 3 month and 9 month follow up.	participants remained abstinent of drug use.	employment for adults with traumatic brain injuries in outpatient settings.	to result in a sig. reduction of drug and alcohol abuse and increased employment likeliness at 9mo.

Evidence for the Use of Community Based Life Goals

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Ownsworth 2008 (5.0)	TBI	Community Life Based Goals	Sponsored by a grant from the Centre of National Research on Disability and Rehabilitation Medicine (CONROD and a National Health and Medical Research Council Public Health Fellowship. No mention of COI.	N = 35 with brain injury units and community-based rehabilitation services over 12 months	Age range 21-62 years old, 19 males & 16 females, and mean age of 43.89.	Individual Intervention (N = 10) vs Group Intervention (N = 11) vs Combined Intervention (N = 10)	3 months	Pre-post comparison and pre-follow-up comparison, PCRS: P=0.482 and P=0.150 respectively compared to P<0.025 and P=0.109 for Group and P=0.463 and P=0.114 for Combined groups.	"These findings generally support the efficacy of brief intervention formats following acquired brain injury, although further research is needed to examine clients' suitability for particular interventions."	Small sample sizes. Wait-list control bias. Data not well reported as compared to controls. Authors interpretations that trend towards better results with individual than group approach not able to verify because of data

										reporting limitations.

Evidence for the Use of Return to Work

Author Year Score	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Thomas 2015 (6.5)	TBI	RCT	Sponsored by Injury Research Center of the Medical College of Wisconsin. No COI.	N = 99 with mild TBI / concussion.	Aged 11 – 22 years, 65 males and 34 females.	Intervention or strict rest for 5 days (N = 50) vs Control or usual care for 1-2 days of rest, followed by stepwise return to activity (N = 49).	10 days	At 10-day period, strict rest group reported greater PCSS scores / higher total number of postconcussive symptoms / and higher daily PCSS clustered at day 4: 187.9 vs 131.9 [C], p < 0.03 / 79.4 [I] vs 50.2 [C], p < 0.03 / and 13.95 [C] vs 21.51 [I], p < 0.03. Subgroup analysis; higher postconcussive symptom score at day 10 randomized to strict rest (15.2 [I] vs 7.7 [C], p < 0.04). Those who presented to ED with immediate signs of concussion and those with past history of concussion randomized to strict rest (11.0 [I] vs 14.6 [C], p = 0.22 and 15.1 [I] vs 5.6 [C], p < 0.05.	"Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care."	Data suggest strict rest after acute concussion not beneficial in speeding up recovery or discharge vs usual care in pediatrics patient group.
Salazar, 2000 (5.5)	Return-to-work	*RCT*	No mention of COI. Sponsored by Defense and	N = 120	Mean age: 25.44 years.	Hospital Group (N =67) vs	Follow-up for 1 year.	Return to work was 90% for the hospital group and 94% for the home group (P=.51).	"In this study, the overall benefit of in-hospital cognitive	Data suggest similar efficacy between in hospital cognitive rehab and home

			Veterans Head Injury Program and by the Medical Research Service of the Department of Veterans Affairs.		113 males, 7 females.	Home Group (N =53).		Among patients working at 1 year, 91% of hospital group and 93% of home group were working full time (P>.99). No significant difference between groups in quality of life. No significant differences between groups in verbal and visual memory or attention, general measures of cognitive or psychiatric function. Most patients showed cognitive improvement, but there was a self-reported increase in aggression for both groups. In a post-hoc subset analysis of patients unconscious for more than 1 hour following TBI (n=75), in-hospital group had a greater return-to-duty rate (80% vs 58%; P=.05).	rehabilitation for patients with moderate-to-severe TBI was similar to that of home rehabilitation. These findings emphasize the importance of conducting randomized trials to evaluate TBI rehabilitation interventions."	cognitive rehab for TBI patients.
Twamley 2014 (4.0)	Return-to-work	RCT	Sponsorship by DOD. Dr. Delis receives royalties from the sale of the CVLT-II and D-KEFS could be a potential COI.	N=34	Mean age: 31.99 years. 32 males, 2 females.	Supported Employment + CogSMART (N=16) Vs Enhanced Supported Employment (N=18)	No follow-up.	Significant improvements in CogSMART postconcussive symptoms and prospective memory performance were observed (p=.01; p=.05 respectively). No statistical difference were observed in neuropsychological,k	"In this study, the overall benefit of in-hospital cognitive rehabilitation for patients with moderate-to-severe TBI was similar to that of home rehabilitation. These findings	Pilot RCT. Data suggest Cog SMART "may" improve post concussive symptoms and Veterans with TBI.

								symptom severity, quality of life, or work outcome comparisons. Supported employment plus CogSMART group showed small to medium effect size improvements in psychiatric symptom severity (CAPS: d=.43 and HAM-D: d=.37). relative to the enhanced supported employment group. Five participants in enhanced group obtained competitive work within the first 14-wks of the study compared to 8 participants in the supported plus CogSMART group (d=.49).	emphasize the importance of conducting randomized trials to evaluate TBI rehabilitation interventions."	

Evidence for the Use of Vocational Rehabilitation Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Radford 2013 (5.5)	Vocational Rehabilitation Programs	RCT	Sponsored by the College of Occupational Therapists. No COI.	N = 94 participants with TBI hospitalizations	Mean age of 34.3 yrs, 72 males, 22 females	TBI-VR Group (N =40) vs Usual Care Group (N = 54)	Follow up by questionnaire at 3, 6, 12 months	15% more individuals in the TBI-VR group (27/36, 75%) started working 13 months post hospital discharge than the UC group (27/45,	"Returning TBI people to work following early targeted TBI specialist vocational rehabilitation is likely to be	Data suggest TBI patients trend towards benefit from vocational rehab for early return to work compared to

								50%). Those with moderate or severe TBI had greater outcomes in the TBI-VR group than the UC group: 16/23 (75%) vs 9/21 (43%). This was also the case for minor TBI: 13/14 (93%) vs 14/25 (56%). Mean cost per person in the TBI-VR group was only £75.23 more than the UC group (£2106.94 ± 1542.86 vs £2031.71 ± 2352.24).	cost-effective and may result in improved work outcomes."	usual care group. Moderate-severe TBI patients experienced the most benefit.

Trexler 2010 (4.0)	Vocational Rehabilitation Programs	RCT	This research was in part funded by a US Department of Health and Human Services, Health Resources and Services Administration, Traumatic Brain Injury Planning and Implementation Partnership Grant and by the Dr Lisa Thompson Center for Family Education at the Rehabilitation Hospital of Indiana. No mention of COI.	23, with acquired TBI and caregivers with injury <1yr ago, had been employed and/or attended school 2 years pre-injury with RTW/school goal.	ages 18-60	Resource facilitation (RF, n=12) with contact from RF facilitator Q2Wks to assist in RTW median 8hr. vs. regular follow-up control conditions (n=11).	no contact during 6 months with 6 month follow-up.	Mayo-Portland Adaptability Inventory (M2PI): increased in both groups over treatment period (F=60.65 (p<0.0001)) with greater improvement in RF group vs. controls (F=9.11 (p=0.007)). M2PI employment item: RF group – 64% employed at follow-up vs. 36% of controls. PHQ-9 scores: NS between groups.	"…RF may have a significant impact not only on return to work but also on participation in the community and at home."	Small sample size. Time since injury in controls vs. RF group (124 vs. 64d, p=0.11) but median 85 vs. 52 d suggests highly skewed distribution(s) and caution in evaluating mean values. Data suggest FR 78% more employed than among CR controls.

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