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Draft Comparative Effectiveness Review

Number XXX

Traumatic Brain Injury and Depression

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives: The Vanderbilt Evidence-based Practice Center systematically reviewed evidence addressing key questions on depression after traumatic brain injury including prevalence, optimizing timing and methods for diagnostic screening and approaching treatment.

Data Sources: We searched PubMed MEDLINE®, EMBASE, CINAHL and PILOTS for articles published in English.

Review Methods: We included studies published from January 1966 to June 2009. We excluded those with fewer than 50 participants, participants age 16 or younger, or that did not address a key question. We identified 101 included publications; 12 were good quality, 64 were fair, and 25 poor.

Results: The prevalence of depression after traumatic brain injury was approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 28 percent met criteria for depression three to six months from injury; 32 percent at six to 12 months; and 35 percent beyond 12 months. Higher prevalence measures were reported in many study populations.

Data are sparse to assess the relationship of severity, mechanism, or area of the brain injured to risk of depression. Few risk factors for depression have been studied across populations in models that adjust for confounding factors. Alcohol and substance use, coexisting illness or injury, degree of disability, and older age at injury may contribute to increased risk.

The literature is insufficient to determine whether tools validated in other populations for detecting depression appropriately identify individuals with depression after a TBI. Consideration of potential for coexisting psychiatric conditions is warranted. Anxiety disorders were the most common coexisting condition affecting 31 to 61 percent of those with depression after TBI. PTSD prevalence in the included literature suggests that it may also be common (37 percent). Little to no high-quality evidence is available about outcomes of treatment of depression after TBI. A single RCT of sertraline showed nonsignificant improvements after 10 weeks.

Conclusions: Considerable evidence finds depression to be common after all forms and severities of TBI. At all time points from injury prevalence is higher than the estimated 8-10 percent in the general population. No evidence provides a basis for preferring one timeframe for screening over another, implying repeated screening is imperative. No evidence is available to guide treatment choices for depression after head injury.

Overall the evidence is low to guide screening and care for depression after TBI. Given at least 1.5 million TBIs per year with many potential consequences that impair quality of life and function, substantially greater efforts are warranted to understand the biologic causes, natural history, treatment, and prevention of depression after TBI.

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Executive Summary

Introduction

We do not know to what extent depression contributes to long-term disability following traumatic brain injury (TBI), although depression is one of several potential psychiatric illnesses that may be common following TBI. Major depression may be triggered by physical or emotional distress, and can deplete the mental energy and motivation needed both for recovery efforts from the depression itself and for adapting to the physical, social and emotional consequences of trauma with brain injury. Recovery-related factors can trigger depression and can become chronic if depression is severe and treatment fails. Depression may be masked by other deficits after head injury, such as cognitive changes and flat affect, which may be blamed for lack of progress in post-trauma treatment but actually reflect underlying depression. Currently, clinicians, care givers, and patients lack formal evidence to guide the timing of screening, tools for screening and assessment, treatment choices, and assessment of treatment success.

Importance of Depression

Depression is defined by criteria that, in reality, likely circumscribe a heterogeneous set of illnesses. While no single feature is seen in all depressed patients, common features include sadness, persistent negative thoughts, apathy, lack of energy, cognitive distortions, nihilism, and inability to enjoy normal events in life. Especially in a first episode, individuals and families may not recognize the changes as part of an illness, making identification and self-reporting of the condition challenging. Active screening is essential to recognition, treatment, and prevention of recurrence.

The most salient consequence of depression is suicide. Suicide is usually impulsive and extremely difficult to predict and prevent. At least half of suicides occur in the context of a mood disorder.[1] Depression reduces quality of life, impairs ability to function in social and work roles, causes self-doubts and difficulty taking action all of which can be critical in the context of recovery from TBI. The current criteria from the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR)[2] define the illness in terms of physiologic disturbances of sleep, appetite, attention and concentration, motor activity and energy, and of psychological losses of interest in normal activities, hope, and self-worth while ruminating with excessive sadness, guilt, and suicidal thoughts.

These may be altered following TBI due to other circumstances, e.g. pain that disrupts sleep, which may mask the recognition that the sleep disturbance is also a part and parcel of a burgeoning depression. Depression may be fiscally costly in undermining physical therapy efforts, treatment compliance in general, rehabilitation planning and efforts, and disposition to situations where suicidal risk and behavior cannot be monitored and prevented. The need for systematic evaluation of the prevalence and consequences of depression following TBI is imperative, given the potential for mitigating suicide and unnecessary disability.

Importance of Traumatic Brain Injury

Traumatic brain injury (TBI) occurs when external force from an event such as a fall, sports, assault, motor vehicle accident, or explosive blast injures the brain and causes loss of consciousness or loss of memory.[3] TBI can result from direct impact to the head as well as from rapid acceleration and deceleration of brain tissue which injures the brain by internal impact with the skull. Both mechanisms can cause tissue damage, swelling, inflammation, and internal bleeding.[4]

Traumatic brain injury is responsible for roughly 1.2 million emergency department visits each year with one in four patients requiring hospitalization.[5] Because most estimates of TBI rates are based on hospital use, some individuals with TBI are not counted because they do not seek care or seek care in other settings. The CDC estimates that up to 75 percent of TBI is mild in terms of duration of loss of consciousness and other immediate symptoms, meaning substantial underestimation of the number of individuals affected is likely.

Nonetheless, estimates of direct and indirect costs associated with TBI exceed $56 billion each year.[6] Among individuals who sustain a TBI, approximately 50,000 die each year of their injuries and 80,000 to 90,000 will have a long-term disability. Currently, in total, over 5 million survivors of TBI live with chronic disability.

Military service carries a high risk of TBI. Traumatic brain injury is more common in the military than in civilian populations, even in peacetime. Advances in body protection systems have resulted in fewer deaths with a concomitant rise in TBI that is more often moderate to severe TBI than mild.[4] The military confirms over 50,000 veterans who have returned from current theatres have blast-related TBI.[7] As many as 30 percent of those with any injury on active duty have sustained a TBI.[8] Because TBI is common, serious, and has high personal and economic costs, understanding potential consequences of injury is crucial.

Relationship of Traumatic Brain Injury and Depression

TBIs are associated with a range of short- and long-term outcomes, including physical, cognitive, behavioral, and emotional impairment.[9] Prior estimates, not derived systematically, of depression among individuals with TBI range widely, from 15 to 77 percent.[10-12] Depression associated with TBI can manifest shortly after injury or well into the future.[13-14] In their review of rehabilitation for TBI patients, Gordon and colleagues identified 74 studies of psychiatric functioning after TBI.[15] Their assessment was that TBI is associated with high rates of depression - more than half of cases - and other DSM Axis I and Axis II conditions. Depression was noted to coexist with other psychiatric conditions, including addiction or anxiety. Comorbid psychiatric conditions with depression may complicate screening, diagnosis and management of depression in multiple ways, including masking depression so that it remains undiagnosed or affecting the individual's follow through or adherence to treatment. It is likely that such comorbid conditions complicate treatment response and recovery just as they do in non-TBI depressed patients. However, no systematic examination of this question has been done to date.

Triggers for depression after TBI may include biological, psychological and social factors,[16] and in the post-TBI population, greater attention is often given to the biological factors because of the direct injury to the brain. However, many post-TBI patients do not demonstrate radiological or pathological evidence of brain injury,[17] and in the context of current understanding of depression as a biopsychosocial entity, researchers and clinicians generally

consider all depression to have a complex etiologic basis. Just as in the non-TBI population, the psychological impact of decreased occupational and functional abilities and its potential to affect likelihood of becoming depressed should not be overlooked.[18]

Focus of this Systematic Review

In order to compile the literature in a useful fashion, we included publications that provide a clear description of study participants and that used standardized tools and recognized approaches to identifying depression. We did not address penetrating head injury and did not include research about children younger than 16.

Patients, clinical care providers, families, and support organizations need to know the degree to which depression after TBI is a threat so that anticipatory guidance and care planning can incorporate strategies to address risk of depression, or potentially prevent onset. Care providers in a variety of settings need to know when and how best to screen TBI patients for depression. When depression is identified, information about likely outcomes of treatment and about whether certain options are superior is key to informed decision making. This review is focused on pragmatic aspects of these concerns.

Key Questions

In preparing this report, we have answered the following key questions:

KQ1. What is the prevalence of depression after traumatic brain injury and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?

KQ2. When should patients who suffer traumatic brain injury be screened for depression, with what tools and in what setting?

KQ3. Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, PTSD, substance abuse and major psychiatric disorders?

KQ4. What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing:

a. psychotropic medications
b. individual/group psychotherapy
c. neuropsychological rehabilitation
d. community-based rehabilitation
e. CAM
f. neuromodulation therapies and
g. other therapies?

KQ5. Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?

KQ6. Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, pre-existing mental health status or medical conditions, functional status, and social support?

Methods

Literature search. Our search included examination of results in five databases: PubMed Medline®, the PsycINFO® database of psychological and psychiatric literature, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Published International Literature on Traumatic Stress (PILOTS) database. Controlled vocabulary terms served as the foundation of our search in each resource, complemented by additional keyword terms and phrases selected to represent each of the key concepts in the search. We also employed indexing terms when possible to exclude undesired publication types (e.g. reviews, case reports, letters, etc.) and articles published in languages other than English. We hand-searched reference lists of included articles to identify additional citations. We excluded studies that: included fewer than 50 participants; included participants younger than 16 years of age; did not include an operational definition of depression; or were unable to be used to answer any key question.

Study selection. Two reviewers separately evaluated abstracts for inclusion or exclusion. If one reviewer concluded the abstract should be included for full review of the article, it was retained. For the full article review, two reviewers read each article and decided whether it met our inclusion criteria. Discordance was resolved by team adjudication.

Quality assessment. The research team used a quality assessment approach that ensured capture of key study characteristics most relevant to our key questions. Quality was assessed by two reviewers independently, who resolved differences through discussion, review of the publications and coming to consensus with the team.

Data extraction. All team members shared the task of entering information into the evidence tables. After initial data extraction, another member of the team reviewed the article and checked all table entries for accuracy, completeness, and consistency. The two abstractors reconciled any discordance in information reported in the evidence tables.

Evidence synthesis. We have endeavored to distinguish duplicate populations; however, for a small proportion of publications, the summaries may over-represent the total number of unique studies available and could double count data. In each section we summarize the yield of the search and key characteristics of the content of the aggregate literature.

We present data in summary tables arranged by key features being discussed. Most often this is by the rigor of the TBI definition and depression measurement used in the research. All data extracted is presented in the evidence tables in Appendix C.

In order to characterize estimates of prevalence, and prevalence across time, we calculated weighted averages and report these as a global aggregate as well as by timing of screening, setting, and severity of injury. If a study included a measurement at more than one time point, the participants in that study contribute to the estimates for each time at which depression was assessed.

Literature search yield. As a result of the search, 1,616 nonduplicate articles were identified. One hundred one articles were included in the review, representing 74 distinct populations, with 98 articles pertaining to KQ1, 99 to KQ2, 7 to KQ3, 2 to KQ4, and none identified for KQ5 or KQ6. Detailed reasons and process for exclusions are described in the full report.

Results

KQ1. Prevalence of depression after traumatic brain injury

Content of literature. We identified 98 publications,[7, 12-14, 18-111] from 71 distinct study populations. Thirty-six of the 71 were in the United States, 11 in Canada, 12 in Europe, 5 in Australia, and 8 in other countries. The most common sources of study populations were tertiary care centers, identifying participants from emergency department, intensive care, and inpatient admissions (n = 30), including those that specifically noted trauma center status (n = 8), and rehabilitation programs (n = 17). Neuropsychology labs, private neuropsychology practices, prisons, veterans' records, databases, and psychiatric care facilities each contributed three or fewer populations.

Criteria for defining and characterizing those classified as having TBI were varied with more than half of authors (n = 36) using closed head injury in concert with Glasgow Coma Scores (GCS). American Congress of Rehabilitation Medicine (ACRM) criteria were common (n = 12); as were ad hoc operational definitions (n = 11), and failing to clearly define criteria (n = 9). In total, the majority of the literature provides sufficient detail about inclusion and exclusion criteria and TBI definitions to understand and/or replicate the population studied.

Seventy percent of studies provided cross-sectional measures of depression, meaning that depression status was assessed at a single point in time after TBI; the balance were prospective with two or more assessment of depression status over time. Structured clinical interviews, done specifically for the research or in the course of standardized clinical care protocols, were the most common means of assessing depression status (n = 25). Among written or administered tools the Beck Depression Inventory (BDI; n = 11), Center for Epidemiologic Studies Depression Scale (CES-D; n = 8), and Hospital Anxiety and Depression Scale (HADS; n = 8) were most common. A wide variety of other measures and customized uses of subscales (n = 61) were also used.

Prevalence estimates. We have considered the SCID and other formal structured clinical interview protocols that map to the DSM and/or ICD codes to be the measures of depression that are most relevant to clinical care. Among studies that used a SCID or other structured protocol to reach a formal diagnosis of depression, the prevalence of depression after TBI ranged from 12.2 percent[53] to 76.7 percent[12]. If we focus on the subset of studies with both clearly operationalized criteria for TBI, and use of the SCID or other clinical interview, the range was 12.2 percent[53] to 54.0 percent[96].

Across all timeframes and using all depression measures, in studies with clear TBI definitions, the weighted average for prevalence of depression was 31.8 percent. Among those studies with repeated assessments and/or longer term followup, no clear pattern of expected natural history or peak prevalence emerged. Depression was more common among those with TBI than among normal comparison groups. Household/family members of individuals with TBI may also have increased risk of depression. Results from comparisons to other trauma populations without severe TBI, are variable, with some comparison groups also having statistically comparable risk of depression that exceeds expected prevalence in the general population.

Risk factors. Data are sparse to assess whether severity of injury influences risk of depression. Using structured interviews among those studies with mild or mild/moderate TBI

populations, the overall prevalence of depression was 26.5 percent compared to 32.2 percent in studies that enrolled or followed up populations of all severity. Too few studies isolate a sufficient number of those with mild TBI compared to those with moderate and/or severe injuries to make valid estimates. Likewise, stratification of prevalence by explanatory factors such as age, gender, area of brain injured, or mechanism of injury is not possible within the current body of literature.

Twelve studies in seven distinct study populations report results from multivariate models to identify predictors or risk factors for depression after TBI. Older age at injury, CT with documented intracranial lesion, and higher one-week CES-D scores were sensitive (93 percent) though not specific (62 percent) for identifying those with mild TBI who were depressed by three months after their injury.[50] History of alcohol and substance abuse increase risk.[14, 64] Pain, involvement in litigation related to the injury, and perceived stress were risk factors among those entering rehabilitation care.[23] Psychosocial supports were often described in this literature and data from caregivers, partners, and family members were common. However few models incorporated social support items. One group reported "availability of a confidant" reduced risk of depression,[78] and another that years married were inversely related to risk, while presence and degree of cognitive disability, motor disability, and social aggression elevated risk.[99]

A cluster of reports were focused on investigating whether incorporating information about the area of the brain affected by the injury helped to identify those at highest risk. Imaging research about the areas of the brain injured and the relationship to depression risk has inconsistent results. In aggregate for all those with TBI, onset of major depression within three months of injury has been reported to seven-fold more common (95 percent CI: 1.36 to 43.48) among those with abnormal CT results after injury compared to normal imaging.[50] Focusing on locations of injury, Jorge and colleagues [13, 103] have replicated their findings in several CT-based studies that left anterior lesions involving the left dorsolateral frontal cortex and/or left basal ganglia are associated with increased risk of acute depression ($p = 0.006$) when injury location is assessed in multivariate regression models. They also note that frontal lesions whether left, right or bilateral are associated with decreased risk of acute depression ($p = 0.04$). In contrast delayed-onset major depression was not associated with lesion location. In a subanalysis of depression types, depression alone was related to left hemisphere injury ($p = 0.003$), while depression associated with anxiety was more common among those with right hemisphere injury ($p = 0.003$). A specific assessment of the presence or absence of contusions found the type of injury was not predictive and that depression was somewhat more common among those with contusions (71 percent) than among those without (62 percent). Using MRI, the findings from CT studies are not supported and the only lesion type to emerge as a significant predictor was the protective effect of temporal lesions compared to other injury locations ($p = 0.028$).[38] Study size and timing in relation make this literature more exploratory than conclusive in beginning to understand the relationship between pathophysiology related to the brain injury and risk and timing of onset of depression.

Summary. The prevalence of traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 28 percent met criteria for depression three to six months from injury; 32 percent at six to 12 months; and 35 percent beyond 12 months. Higher prevalence is reported in many study populations. No strong predictors are available to select a screening window or to advise TBI patients or their providers about risk of depression.

KQ2: Screening for Depression after TBI

Content of literature. We identified 99 publications in 72 distinct populations that provide information about timing of screening or comparison of tools. Overlap is virtually complete with those publications included in KQ1, adding only one publication from the United States. As a result, study characteristics for this literature are nearly identical.

Timing of screening. In all timeframes across all measures, depression is common after TBI. No distinct trend is apparent to suggest a peak time of enhanced risk or a related priority window for screening. In general the proportion of those assessed as depressed is lower with structured clinical interviews than standardized instruments. Around one year and beyond both categories of assessments converge around 30 percent (28.5 percent with SCID and 33.7 with other tools).

This review cannot distinguish between whether the data suggests that other tools "over-detect" depression relative to structured clinical interviews or whether differences in study design and population create the observed effect. We also cannot distinguish if features unique to a population with TBI make clinical diagnosis more challenging, or whether evaluators in clinical settings are less likely to classify a patient as depressed early after trauma, deferring definitive diagnosis until later in followup as other sequelae of injury subside or stabilize.

Choice of tools for screening. Studies often used more than one instrument, reporting different facets of the scores or evaluation, such as correlations among subscales of separate instruments, or relationship of scores by different evaluators. Statistical analyses were generally not intended to directly assess clinical utility. Comparison of diagnostic test characteristics, agreement of classification, and use of expert SCID as a gold-standard for comparisons were rare. Three publications compared SCID to candidate tools for assessment of depression, the BDI,[90] PHQ-9,[112] and HADS.[28] None of the tools reported simultaneous sensitivity and specificity above 90 percent. With modification of the scoring algorithm as proposed by the authors, the PHQ-9 achieved a sensitivity of 93 percent, specificity of 89 percent, positive predictive value of 63 percent and negative predictive value of 99 percent. The BDI had poor sensitivity of 48 percent and 32 percent at specificities of 80 and 90 percent, respectively. The HADS provided 54 percent sensitivity and 76 percent specificity. One team[31] reported results of an expert consensus process to select subscale domains of three screening tools (NFI, POMS-D, CES-D) that correspond to the DSM-IV criteria for major depressive episode, and found in application that the three tools were highly correlated ($r > 0.80$) in their identification of depressed individuals. Nonetheless, SCIDs were not actually done in the study.

Summary. Prevalence of depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another. Likewise, the literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBI's. Nor does the literature support any one tool over the others.

KQ3. Prevalence of Concomitant Psychiatric Conditions

Content of literature. We identified seven publications[13, 57, 59, 91, 96, 98, 110] in six populations that reported prevalence of concomitant psychiatric conditions within the population of depressed TBI patients,[13, 96, 98] or compared rates of comorbid conditions in those with and without depression.[57, 59, 91, 110] Papers that reported the overall prevalence of psychiatric conditions among the general population of TBI patients with no data on their association with depression were excluded.

Study designs included four prospective cohorts,[13, 57, 59, 98, 110] one retrospective cohort[91] and one cross-sectional study.[96] All studies were conducted in the United States. One was conducted at an academic medical center;[57] one at a rehabilitation center;[96] one in the community;[91] one at two hospitals within the same state;[59] and two at trauma centers.[13, 98, 110] The most common condition studied in combination with depression was anxiety.[13, 59, 91, 96] Depression was diagnosed via clinical interview in most of the studies.[13, 57, 59, 91, 96, 98]

Co-existing psychiatric conditions. Eight to 93 percent of depressed participants had one or more concomitant conditions. Anxiety was the most commonly detected coexisting condition. In the one study that compared rates of comorbid anxiety in those with and without depression, it was significantly more common in the depressed group (76.7 versus 20.4 percent, $p<0.001$).[59]

Assessing depression with the PHQ-9, and PTSD with the PCL-C, 37 percent of individuals who also had depression after TBI had PTSD, compared to none among those who were not depressed.[110] Anxiety and aggression outcomes have been investigated among patients with closed head injury and those with multiple trauma, but no central nervous system involvement.[59] A third of patients had major depressive disorder (mood disorder with major depressive features). Over the course of followup, 23 of 30 (77 percent) of patients with major depressive disorder also had anxiety, compared with 9 of 44 (20.4 percent) of nondepressed patients. Of note, PTSD was included with anxiety in this study, and was the defining psychiatric feature for seven of the 23 patients diagnosed with anxiety. Similarly, 17 of 30 (56.7 percent) depressed patients exhibited aggression, compared to 10 of 44 (22.7 percent) of those without depression.

A cohort of 188 individuals with TBI who were enrolled in a larger study of mood disorders and psychosocial functioning after TBI was assessed twice over 12 months for depression and other psychiatric comorbidities. Individuals were divided into four groups for analysis: no depression at any point, resolved depression (present at entry but not 12 months), late-onset depression (present at 12 months but not study entry) and chronic depression (present throughout the study). At study entry, co-existing psychiatric conditions were most frequent among those individuals who would have late onset depression (74 percent of late onset patients) and lowest among those in the chronic depression group (26 percent). At re-assessment, the presence of psychiatric conditions had increased in every group except those never diagnosed with depression. Among the psychiatric conditions examined, anxiety was most common at both study entry and at 12 months (19 and 16 percent respectively).

Summary. When conditions were reported individually, General Anxiety Disorder (GAD) was most prevalent and affected from 31 to 61 percent of study participants in three papers.[13, 59, 96] PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and no patients without depression,[110] and panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression.[96] Consideration of potential for co-existing psychiatric conditions is warranted.

KQ4. Outcomes of Treatment for Depression after TBI

Content of literature. Only two publications,[113-114] addressed a treatment for individuals diagnosed with depression after a traumatic brain injury. One of the treatment studies was conducted in the United States[113] and the second was in Canada.[114] Both were studies of antidepressant efficacy, the first being an RCT of sertraline; the second, an open-label case series of the effects of citalopram.

The study on sertraline was a double-blind placebo controlled trial, with block randomization, in which treatment was administered for 10 weeks.[113] Participants were at least six months post-TBI, and TBI included documented loss of consciousness or other evidence, such as pathology or imaging. Diagnosis of depression was established by DSM-IV criteria and a HAM-D score higher than 18. Dosage of sertraline was not fixed, and could be adjusted at two-week intervals, with a maximum dosage of 200mg/d. The primary outcome of interest was a change in depression status measured with the HAM-D. A positive response was considered to be a decrease of 50 percent, or a drop below 10 on the HAM-D. Of those that completed the study, 59 percent of the treated group and 32 percent of the control group had a positive response; the difference in response rates between the two groups was not statistically significant ($p = 0.08$).

The second study[114] investigated the effect of citalopram on depressive symptoms after TBI, using an open-label, single arm (case series) design. The study was limited to individuals with mild to moderate TBI. Mild TBI was defined as loss of consciousness at time of injury of 20 minutes or less, an initial GCS of 13-15 and post traumatic amnesia of less than 24 hours. Moderate to severe TBI had a GCS of less than 13, a PTA greater than 24 hours or an abnormal CT image. The study intended to evaluate the effects of a six-week course of treatment in 54 patients, however, low response rates resulted in a study extension for 26 participants to ten weeks. Therefore, although six week data were available for all 54 completers, 10-week data were available for 26 participants. The primary outcome measured was a change on the HAM-D score, with an improvement of 50 percent or more designated a positive response, and a score of less than eight defined as remission. In the six week data (n=54), 27.7 percent were classified as responders and 24.1 percent were in remission. Among participants with data at 10 weeks, 46.2 percent were responders and 26.9 were in remission. Of the 11 individuals who dropped out of the study, six were in the intended six-week group and 5 were in the intended 10-week group. Ten of the eleven experienced an adverse event.

Discussion

The amount of literature about traumatic brain injury is increasing rapidly, with the focus on the relationship between TBI and depression also growing. As is typical of advancing areas of research, early publications about TBI and depression have been predominantly cross-sectional, with little apparent consensus about measures or key covariates and a high degree of variability in quality of publications. Prospective studies of sufficient size to enable multivariate modeling of predictors of outcome or analysis of outcome by factors such as severity are rare. Achieving representative study populations is challenging because enumerating the entire population eligible for followup is hampered by the portion of the population who do not seek care for head injury. While studies in specialized settings like neuropsychiatric clinics or rehabilitation

programs can be applicable to estimating risk in those settings they cannot be generalized to the base population of all those with injuries.

Overall, the content of the current literature is fair to poor with a preponderance of study designs that do not provide strong evidence. As a result the strength of the literature is low for understanding the predictors, prevalence, natural history, treatment options, and modifiers of outcomes of depression that follows TBI. Nonetheless, considerable evidence suggests depression after all forms and severity of TBI is common.

We find a concerning lack of high quality evidence to inform clinical-decision making for the one to two million individuals in the United States who experience traumatic brain injury each year. Lack of treatment studies focused on this population is especially remarkable. Given how common, concerning and debilitating the combination of TBI and depression can be, a priority on promoting high-quality research in the United States is imperative.

Evidence Report

Chapter 1. Introduction

We do not know to what extent depression contributes to long-term disability following traumatic brain injury (TBI). Depression is one of several potential psychiatric illnesses that is common following TBI. Major depression may be triggered by physical or emotional distress, and can deplete the mental energy and motivation needed both for recovery efforts from the depression itself and for adapting to the physical, social and emotional consequences of trauma with brain injury. Recovery-related factors can trigger depression which can become chronic if depression is severe and treatment fails. Depression may be masked by other deficits after head injury, such as cognitive changes and flat affect, which may be blamed for lack of progress in post-trauma treatment but actually reflect underlying depression. Currently, clinicians, care givers, and patients lack formal evidence to guide the timing of screening, tools for screening and assessment, treatment choices, and assessment of treatment success.

Importance of Depression

Depression is defined by criteria that, in reality, likely circumscribe a heterogeneous set of illnesses. While no single feature is seen in all depressed patients, common features include sadness, persistent negative thoughts, apathy, lack of energy, cognitive distortions, nihilism, and inability to enjoy normal events in life. Especially in a first episode, individuals and families may not recognize the changes as part of an illness, making identification and self-reporting of the condition challenging. Active screening is essential to recognition, treatment, and prevention of recurrence.

The most salient consequence of depression is suicide. Suicide is usually impulsive and extremely difficult to predict and prevent. At least half of suicides occur in the context of a mood disorder. Depression reduces quality of life, impairs ability to function in social and work roles, causes self-doubts and difficulty taking action all of which can be critical in the context of recovery from TBI. The current criteria from the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) define the illness in terms of physiologic disturbances of sleep, appetite, attention and concentration, motor activity and energy, and of psychological losses of interest in normal activities, hope, and self-worth while ruminating with excessive sadness, guilt, and suicidal thoughts. These may be altered following TBI due to other circumstances, e.g. pain that disrupts sleep, which may mask the recognition that the sleep disturbance is also a part and parcel of a burgeoning depression. Depression may be fiscally costly in undermining physical therapy efforts, treatment compliance in general, rehabilitation planning and efforts, and disposition to situations where suicidal risk and behavior cannot be monitored and prevented. The need for systematic evaluation of the prevalence and consequences of depression following TBI is imperative, given the potential for mitigating suicide and unnecessary disability.

Overview of Traumatic Brain Injury

Traumatic brain injury (TBI) occurs when external force from events such as falls, assault, motor vehicle accidents or blasts injures the brain. It may occur as a result of a direct hit to the head, or from rapidly accelerating and decelerating wind accompanied by pressure changes that can injure the brain directly or propel other objects into the head (as from a blast).[4] TBI is often accompanied by symptoms that may be severe or mild, and in cases of mild TBI (mTBI), can

include nausea, headache, balance problems, blurred vision, memory loss or difficulty concentrating.[115]

Impact of Traumatic Brain Injury

The CDC estimates that 1.5 million non-military individuals in the US sustain a traumatic brain injury each year.[5] Because these estimates are based on hospital utilization data, and some individuals with mild TBI likely do not seek care or seek care in other settings, they probably underestimate the impact of TBI, particularly in the presence of sports related injury. They also do not include TBI that occurs in the military setting. Nonetheless, estimates of direct and indirect costs associated with TBI exceed $56 billion and may be increasing.[6] Among individuals who sustain a TBI, approximately 50,000 die each year of their injuries and 80,000 to 90,000 have a long-term disability. Traumatic brain injuries are considered mild, moderate or severe and are categorized using the Glasgow Coma Scale Score (GCS); a GCS of 13-15 is considered mild, 9-12 moderate and 3-8 severe. Most TBIs are mild, and CDC estimates that 75 percent of civilian TBI falls into this category (http://www.cdc.gov/ncipc/pub-res/mtbi/mtbireport.pdf).[116] Because of this, many TBIs likely remain unreported and untreated.

Military Traumatic Brain Injury

Traumatic brain injury is more common in the military than in civilian populations, even in peacetime. Within the military, the risk for TBI varies among specialties. Paratroopers for example are reported to be at higher risk for TBI.[117] Over the past decade, advances in body protection systems have resulted in fewer deaths among combat forces, but a concomitant rise in TBI has been observed.[4] Indeed, prevalence of combat-related brain injuries in forces active in Iraq and Afghanistan appears higher than in any prior conflict. Among patients with combat-related injuries at Walter Reed Army Medical Center from 2003 to 2005, 30 percent had sustained a TBI.[8] A major cause of TBI in the current conflicts is blast injury, in which injuries occur as a result of changes to atmospheric pressure, objects hitting people as a result of the blast, or people being thrown against objects.[118] Unlike the civilian population, however, the military population has a higher rate of moderate and severe TBI (56 percent) than mild TBI.[118]

Civilian Traumatic Brain Injury

Outside of the military theater, TBIs are most commonly associated with falls (28 percent), motor vehicle-traffic accidents (20 percent), being struck by objects (19 percent), and assault (11 percent).[119] Much of the research in the non-military population, especially on mild TBI, is derived from the sports injury literature. Because athletes tend to represent a healthier subpopulation, this literature may not be entirely applicable to the general population of individuals who sustain a TBI. However, it is likely the most robust source of information on TBI in civilians in general.

Relationship of TBI to Post-injury Psychiatric Conditions

TBIs are associated with a range of short- and long-term sequelae, including physical, cognitive, behavioral and emotional outcomes.[9] Symptoms of depression appear common in individuals who have sustained a TBI, with estimates of post-TBI depression ranging from 15 to 77 percent in the published literature.[10-12] Depression associated with TBI can manifest shortly after injury or well into the future,[13-14] and rates reported are likely affected by timing of

screening and tools used. In their review of TBI rehabilitation, in which they selected studies from PubMed Medline®, CINAHL, and PsycINFO®, Gordon and colleagues identified a total of 74 studies addressing psychiatric functioning after a TBI.[15] Their assessment was that TBI is associated with high rates of depression (up to more than half of cases) and of other DSM Axis I and Axis II conditions, including paranoid, schizoid and avoidant personality. Furthermore, depression was noted to be comorbid with other psychiatric conditions, including addiction or anxiety, in a number of studies.

Depression diagnosed post-injury is thought to be a product of multiple biopsychosocial factors including neuroanatomical or pathophysiological changes (i.e., brain lesions and specific location of lesions) as well as psychosocial factors such as concerns about disability or poor functional status.[13, 120]

Mechanism for post-TBI depression and implications for treatment. The exact mechanism by which individuals with TBI are at greater risk for depression has not been elucidated, although several causes seem possible. For example, mechanisms of post-TBI cellular injury include apoptosis and necrosis. [121] It seems likely that such mechanisms would affect the presentation and treatment of depression. For example, a self-reported history of blast exposure was associated with more headache and tinnitus than non-blast exposure injury mechanisms, but depression rates were similar (respectively 21.2 percent for n=156 versus 15.8 percent for n=38, p = 0.65).[122]

Lesion types and locations also may be important, but since pharmacologic treatments address widespread network phenomena, they simultaneously target function in multiple regions, suggesting that choice of medical treatment may depend more on potential harms than mechanism by which the depression is caused. Cognitive therapy may be contra-indicated in the presence of severe concomitant cognitive deficits, as it is in depression of non-traumatic etiology, but this assumption has yet to be empirically examined in the TBI population. Other psychotherapy model selections may turn out to depend more on cognitive capacity, psychological-mindedness and emotional lability than on the involvement of specific biological lesions or magnitude of psychosocial factors.

Timing of depression onset. Clinical care providers and families need to know when and how to screen TBI patients for depression. However, literature on the timing of depression onset should be interpreted carefully, since decisions about when and how to conduct screening within the study could bias results. Intuitively, early-onset depressions might seem more likely to have a neuroanatomic source, while later onset might be presumed to be related to patients' realizations of impairment severity and limitations that are likely to become persistent. These differences could influence interpretation of timing and methods of depression screenings, if indeed earlier screening captures the "neurobiological" depressions and misses the later onsets of "situational" reactions associated with ongoing treatments, complications, or unyielding plateaus in improvement.

Pre-morbid conditions and TBI. Also of concern is the way in which pre-injury status may have affected both the likelihood of sustaining an injury and the future risk of depressive disorder. For example, the relationship observed between alcohol use or abuse and TBI may be circular in that pre-injury use can increase the risk of injury but may also be related to an increased risk of psychiatric sequelae when an injury does occur. Other factors, such as demographics and support systems in place prior to injury may also confound relationships between injury and depression, and may also affect the perceived need for screening, the criteria for diagnosis, diagnostic elements, goal-setting, and successful assessments with treatment.[120]

Diagnosing depression in patients with TBI. Significant overlap between the brain regions associated with the core symptoms of depression and those that are often damaged in TBI (especially frontal lobe lesions), makes accurate diagnosis of depression challenging. Symptoms of postconcussion syndrome (PCS), which is common after TBI, may include: cognitive deficits, disordered sleep, irritability, aggression, anxiety, depression, changes in personality, affective lability, and apathy or lack of spontaneity. Many of these symptoms are also commonly present in a variety of mental disorders such as both unipolar and bipolar mood disorder and anxiety disorders. Therefore it can be difficult to distinguish, especially in a single diagnostic interview, if these symptoms truly reflect an independent psychiatric disorder or whether they are better understood as simply additional symptoms of TBI or PCS.[123] Longer periods of observation may be needed to assess the degree to which an intrinsic variability of post-TBI symptoms over time is associated with, or dissociated from, the sadness and disinterest that is considered a hallmark characteristic of depression. Additionally, atypical presentations of depression are anticipated in the TBI population, where paradoxical laughter may appear in lieu of tears to express sadness. Furthermore, the timing of the assessment may affect whether depression is suspected or preliminarily identified. Reviews should address questions of how and when depression might best be assessed.

Treatment Options

This review focuses specifically on depression following TBI and the treatment of depression in this context (i.e., not the treatment of the TBI per se). Treatment options for depression after a TBI theoretically include the range of psychotropic medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other, non-FDA approved uses of both older and novel medications, as well as psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine (CAM) and neuromodulation therapies (ECT and others) that may be routinely or only recently applied to the treatment of non-TBI associated depressions. Decisions about treatment approach may be affected by the clinician's understanding of the etiology of the initial injury as well as issues of timing of onset of the depression and concomitant conditions.[124] As with nonpsychotic, unipolar depression in the general population,[125-126] in TBI an evidence-based modality of psychotherapy would be a first option with the option to initiate antidepressant medications concomitantly or in sequence.

Treatment harms, included well recognized side effects, may also be of particular concern in this population, because systematic evidence is generally available for most medications only for intact, depressed but otherwise healthy individuals. For example, many psychotropic medications can lower the seizure threshold in a population already potentially predisposed to seizure due to TBI. When patients do have seizure disorders or other TBI-related outcomes, they may already be on medication, and therefore at risk for potential drug-drug interactions. Other side effects, such as gastrointestinal distress or weight gain, may also occur in this population, and it is not clear if they may occur at lower doses than in the non-injured population. In patients who present with apathy associated with TBI that is misdiagnosed as depression, antidepressants can sometimes worsen this symptom just as they do in the non-TBI depressed population by causing emotional blunting.[124]

Key Questions and Analytic Framework

Key Questions

We synthesized evidence in the published literature to address these key questions:

KQ1. What is the prevalence of depression after traumatic brain injury and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing incident clinical depression?

KQ2. When should patients who suffer traumatic brain injury be screened for depression, with what tools and in what setting?

KQ3. Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, PTSD, substance abuse and major psychiatric disorders?

KQ4. What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing:

a. psychotropic medications
b. individual/group psychotherapy
c. neuropsychological rehabilitation
d. community-based rehabilitation
e. CAM
f. neuromodulation therapies and
g. other therapies?

KQ5. Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?

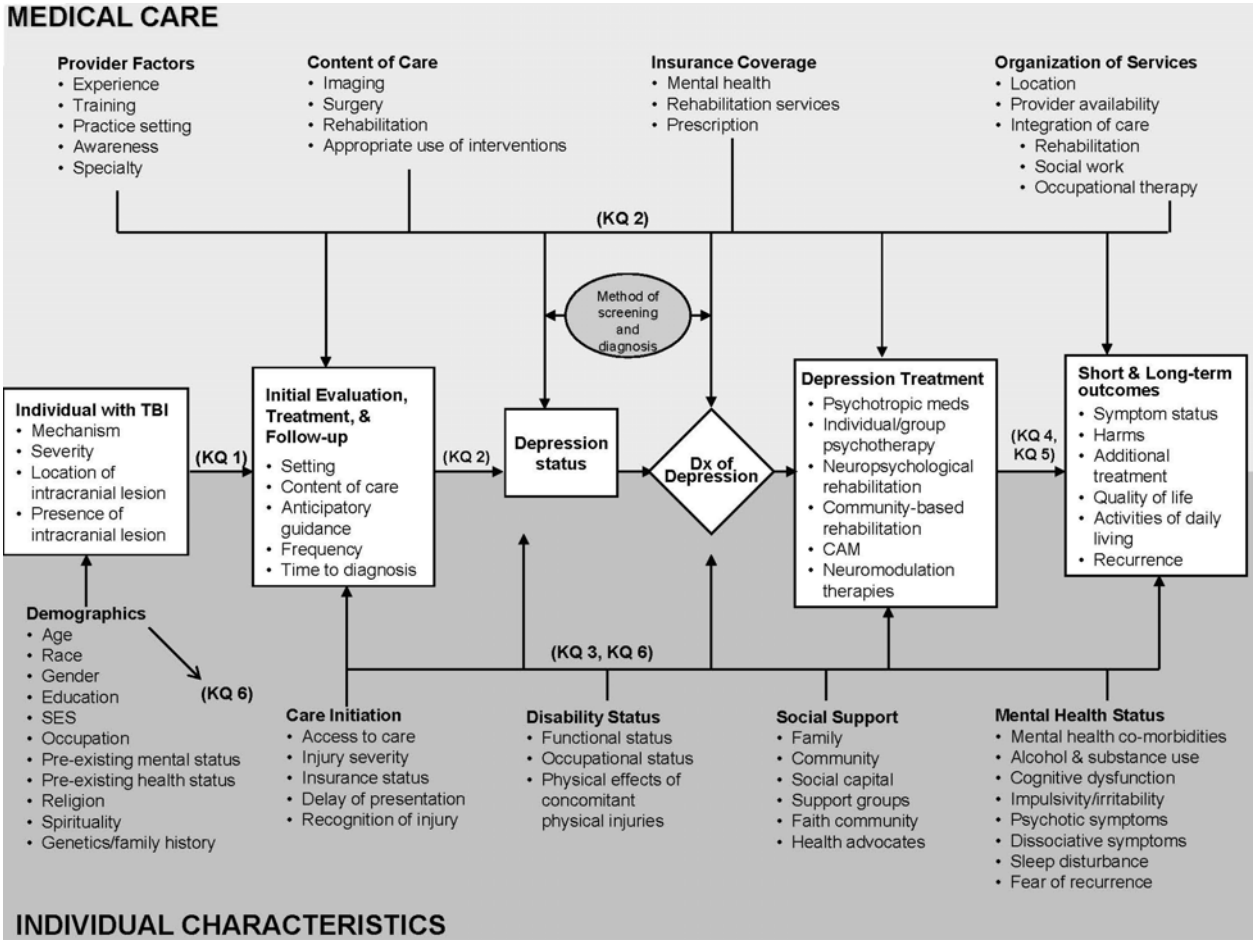
KQ6. Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, pre-existing mental health status or medical conditions, functional status, and social support?

Analytic Framework for TBI and Depression

The context in which diagnosis and treatment of depression occurs for individuals after TBI is complex. Our analytic framework emphasizes that care takes place at the interface of the health care system and the individual (Figure 1). The pathway through care is indicated in the boxes along the center line where the person and care meet. Each key question is indicated within the framework at the relevant point of influence in care. Each of the domains listed among individual and system factors, such as demographics, social support, provider factors, and healthcare coverage status, has been shown to influence care trajectories and outcomes across a range of conditions. Making these domains explicit as they surround and influence the care pathway provides the framework in which the review team and technical expert panel conducted this review. To the degree that individuals or care settings vary in context-specific points of influence the literature may or may not be applicable. We recognized for TBI and depression that there is a dearth of literature for a large portion of these domains and aimed to focus where expert guidance felt evidence was most likely. Overall, we sought to examine factors within the central care pathway as well as in selected contextual domains like setting (a portion of KQ2),

psychiatric comorbidities that could complicated care (KQ 3), and influence of individual characteristics on outcomes as a step towards enhancing applicability of the results (KQ 6). Portions of the framework that are unexplored in the scientific literature are highlighted in the considerations of future research needs.

Figure 1. Analytic framework for TBI and Depression



Organization of this Evidence Report

Chapter 2 describes our methods including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and for extraction of data into evidence tables, and compiling evidence. We also describe the approach to grading the quality of the literature and to describing the strength of the literature.

Chapter 3 presents the results of the evidence report by key question, synthesizing the findings across treatment type. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies to bring into focus the number of duplicate publications in this literature in which multiple publications are derived from the same study population. Chapter 4 discusses the results in Chapter 3 and enlarges on methodologic considerations relevant to each key question. We also outline the current state of the literature and challenges for future research on depression after TBI.

Technical Expert Panel (TEP)

We identified technical experts on the topic of traumatic brain injury and depression in the fields of trauma surgery, neurology, psychiatry, psychology, military/wartime health care, and patient advocacy to provide assistance during the project. The TEP (see Appendix E) was expected to contribute to AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included seven members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and key questions at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on the information and categories included in evidence tables;
- Develop a hierarchy of participant characteristics and outcomes to systematically assess;
- Advise about the clinical availability, use, and most common doses for therapeutics.

Because of their extensive knowledge of the literature, including numerous articles authored by TEP members themselves, and their active involvement in professional societies and as practitioners in the field, we also asked TEP members to participate in the external peer review of the draft report.

Uses of this Report

This report is intended to describe the extent to which depression occurs after TBI, appropriate timing and methods for diagnosis, and available evidence for treatment. It should be of use to groups and individuals who treat patients with traumatic brain injury; for example research and clinical psychiatrists, psychologists, physiatrists, trauma surgeons, neurologists, speech, occupational, and physical therapists, and primary care physicians. In particular, evidence in the report could be used to prioritize need for screening for depression in those patients. Of particular importance is the role of this report for guiding future research by identifying current gaps, particularly in the treatment literature, given the near absence of research on treatment for depression in TBI-affected populations. Future research recommendations could be helpful to investigators, funders and policy makers, with the goal of advancing understanding the causes, natural history, and most effective care of individuals with depression after TBI.

Chapter 2. Methods

In this chapter we document the procedures that the Vanderbilt Evidence-based Practice Center used to develop this comprehensive evidence report on the Treatment of Depression after Traumatic Brain Injury. We first describe our strategy for identifying articles relevant to our key questions, our inclusion/exclusion criteria, and the process we used to abstract relevant information from the eligible articles and generate our evidence tables. We also discuss our criteria for grading the quality of individual articles and for rating the strength of the evidence as a whole. Finally, we describe the peer review process.

Literature Review Methods

Inclusion Criteria

Our inclusion criteria were developed in consultation with the TEP, to capture the literature most tightly related to the key questions. Criteria are summarized below.

Table 1. Inclusion and exclusion criteria for treatment of depression after traumatic brain injury

Category	Criteria
Study population	Adults aged ≥16 years old
Study settings and geography	Developed nations: United States, Canada, United Kingdom, Western Europe, Japan, Australia, New Zealand, Israel, South America
Publication languages	English only

Admissible evidence (study design and other criteria)	Admissible designs
	Randomized controlled trials, cohorts with comparison, case-control, and case series (n ≥ 50)
	
	Other criteria
	• Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results
	• Patient populations must include participants that have been diagnosed with depression following a traumatic brain injury received in adulthood
	• Studies must address one or more of the following for depression after traumatic brain injury:
	  o Treatment modality
	  o Symptom management approach
	  o Short- and long-term outcomes and quality of life
	• Relevant outcomes must be able to be abstracted from data presented in the papers

We limited the review to studies published in developed countries to better approximate the U.S. healthcare system in terms of access to screening and treatment services. We did not have translation services available to us to review non-English papers, and our TEP agreed that the vast majority if not all of the relevant literature would be published in English. Furthermore, this review is intended to inform U.S. healthcare and most research in this population is published in studies. Empirical evidence on the potential for bias created by excluding non-English studies

also suggests little effect (REF). All study designs except individual case reports were included in order to be inclusive and identify all possible prevalence, screening and treatment studies. The decision to require at least 50 participants in each study was made in concert with our TEP, and resulted in the exclusion of only 36 studies, of which one was an RCT. The adult trauma population is defined at the Level I trauma center as greater than or equal to 16 years of age. Short and long term outcomes in traumatic brain injury in children is pathologically distinct from the adult population.[127] We chose to limit this study to the adult population of traumatic brain injury and outcomes associated with depression. In order to ascertain prevalence, and to further assess potential modifiers of likelihood of being depressed, it was important that studies use an acceptable means of diagnosing depression. We accepted a structured clinical interview, or any validated diagnostic tool, excluding for these questions any studies that relied on simply self-report of depressed status, or that did not describe their approach to depression diagnosis.

Additional criteria. In order to answer Key Question 1, studies had to provide some measure of prevalence. We excluded studies that did not provide prevalence data (e.g. for which only mean depression scores were available).

In order to answer Key Question 2, studies had to provide data that allowed prevalence to be assessed in accordance with a specific timeframe, setting or tool (or some combination of these). Therefore, studies that did not provide any information about when depression screening took place relative to injury were excluded.

In order answer Key Question 3, we required that studies present data on comorbid psychiatric conditions within the depressed population separately from the nondepressed population as our intent was not to measure these conditions in the general TBI population, but to explain their specific relationship to depression.

This review focused on the prevalence of diagnosed depression in populations that had sustained a documented traumatic brain injury, and on the treatment of those populations. We excluded studies of individuals with penetrating head injuries because penetrating injury, such as gunshot wounds, create specific and severe tissue damage along the course of the injury as well as associated bleeding and inflammation. The mechanism of injury associated with blunt force trauma to the head more often leads to a diffuse pattern of injury that may affect the entirety of the brain. Although long-term outcomes may be similar in some penetrating head injury cases, our focus on the more global nature of blunt force trauma and its consequences lead us to exclude studies of penetrating head injuries from this review.

Literature Search and Retrieval Process

Databases: Our search included examination of results in five databases: PubMed Medline, the PsycINFO® database of psychological and psychiatric literature, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Published International Literature on Traumatic Stress (PILOTS) database. We also hand-searched the reference lists of relevant articles to identify additional citations for review.

Search terms: Controlled vocabulary terms served as the foundation of our search in each resource, complemented by additional keyword terms and phrases selected to represent each of the key concepts in the search. We also employed indexing terms when possible to exclude undesired publication types (e.g. reviews, case reports, letters, etc.) and articles published in languages other than English.

Tables 2-6 outline our search terms and results yielded by each of the databases. Our searches were executed between March and June 2009. From PubMed, we identified 1,441 items for further review; PsycINFO® yielded 294 items; EMBASE yielded 195 items; CINAHL yielded 108 items; and PILOTS yielded 103 citations. After eliminating duplicate citations, 1617 citations comprised our pool of citations for review.

Table 2. Pubmed search strategies (last updated June 2009)

Search #	Terms
#1	(Brain Concussion[mh] OR brain injuries[mh:noexp] OR Brain Hemorrhage, Traumatic[mh] OR Epilepsy, Post-Traumatic[mh] OR Head Injuries, Closed[mh] OR Head Injuries, Penetrating[mh] OR Intracranial Hemorrhage, Traumatic[mh] OR Craniocerebral Trauma[mh] OR TBI[tiab] OR head injuries[tiab] OR head injury[tiab] OR traumatic brain injury[tiab] OR traumatic brain injuries[tiab] OR neurotrauma[tiab] OR diffuse axonal injury[mh] OR diffuse axonal injury[tiab] OR brain trauma[tiab] OR head trauma[tiab])
#2	Depressive Disorder[mh] OR Depression[mh] OR depressive[tiab] OR depression[tiab] OR depressed[tiab] OR sadness[tiab] OR sad[tiab] OR hopelessness[tiab] OR suicidal[tiab] OR suicide[tiab] OR Mental Disorders[mh:noexp] OR mood[tiab]

* Numbers do not total due to exclusions in more than one category (15 items were indexed as both letter and case report, 2 as comment and case report, 33 as review and case report, 4 as editorial and comment, 12 as letter and comment, 1 as review and comment, and 2 as editorial and review).

Table 3: PsycINFO® search strategies

Search #	Terms
#1	DE=("head injuries" or "brain concussion" or "traumatic brain injury") or KW=("head injury" or "head injuries" or "traumatic brain injury" or "traumatic brain injuries" OR "craniocerebral trauma" or neurotrauma or "brain trauma" OR "head trauma" OR TBI)
#2	DE=("depression emotion" or "major depression" or "hopelessness" or "sadness" or "suicidal ideation" or "suicide") or KW=(depressive or sad or hopeless or sadness)
#3	#1 AND #2 AND LA=(English) AND PO=(Human)

***** Denotes number of citation retrieved from peer-reviewed journals

Table 4: EMBASE search strategies

Search #	Terms
#1	head injury/ or brain concussion/ or brain contusion/ or diffuse axonal injury/ or postconcussion syndrome/ or traumatic brain injury/ or ("craniocerebral trauma" or "brain trauma" or "head trauma" or TBI or "traumatic brain injury" or "traumatic head injury" or "traumatic brain injuries" or "traumatic head injuries").ab. or ("craniocerebral trauma" or "brain trauma" or "head trauma" or TBI or "traumatic brain injury" or "traumatic head injury" or "traumatic brain injuries" or "traumatic head injuries").ti.
#2	mental disease/ or mood disorder/ or depression/ or major depression/ or suicidal ideation/ or hopelessness/ or (depressive or sad or sadness or hopeless).ti. or (depressive or sad or sadness or hopeless).ab.
#3	1 and 2 and english.lg. and human/

Table 5: CINAHL search strategies

Search #	Terms
S1	("traumatic brain injury") or (MH "Brain Injuries+") OR "neurotrauma" OR "brain injuries" OR "TBI" OR "concussion" OR "head injuries" OR "head injury" OR "head trauma" OR "brain trauma"
S2	((MH "Depression+") OR "depressive disorder" OR "sadness" OR "depressed" OR (MH "Suicide") or (MH "Suicide, Attempted") or (MH "Suicidal Ideation") OR "suicide" OR "hopelessness" or (MH "Hopelessness") OR "mood")
S3	S1 AND S2 AND LA English
S4	S3 AND Exclude MEDLINE Records

Table 6: PILOTS search strategies

Search #	Terms
#1	(DE="head injuries") or ("brain concussion" OR concussion OR "traumatic brain injury" OR "TBI" OR neurotrauma OR "traumatic brain injuries" OR "head trauma" OR "craniocerebral trauma" OR "brain injury" OR "brain injuries")
#2	(DE="depressive disorders") or (depression OR depressed OR depressive OR suicidal OR suicide OR sadness OR hopelessness)
#3	#1 AND #2 AND LA=(English)
#4	#3, limited to peer-reviewed journals

Methods for developing weighted averages for depression prevalence. The following processes were applied in order to select studies to be used in developing the prevalence histograms in the results section of KQ2:

Prevalence

- If a study was longitudinal with time since injury greater than 12 months and several followup measures sequentially following initial measure, the study was then included in the spreadsheet duplicate times for each time period (e.g., 2 years, 5 years, 10 years) under the " >12 months" column.
- If a study included different tools with prevalence measure for each, the study was included in the spreadsheet multiple times, once for each tool.

Glasgow Coma Scale

- If a study listed mean GCS score with percentages accounting for each severity group, the study was listed as including all TBI severity groups.
- If a study listed no GCS score, the study was not included in severity analysis
- If a study listed average GCS score with standard deviation or range, TBI severity groups fell into groups which fell into range. (e.g., GCS mean 8.0 ± 3.0, range 4-13, then TBI severity groups would be mild to severe and all TBI severity groups would be included in the spreadsheet)

Setting

- Setting was extracted from Evidence Tables

In addition, studies that explicitly evaluated approaches to diagnosing depression in TBI populations were included for the second part of KQ2. Studies for this sub-section were required to compare at least two tools for assessing depression and provide some statistical means of assessing validity and/or reliability.

For KQ3, we required that studies present data on comorbid psychiatric conditions within the depressed population separately from the nondepressed population as our intent was not to measure these conditions in the general TBI population, but to explain their specific relationship to depression.

Categorization of TBI measures for reporting. For the purpose of reporting results, we prioritized discussion of papers that adequately described severity levels of TBI in the patient population. Ideally these are defined by approaches endorsed by professional organizations including Glasgow Coma Scale, Centers for Disease Control and Prevention, World Health Organization, and American Congress of Rehabilitation Medicine criteria. Studies in which TBI was defined using an ad hoc approach or by patient self report are presented in Appendix C.

Categorization of depression diagnoses. In part due to the heterogeneity in both etiology and expression of depression, descriptions in the literature vary from a strict DSM-IV-TR definition of Major Depressive Disorder diagnosed via a SCID to a positive response to a simple inquiry asking if the patient has ever felt depressed after their injury. For purposes of the review, therefore, we considered participants to be depressed if they were designated as such by the authors of the studies, and endeavored to document the definition used within each study.

Identifying duplicate populations. Because the same study population can be used to do multiple analyses, we developed an algorithm to identify distinct research populations for inclusion in prevalence calculations. We referred to sets of papers that used the same study population as "families" and attempted to identify the "parent" study to provide a representative prevalence estimate.

Most straightforward, of course, were those families of papers in which references were provided that detailed explicitly the relationship between the individual studies, allowing us to identify the parent paper. When such references were not provided, we used a multi-step process to cluster papers and then a thorough review of methods and results to identify overlapping or identical populations. Papers were initially clustered by country, then by authors and author affiliations, and potential sets examined together. Within the potential sets of families, we assessed inclusion and exclusion criteria, screening methods, and settings of these studies. In a second step, population descriptors such as average time from injury, age, and population size were examined for identical measures across multiple papers. Of note, it is altogether possible for these characteristics not to match in family papers particularly in the case of longitudinal studies in which sequential analyses were conducted over time.

Within sets of publications identified as families, individual papers were designated as a "parent" or "child" paper for the purposes of abstracting prevalence data. We attempted to designate the most complete paper as the parent, which meant that it may not have been the earliest or latest publication from the data set. Factors that played into this determination included assessment of depression as the main outcome, population size (larger populations over smaller populations), inclusion of prevalence information, and inclusion of results over different time periods. Using this approach, we identified 68 unique populations: 52 single studies and 16 parent studies. The sixteen parent studies included 27 associated child studies.

Only parent studies were included in summary tables and prevalence calculations for Key Questions 1 and 2. Families are identified in Appendix C: Evidence Tables, with notes in the author field referring to associated studies. Studies utilizing clearly identical populations were combined into a single evidence table when possible.

Grey Literature Search Methods

We conducted a review of the literature for depression in the context TBI through a systematic search of resources likely to retrieve grey literature and fugitive information items

(Appendix A). Resources were chosen for their relevance to the topic and for their utility in locating unpublished or nontraditional information.

Search of the Grey Literature

We adapted our approach to the published literature for this survey of grey information sources with selected terms related to TBI and depression. Each database and resource searched (Appendix A) has unique features and characteristics that were utilized to improve sensitivity and specificity of our retrieval.

Utilizing the search engine Google®, our team searched the Internet using a combination of keywords to identify technical reports and other relevant data. We used the limit "allintext:" to retrieve only information with our keywords included on the web page and the feature "site: .gov,.org,.edu, .mil" to limit our search to only web pages from those designations. United States and international government resources and registries were employed to locate current clinical trial protocols and newly funded research projects. Given their strength in indexing unpublished resources, PsycINFO®, a psychology and psychiatry database, and BIOSIS Previews, a Biosciences database, were used to locate current conference proceedings, dissertations, and other grey literature sources. As a means to improve precision of the search strategy, we limited our retrieval to dissertations, meeting abstracts/papers, technical reports, and conference proceedings. To improve the depth of our grey literature review, our team explored several other resources that did not retrieve any additional information.

Literature Synthesis

Development of Evidence Tables and Data Abstraction Process

The staff members and clinical experts who conducted this review jointly developed the evidence tables. We designed the tables to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to our KQs, in particular the need to appropriately design evidence tables for prevalence versus treatment studies. We based the format of our evidence tables on successful designs used for prior systematic reviews.

The team was trained to abstract by abstracting several articles into evidence tables and then reconvening as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. Another member of the team also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The two abstractors reconciled disagreements concerning the information reported in the evidence tables. The full research team met regularly during the article abstraction period and discussed global issues related to the data abstraction process. In addition to outcomes related to treatment effectiveness, we abstracted all data available on harms. Harms encompasses the full range of specific negative effects, including the narrower definition of adverse events.

The final evidence tables are presented in their entirety in Appendix C. Studies are presented in the evidence tables alphabetically by the last name of the first author. When possible, studies

resulting from the same study population were grouped into a single evidence table. A list of abbreviations and acronyms used in the tables appears at the beginning of that appendix.

Two reporting conventions for describing studies in the evidence table were adopted that warrant explanation, namely those for study design and setting of the study. For settings we allowed five options, with the operating principle being that the setting should reflect the entity from which the participants were drawn, as this can be a reflection to some degree of injury severity, acuity or the reason that the individuals were seeking care and thus identified for the study.

- Tertiary care: academic medical centers and tertiary care hospitals
- Trauma center(s)
- Psychiatric/specialty center(s): psychiatry clinic, disability programs
- Rehabilitation center(s)
- Other: community, private practice, prison, non-academic VA

Study designs for this review were somewhat more difficult as "standard" study design definitions for systematic review are most often based on reviews of the treatment literature, and our primary focus was necessarily (due to a paucity of treatment studies) on assessment of prevalence. In this case, we were reviewing studies that may, for example, have been intended as cohort studies in populations with TBI and exposure groups other than depression. The characteristic used to define the cohorts in the study was not relevant for our review, but because the authors captured data on prevalence of depression in the study population, we were able to include the study. Therefore, for our purposes we defined studies in which a group of individuals was systematically described as having a TBI and then "sorted" through diagnosis into depressed and non-depressed groups to be cohort studies, even if there were other exposure groups or no groups defined by the authors. These cohorts could then be retrospective or prospective per the usual definitions about when data were collected. We also allowed for the usual definition of randomized controlled trials for the treatment portion of the review and for cross-sectional studies, in which participants were identified at one time-point with no longitudinal collection of data.

Assessing Methodological Quality of Individual Studies

We developed our approach to assessing the quality of individual articles based on our prior experience with conducting systematic reviews. In particular, we used distinct quality rating approaches for the studies used to measure prevalence and those for treatment.

Quality as it relates to prevalence studies is largely a function of appropriately identifying, defining, and enumerating the target population in which prevalence is to be measured. Prevalence estimates may be biased if the study population included has higher or lower rates of the outcome (in this case, depression) than does the population to which the prevalence estimate is intended to apply. Therefore, we based our quality assessment of prevalence studies on the authors' appropriateness in defining both TBI and depression (including tools used for measurement), in their provision of descriptive information about the TBI (such as mechanism and severity), their follow-up and retention methods including ability to not lose participants to follow up (which would bias estimates if depressed individuals either were or were not lost to follow up at different rates from non-depressed individuals). Therefore, we used eight primary questions with some sub-questions to assess quality of the prevalence literature.

Prevalence studies.

Definition of TBI: Because no single definition of TBI is consistently used in the literature, we worked with our clinical experts to develop a list of "best" approaches to defining or diagnosing TBI. Studies had to use one of these in order to be awarded the highest quality score under this criterion. Studies that specified an operational definition that was not included on the list of "best" definitions were given one plus. A complete lack of definition, or self-report (i.e., no evidence of clinical diagnosis) received a minus.

Severity of TBI: The severity of TBI is known to influence the trajectory of recovery, and thought to affect the risk of post-TBI depression. Therefore, studies should provide measures of TBI severity for included participants.

Definition of Depression: As with the definition of TBI, we worked with clinical experts to categorize and rank approaches to diagnosing depression. The full categorization is provided below, and for quality purposes we applied the following:

Was a clinical scale or operational definition provided?

++ = SCID or other structured interview by a trained mental health care provider such as a physician, psychologist, etc

+ = Operational definition or scale provided, but not a structured interview

- = Other definition, self-report, or not reported (NR)

Table 7. Categorization of Depression Measures for Reporting

Category A	SCID or other structured interview by a clinician (e.g., physician or psychologist)
Category B	Validated instruments other than clinical interview, including HAM-D, BDI, HADS, CES-D, NFI or SCL-90
Category C	Other definition, self report, ad hoc, chart review or no definition provided

Participant selection: For measuring prevalence and comparing studies of prevalence, it is necessary to clearly identify the population from which the cases arise. Therefore, we required that investigators clearly describe the participants, including the source, and that this description be adequate such that another researcher could create a comparable study population.

Sampling and screening methods: We used a three-part approach to assessing appropriate sampling and screening methods, requiring first that the pool of potentially eligible participants be clearly enumerated, second that the number meeting eligibility requirements be provided, and third that the number of participants at onset and conclusion of the study (if applicable) also be provided.

Loss to follow up: For longitudinal studies, we assessed the proportion of participants still in the study at completion. We expected less than 25 percent loss for high quality, between 25 and 50 percent for good quality, and studies that lost more than 50 percent of participants received a low quality (minus) score for this variable.

Two potentially important characteristics of participants that could affect prevalence are prior history of psychological conditions (i.e., psychological conditions in the post-TBI period may not be new onset) and time since injury. Therefore, for adequate quality we required that information on both of these be provided by the authors. We did not specify what information or the degree of information needed.

Treatment studies. For treatment studies, we assessed creation and comparability of comparison groups (selection bias), loss to follow up and drop out (attrition bias), statistical analysis, including evidence of adequate power, and external validity (also known as applicability).

Internal validity. The criteria for assessing internal validity were as follows:

Randomized allocation to treatment. This assessment combines randomization and method of randomization into a single criterion with a three-point scale.

Rationale: By randomly assigning groups to the intervention of interest, other factors that may confound the results are equally distributed between groups (assuming a large enough sample size). This equal distribution minimizes the chances of over- or underestimation of treatment effect based on unequal distribution of confounding factors.

If randomized, we also evaluated the study for randomization methods, using the rationale described in Matchar and colleagues, 2001.[128]

Rationale: "Pseudo-randomization" methods may be susceptible to bias, as demonstrated by evidence of unequal distribution of subject characteristics[129] and larger effect sizes compared with studies using more rigorous methods.[130] In addition, methods of allocation concealment are also important in preventing bias (e.g., use of prepared sealed envelopes).

We combined these elements into a single operational definition, as described below:

Operational definition: Criterion met if randomization methods were not susceptible to bias, such as computer-generated numbers in sealed sequentially numbered envelopes (+). Criterion not met by studies that either used methods more prone to bias, such as alternate medical record numbers, or did not describe randomization methods or methods of allocation concealment (-). Criterion not applicable if treatment was not randomly allocated (NA).

Masking.

Rationale: Masking, also known as blinding, refers to the concealment of treatment allocation from the care provider, the assessor, and the patient. In certain trials, particularly surgical trials, masking the patient or the surgeon from the treatment allocation can be challenging or impossible. Similarly, masking the assessor assigned to record immediate post-procedural outcomes such as wound healing can also be difficult. Nevertheless, when possible, masking prevents expectations from influencing findings.

Operational definition: Criterion was met if assessors and participants were masked to treatment or group (+). Criterion was not met if either care provider, assessor, or patient were not masked (-). Criterion not applicable if treatment was not randomly allocated (NA).

Adequate description of patients and control selection criteria.

Rationale: Patient characteristics that might affect outcomes (such as severity of symptoms, duration of symptoms, failure of prior treatment, or medical comorbidities) are likely to differ between two interventions. If these differences are not characterized, then erroneous conclusions may be drawn.

Operational definition: Criterion met if (a) inclusion and exclusion criteria for participation in the study were well described.

We expected that the study population should be adequately described to make clear the potential for confounding in the analysis. We expected the study authors to adequately describe the study population such that it could theoretically be reproducible by another investigator. We expected comparable methods to be used to identify and screen participants across exposure or treatment groups.

Description of loss to followup.

Rationale: Failing to account for patients lost to followup may lead to erroneous conclusions, especially if the loss to followup is related to either the underlying disease or the intervention

(e.g., patients seeking care elsewhere because of continuing symptoms or unacceptable side effects of treatment).

Operational definition: Criterion met for adequate followup (+) if (a) loss to followup was explicitly reported and (b) no more than 20 percent of any study arm was lost to followup. Those studies with less than 10 percent lost to followup were given an extra (+). Studies with greater than 20 percent lost to followup were considered inadequate for this measure (-).

Description of dropout rates.

Rationale: Dropout rates may reflect differences in clinically important variables, such as side effects or treatment response. Failure to account for dropouts may result in erroneous conclusions similar to those seen with failure to account for loss to followup.

Operational definition: Criterion met if (a) patients dropping out of the study prior to completion were reported and (b) no more than 20 percent in any study arm left the study for reasons related to the study intervention or withdrawal of consent. Those studies with less than 10 percent dropout were given an extra (+). Studies with greater than 20 percent dropout were considered inadequate for this measure (-).

Power calculation provided.

Rationale: Many studies, especially case series, lack sufficient power to detect clinically important differences in outcomes or patient characteristics.

Operational Definition: Criterion met if a power calculation (pre or post) was provided.

Recognition and description of statistical issues.

Rationale: Use of inappropriate tests may lead to misleading conclusions. For example, variables such as depression scores are often not normally distributed; use of means instead of medians when data may be affected by outlying observations can be misleading.

Operational definition: Criterion met if (a) appropriate statistical tests were used (e.g., nonparametric methods for variables with nonnormal distributions, or survival analysis techniques to account for loss to followup and dropouts) and (b) potential study limitations regarding design and analysis were discussed. Criterion not met if (a) inappropriate statistical tests were used or (b) study limitations were not discussed. An intention-to-treat (ITT) analysis was required of clinical trials.

External validity. The criteria for assessing external validity were as follows:

Baseline characteristics: We created a composite score for adequacy of the description of baseline characteristics. We expected the severity of the TBI and time since the TBI event to be presented. If either of these were omitted, criteria were not met.

Strength of Available Evidence

Strength of evidence is typically assigned to reviews of medical treatments after assessing four domains: risk of bias, consistency, directness and precision.[131] Although these categories were developed for assessing the strength of treatment studies, the domains apply also to studies of prevalence and screening. Available evidence for each key question was assessed for each of these four domains; the domains were combined qualitatively to develop the strength of evidence for each key question.

We graded the body of literature for each key question and present those ratings as part of the discussion in Chapter 4. The possible grades were:

I. High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.

II. Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

III. Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.

IV. Insufficient: Evidence is either unavailable or does not permit a conclusion.

External Peer Review

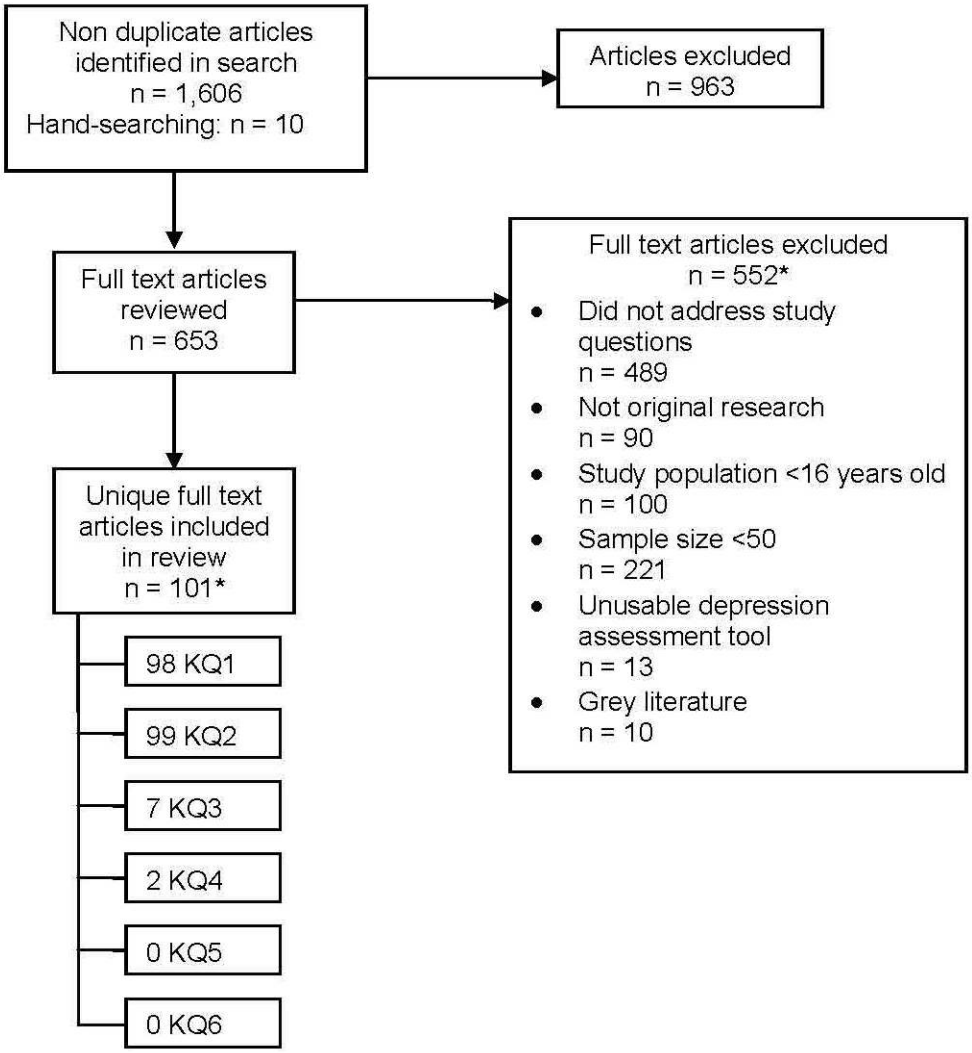
As is customary for all systematic evidence reviews done for AHRQ, this report was reviewed by a wide array of individual outside experts in the field, including our TEP, and from relevant professional societies and public organizations. AHRQ also requested review from its own staff. The Scientific Resource Center sent XX invitations for peer review. Reviewers included clinicians (e.g., trauma surgeons, military and combat physicians, physical medicine and rehabilitation physicians, and psychiatrists), representatives of federal agencies, advocacy groups, and potential users of the report.

The Scientific Resource Center charged peer reviewers with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and KQs. We also asked reviewers to complete a peer review checklist. The Scientific Resource Center received XX responses in addition to comments from AHRQ staff. The individuals listed in Appendix E gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate.

Chapter 3. Results

Article selection process. Once we identified articles through the electronic database searches, review articles, and bibliographies, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated each abstract for inclusion or exclusion, using an Abstract Review Form (Appendix B). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. The group included six physicians (KH, OG, RS, SM, FP, SK), and two senior health services researchers (MM, RJ). Of the entire group of 1606 articles, 653 required full text review. For the full article review, two reviewers read each article and decided whether it met our inclusion criteria, using a Full Text Inclusion/Exclusion form. Reasons for article exclusion are listed in Appendix D.

Figure 2. Disposition of articles for TBI and Depression



KQ = key question
*The number of articles addressing key question and those excluded exceed the total number of articles in each category because some of articles fit into multiple exclusion categories or addressed more than one key question.

KQ1. Prevalence of Depression in Traumatic Brain Injury

Understanding the meaning of prevalence estimates requires knowing about both the TBI population and the method of depression ascertainment. In this section we describe prevalence in the context of the definition of traumatic brain injury and severity level, as well as the measure of depression used in the research.

Prevalence

We sought publications that provided a defined group of individuals with TBI and used a validated measure of depression to assess the proportion of the population who met specified criteria for depression. We excluded reports relying on simple self-report or single screening items. This key question focuses on prevalence because prior and existing depression at the time of head injury are difficult to document in order to formally study incidence.

We identified 98 publications,[7, 12-14, 18-111] from 71 distinct study populations (see Appendix C, Evidence Table 1.). Thirty-six of the 71 were in the United States, 11 in Canada, 12 in Europe, 5 in Australia, and 7 in other countries (Table 8). The most common sources of study populations were tertiary care centers identifying participants from emergency department, intensive care, and inpatient admissions (n = 30), including those that specifically noted trauma center status (n = 8), and rehabilitation programs (n = 17). Neuropsychology labs, private neuropsychology practices, prisons, veterans' records, databases, and psychiatric care facilities each contributed three or fewer populations.

Criteria for defining and characterizing those classified as having TBI were varied with more than half of authors (n = 36) using closed head injury in concert with Glasgow Coma Scores (GCS). American Congress of Rehabilitation Medicine (ACRM) criteria were common (n = 12); as were ad hoc operational definitions (n = 11), and failing to clearly define criteria (n = 9). In total, the majority of the literature provides sufficient detail about inclusion and exclusion criteria and TBI definitions to understand and/or replicate the population studied.

Seventy percent of studies provided cross-sectional measures of depression, meaning that depression status was assessed at a single point in time after TBI; the balance were prospective with two or more assessment of depression status over time. Structured clinical interviews, done specifically for the research or in the course of standardized clinical care protocols, were the most common means of assessing depression status (n = 28). Among written or administered tools the Beck Depression Inventory (BDI; n = 11), Center for Epidemiologic Studies Depression Scale (CES-D; n = 8), and Hospital Anxiety and Depression Scale (HADS; n = 8) were most common. A wide variety of other measures and customized uses of subscales (n = 61) were also used. Studies often used more than one instrument, reporting different facets of the scores or evaluation. Comparison of diagnostic test characteristics, agreement of classification, and use of expert SCID as a gold-standard for comparisons were rare (see KQ2); while statistical analyses of correlation of scores or relationships of domains were frequent but generally not intended to directly assess clinical utility.

Table 8. Characteristics of included TBI and depression studies

Characteristic	Population Studied				
	US (n = 36)	**Canada** (n=11)	**Europe** (n=12)	**Other** (n=12)	**Total** (n=71)
Assessment of depression:					
Cross-sectional	22	8	9	11	50
Prospective	14	3	3	1	21
Setting					
Trauma center(s)	7	0	0	1	8
Tertiary care center(s)	9	6	9	6	30
Rehabilitation center(s)	8	2	3	4	17
Psychiatric/specialty center(s)	2	0	0	0	2
Other	10	3	0	1	14
Operational Def of TBI*					
CDC Criteria	1	0	0	0	1
WHO Criteria	1	0	0	0	1
ACRM Criteria	7	5	0	0	12
GCS Score	19	5	5	7	36
Self-Report	2	0	0	1	3
Other	2	0	6	3	11
Not Defined	6	1	1	1	9
Depression Tool Used*					
SCID	19	4	1	2	25
Other structured interview	1	0	2	0	3
MMPI	2	2	0	0	4
HAM-D	2	0	2	1	5
BDI	6	1	1	3	11
CES-D	7	0	0	1	8
HADS	2	0	4	2	8
NFI	5	0	0	0	5
SCL-90	2	0	1	1	4
Other	14	8	11	10	43

* Inclusive: total is greater than number of studies because some publications used multiple definitions or tools.

For this report, we have considered the SCID and other formal structured clinical interview protocols that map to the DSM and/or ICD codes to be the measures of depression that are most relevant to clinical care. Ideally patients and care providers want to know what proportion of those with TBI may meet clinical criteria for diagnosis and treatment of depression. Among studies that used a SCID or other structured protocol to reach a formal diagnosis of depression, the prevalence of depression after TBI ranged from 12.2[53] to 76.7 percent.[12] If we focus on the subset of studies with both clearly operationalized criteria for TBI and use of the SCID, the range was 12.2[53] to 54.0 percent.[96] Across all timeframes and depression measures, in studies with clear TBI definitions, the weighted average for prevalence of depression was 29.6 percent.

Table 9 summarizes context, size of study, measures, and prevalence of depression among studies with clear definitions of TBI. Appendix C includes a similar summary table for studies

that provided less information about TBI criteria. In both sets of studies – those with and without optimal definitions of TBI – the observed prevalences are compatible. In these tables, results are organized by timeframe in which the depression assessment was conducted relative to the injury and by method of assessment. Across all included populations, measures, and timeframes the aggregate prevalence was 31.6 percent.

Among those studies with longer term followup, no clear pattern of expected prevalence or natural history emerges:

- Veterans who were hospitalized for TBI approximately 50 years earlier had an 11.2 percent point prevalence of depression, statistically higher than the 8.5 percent among those hospitalized for conditions other than TBI.[14]
- Assessment of a group with severe TBI at a mean of 14 years from injury was associated with 44.7 percent prevalence.[18]
- Among studies with assessments five to 10 years from TBI, reported prevalences were 9.8 percent[92], 23 percent[90],. 29.5 percent[44], and 70 percent.[99]
- Those with assessments three to five years from TBI, reported prevalences that ranged from 34 to 77 percent.[12, 19, 25, 42, 52, 72]

Among the studies that included comparison groups 19 reported higher prevalence of depression among those with TBI than those without.[7, 12, 14, 22, 30, 36, 40-42, 59, 62, 70-71, 79, 84-86, 88, 99] Exceptions included comparison to: a psychiatric population control group with an equivalent proportion having depression (30 percent);[24] patients with multiple serious injuries from trauma that did not include TBI to patients with TBI in which both groups had 76 percent with depression;[35] and a matched control group from the same district in Finland in which both groups had approximately six percent prevalence.[48] In no instance was the comparison group significantly more affected by depression.

Table 9. Prevalence of depression by timing of assessment

Author, Year Country Setting	**N with TBI,** (% with Depression Measure)	**GCS Score**	**Assessment Method** (mean score)	**Prevalence %**
		Unspecified time from injury		
Bombardier et al.[110] 2006 US Trauma center	141 (87.9)	3-15	PHQ (NR)	21.8
Evans et al.[45] 2005 US Rehabilitation center	96 (100)	3-15	CES-D (NR)	54.0
Hoge et al.[7] 2008 US Veterans records	384 (95.8)	CDC/WHO criteria	PHQ (NR)	13.0
Kant et al.[94] 1998 US Psychiatric/specialty center	83 (100)	3-15	BDI (18.03) AES (38.84)	10.8 60.2

Table 9. Prevalence of depression by timing of assessment (continued)

Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
Ruocco et al.[24] 2007 US Neuropsych. clinic	231 (100)	13-15	MCMI-III Depressive (46.62) MCMI-III Major Depression (56.70)	16.9 30.3
< 3 months since injury				
Gomez-Hernandez et al. [95] 1997 Spain Tertiary care center	65 (100)	3-15	SCID	35.4
Jorge et al.[13, 98, 101-104] 1993 US Trauma center	66 (100)	3-15	SCID	28.8
Jorge et al.[59, 63] 2004 US Other	91 (81.3)	12.3 (mean)	SCID	20.2
McCauley et al.[70] 2001 US Tertiary care center	115 (100)	9-15	SCID CES-D (22.5) VAS-D (40.1)	21.7 NR NR
McCauley et al.[49-50] 2005 US Trauma center	340 (100)	9-15	SCID	15.0
Rao et al.[21] 2008 US Tertiary care centers	54 (100)	3-15	SCID	13.0
Rapoport et al.[64, 66] 2003 Canada Tertiary care center	210 (100)	13-15	SCID	16.7
Kashluba et al.[41] 2006 Canada Tertiary care centers	110 (100)	13-15	PCL (NR)	40.0
Rapoport et al.[69] 2002 Canada Tertiary care center	323 (87.3)	3-15	NRS (NR)	Mild/Mod: 34.3
Sherer et al.[27] 2007 US Rehabilitation center	69 (100)	8.0 (mean)	CES-D (11.6)	31.9

Table 9. Prevalence of depression by timing of assessment (continued)

Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
3 to 6 months since injury				
Brown et al.[55] 2004 US Trauma center	135 (100)	14.47 (mean)	SCID	16.3*
Gomez-Hernandez et al.[95] 1997 Spain Tertiary care center	65 (73.8)	3-15	SCID	37.5
Jorge et al.[101, 13, 98, 102-104] 1993 US Trauma center	66 (81.8)	3-15	SCID	29.6
Jorge et al.[59, 63] 2004 US Tertiary care centers	91 (81.3)	12.3	SCID	32.4
Levin et al.[71] 2001 US Trauma center	69 (100)	9-15	SCID CES-D (22.14) VAS-D (40.79)	17.4 NR NR
Dunlop et al.[106] 1991 US Disability database	68 (100)	9.2 (mean)	NRS (NR)	50.0
Kashluba et al.[41] 2006 Canada Tertiary care centers	110 (100)	13-15	PCL (NR)	39.1
McCauley et al.[73] 2001 US Trauma centers	210 (100)	ACRM criteria	NRS-R (NR)	51.0
Rapoport et al.[69] 2002 Canada Tertiary care center	323 (87)	3-15	NRS (NR)	Severe: 48.9
6 to 12 months since injury				
Chamelian et al.[37, 54] 2004 Canada Tertiary care center	90 (100)	9-15	SCID GHQ (0.85)	12.9 NR
Gomez-Hernandez et al.[95] 1997 Spain Tertiary care center	65 (64.6)	3-15	SCID	38.1
Gomez-Hernandez et al.[95] 1997 Spain Tertiary care center	65 (66.2)	3-15	SCID	32.6

Table 9. Prevalence of depression by timing of assessment (continued)

Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
6 to 12 months since injury				
Jorge et al.[13, 98, 101-104] 1993 US Trauma center	66 (65.2)	3-15	SCID	25.6
Jorge et al.[59, 63] 2004 US Tertiary care centers	91 (100)	12.3 (mean)	SCID	40.5
Mooney et al.[74] 2001 US Rehabilitation center	80 (100)	13-15	SCID	44.0
Rapoport et al.[36, 39] 2006 Canada Rehabilitation center	69 (71)	9-15	SCID Major	12.2 18.8
Rapoport et al.[53] 2005 Canada Tertiary care center	74 (100)	9-15	SCID	28.4
Bay et al.[31, 67] 2002/2007 US Tertiary care center	75 (100)	>8	CES-D (20.45) NFI (30.69)	64.0 14.7
Bryant et al.[77] 2001 Australia Rehabilitation center	96 (100)	8.00 (mean)	BDI (16.5)	45.8
Dunlop et al.[106] 1991 US Disability database	68 (100)	9.2 (mean)	NRS (NR)	28.0
Ghaffar et al.[34] 2006 Canada Tertiary care centers	191 (63.9)	14.9 (mean)	GHQ	28.7
Hawley and Joseph [20] 2008 UK Rehabilitation centers	563 (29) at 10 years	3-15	HADS (NR)	20.5
Kersel et al.[32, 75] 2001 New Zealand Tertiary care center	69 (84)	<9	BDI (NR)	24.0
McCleary et al.[86-88] 1998 US Tertiary care center	105 (100)	3-15	SCL-90 (NR) NRS (NR)	24.4 33.0

Table 9. Prevalence of depression by timing of assessment (continued)

Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
		>12 months since injury		
Al-Adawi et al.[28] 2007 Oman Tertiary care center	68 (100)	3-15	CIDI (NR) HADS (NR)	57.4 19.1
Ashman et al.[57-58] 2004 US Tertiary care center	188 (100)	ACRM criteria	SCID	24.0
Ashman et al.[57-58] 2004 US Tertiary care center	188 (100)	ACRM criteria	SCID	35.0
Ashman et al.[57-58] 2004 US Tertiary care center	188 (44.1)	ACRM criteria	SCID	21.0
Fann et al.[96] 1995 US Rehabilitation center	50 (100)	3-15	SCID	54.0
Gomez-Hernandez et al.[95] 1997 Spain Tertiary care center	65 (56.9)	3-15	SCID	27.0
Huang et al[46] 2005 US Tertiary care center	59 (100)	3-15	SCID ZDS (39.6)	13.6 16.9
Jorge et al.[13, 98, 101-104] 1993 US Trauma center	66 (65.2)	3-15	SCID	25.6
Kennedy et al.[44] 2005 US TBI referral center	78 (30)	9.3 (mean)	SCID	30.0
Rapoport et al.[36, 39] 2006 Canada Rehabilitation center	77 (59.7) at 1 yr	9-15	SCID	12.2
Whelan-Goodinson et al.[19] 2008 Australia Tertiary care center	100 (100)	<15	SCID	34.0

Table 9 Prevalence of depression by timing of assessment (continued)

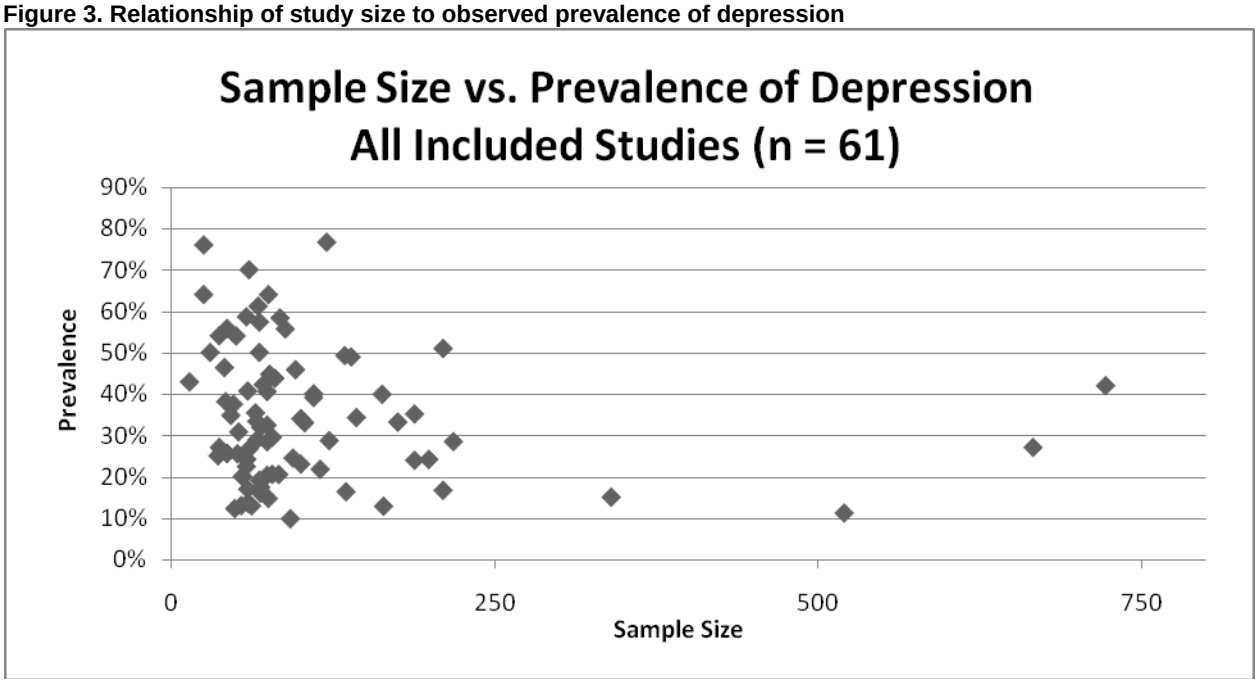
Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
>12 months since injury				
Bay and Donders[23] 2008 US Rehabilitation center	84 (100)	9-15	NFI-D (31.71)	58.0
Chiu et al.[33] 2006 Taiwan Tertiary care centers	199 (100)	3-15	CES-D: 0-16: 76.1%, 17-60: 23.9%	23.9
Deb et al.[82-83 29]1999 UK Tertiary care center	196 (83.7)	3-15	SCAN (NR) Behavior checklist (NR)	12.8 19.5
Franulic et al.[60] 2004 Chile Tertiary care center	71 (100)	12.5 (mean)	HAMD (NR)	42.3
Frenisy et al.[35] 2006 France Tertiary care center	25 (100)	<8	NRS-R (NR) SCL 90-R (9.72)	76.0 NR
Gagnon et al.[42] 2006 Canada Rehabilitation Center	30 (100)	3-13	BDI (10.47)	50.0
Keiski et al.[26] 2007 Canada Neuropsych. clinic	53 (81.1)	13-15	PAI (NR)	55.8
Kersel et al.[32, 75] 2001 New Zealand Tertiary care center	69 (84)	<9	BDI (NR)	24.1
Lima et al.[22] 2008 Brazil Tertiary care center	50 (72)	13-15	HADS (NR)	25.0
McCleary et al.[86-88] 1998 US Tertiary care center	105 (100)	3-15	SCL-90 (NR) NRS (NR)	20.0 33.3
Mooney et al.[47, 74] 2005 US Tertiary care center	67 (100)	13-15	BDI-II (22.03)	61.2
Popovic et al.[52] 2004 Serbia Tertiary care center	67 (64.2)	3-13	ZDS (41.2)	46.3
Seel et al.[61, 65] 2003 US Rehabilitation centers	666 (100)	8.6 (mean)	NFI-D (NR)	27.0

Table 9. Prevalence of depression by timing of assessment (continued)

Author, Year Country Setting	N with TBI, (% with Depression Measure)	GCS Score	Assessment Method (mean score)	Prevalence %
>12 months since injury				
Sherman et al.[80] 2000 Canada Neuropsych. clinic	175 (100)	ACRM Criteria	MMPI (NR)	33.0
Stalnacke[25] 2007 Sweden Tertiary care center	201 (81)	13-15	BDI (6.88)	
			Mild to Mod	25.0
			Mod to Severe	15.0

No evidence suggests that study setting, country, or size of study population influences the observed prevalence. As expected, smaller studies report a wider range or prevalence and estimates from larger studies are closer to the mean estimates (Figure 3).

Figure 3. Relationship of study size to observed prevalence of depression



Data are sparse to assess whether severity of injury influences risk of depression. Using structured interviews in those with mild or mild/moderate TBI, the overall prevalence of depression was 17.0 percent compared to 32.2 percent in studies that enrolled or followed up populations of all severity. Too few studies isolate a sufficient number of those with mild TBI compared to those with moderate and/or severe injuries to make valid severity-based estimates. Likewise, stratification of prevalence by explanatory factors such as age, gender, area of brain injured, or mechanism of injury is not possible within the current body of literature.

Twelve studies in seven distinct study populations report results from multivariate models to identify predictors or risk factors for depression after TBI. Older age at injury, CT with documented intracranial lesion, and higher one-week CES-D scores were sensitive (93 percent) though not specific (62 percent) to identify those with mild TBI who were depressed by three months after their injury.[50] History of alcohol and substance abuse increase risk.[14, 64] Pain,

involvement in litigation related to the injury, and perceived stress were risk factors among those entering rehabilitation care.[23] Psychosocial supports were often described in this literature and data from caregivers, partners, and family member were common. However few models incorporated social support items. One group reported "availability of a confident" reduced risk of depression,[78] and another that years married were inversely related to risk, while presence and degree of cognitive disability, motor disability, and social aggression elevated risk.[99]

A cluster of reports was focused on investigating whether incorporating information about the area of the brain affected by the injury helped to identify those at highest risk. Imaging research about the areas of the brain injured and the relationship to depression risk has inconsistent results. In aggregate for all those with TBI, onset of major depression within three months of injury has been reported to seven-fold more common (95 percent CI: 1.36 to 43.48) among those with abnormal CT results after injury compared to normal imaging.[50] Focusing on locations of injury, Jorge and colleagues [13, 103] have replicated their findings in several CT-based studies that left anterior lesions involving the left dorsolateral frontal cortex and/or left basal ganglia are associated with increased risk of acute depression ($p = 0.006$) when injury location is assessed in multivariate regression models. They also note that frontal lesions whether left, right or bilateral are associated with decreased risk of acute depression ($p = 0.04$). In contrast delayed-onset major depression was not associated with lesion location. In a subanalysis of depression types depression alone was related to left hemisphere injury ($p = 0.003$), while depression associated with anxiety was more common among those with right hemisphere injury ($p = 0.003$) A specific assessment of the presence or absence of contusions found the type of injury was not predictive and that depression was somewhat more common among those with contusions (71 percent) than among those without (62 percent). Using MRI, the findings from CT studies are not supported and the only lesion type to emerge as a significant predictor was the protective effect of temporal lesions compared to other injury locations ($p = 0.028$).[38] Study size and timing in relation make this literature more exploratory than conclusive in beginning to understand the relationship between pathophysiology related to the brain injury and risk and timing of onset of depression.

Overall the quality of studies that provided prevalence estimates was 11 good quality (11.2 percent), 62 fair quality (63.3 percent), and 25 poor quality (25.5 percent). Many of these studies were not explicitly designed to assess prevalence and are of higher quality for their intended aims. Overall the strength of the evidence to estimate prevalence is moderate. Factors included in the assessment were varied methods for defining TBI and depression, small study populations, and predominance of populations such as those in tertiary care referral centers, trauma centers, and rehabilitation programs that cannot represent the entire denominator of individuals with head injury in the United States. Experts suggest this shortcoming relates to a lack of funding resources to identify and follow large cohorts of varied injury severity and mechanism over time. However, despite these limitations, no evidence suggests depression prevalence is not elevated in general TBI populations.

KQ2. Screening for Depression after TBI

After answering the question of prevalence of depression in the traumatic brain injured (TBI) patient, the next step is identifying the timing of screening for depression, which screening tools to utilize and optimal setting for screening to occur.

In all timeframes and with all measures, depression is common (Table 10). No distinct trend is apparent to suggest a peak time of enhanced risk or a related priority window for screening. In general, the proportion of those diagnosed as depressed with structured clinical interviews is lower than standardized instruments. This would be expected, as the majority of tools are designed to be more sensitive than specific in order not to miss potential cases. Around one year and beyond both categories of assessments converge around 33 percent.

This review cannot distinguish between whether this suggests that other tools "over-detect" depression relative to structured clinical interviews or whether differences in study design and population create the observed effect. We also cannot distinguish if features unique to a population with TBI make clinical diagnosis more challenging, or whether evaluators in clinical settings are less likely to classify a patient as depressed early after trauma, deferring definitive diagnosis until later in followup as other sequelae of injury subside or stabilize.

As presented in Table 10, prevalence of depression is higher in all timeframes than would be expected from population-based estimates. These estimates may center around 30 percent in all windows for a number of reasons. In one scenario, prevalence reaches this level quickly; depression is under-recognized or poorly responsive to treatment; and overall, the same individuals are affected over time and therefore available in each time window to be detected. In another scenario, there could be an initial wave of "reactive" depression that resolves in some individuals such that later timeframes reflect continued symptoms in some and new onset of depression in others. In this scenario individuals are moving in and out of the "case" group over time but the average proportion at any one time approaches a third.

Overall the quality of studies that provide information to assess when to screen was 11 good quality (11.1 percent), 63 fair quality (63.6 percent), and 25 poor quality (25.3 percent). The strength of the body of evidence is low for selecting time and setting for screening. Deficits relate to the high proportion of the literature which is cross-sectional so that natural history information cannot be provided, and the small proportion of studies that are prospective having, as a group, relatively few followup intervals. From an ethics perspective this uncertainty suggests we are obligated to recognize that those with TBI likely have elevated risk of depression and to screen frequently until evidence becomes available to better target timing of evaluations or to confirm that risk is elevated and stays elevated relative to the general population.

Overall the quality of studies that provide information comparing tools is poor. While many studies evaluate psychometric properties and validation of tools and subscales, few examine the diagnostic test characteristics of tools for clinical use in comparison to a gold standard such as the SCID. Given that TBI is relatively common and that psychiatric and psychological evaluation services can be challenging to access, there would be substantial value in understanding which tools perform best in selecting those individuals most likely to need treatment while still retaining a high negative predictive value so that cases are not missed. Thus the strength of the body of evidence is low for selecting method of screening.

Table 10. Prevalence of depression by method of assessment, setting, and time from injury

	Structured Clinical Interview Protocols					**Other Validated Depression Assessment Tools**				
	Time from Injury to Assessment					Time from Injury to Assessment				
	0-3 mos	3 - 6 mos	6 - 12 mos	12 + mos	**All times**	0-3 mos	3 - 6 mos	6 - 12 mos	12 + mos	**All times**
All study settings and TBI severity										
Studies with data (n)	8	5	6	15	**34**	4	3	11	31	**49**
Prevalence (%)	18.7	24.3	31.9	34.7	**28.3**	34.3	45.7	35.5	32.0	**33.6**
Tertiary care populations										
Studies with data (n)	3	0	3	7	**13**	2	2	3	11	**18**
Prevalence (%)	17.7	0	28.3	38.3	**31.3**	36.8	44.6	36.3	28.2	**32.9**
Trauma center populations										
Studies with data (n)	3	4	2	3	**12**	0	0	4	7	**11**
Prevalence (%)	19.8	22.4	31.8	20.9	**21.7**	0	0	37.6	39.3	**39.6**
Rehabilitation centers										
Studies with data (n)	1	0	0	3	**4**	2	0	5	5	**12**
Prevalence (%)	15.9	0	0	42.5	**36.4**	29.2	0	33.4	34.6	**33.8**
All levels of TBI severity										
Studies with data (n)	4	3	3	7	**17**	1	1	4	8	**14**
Prevalence (%)	24.7	34.0	31.8	34.9	**32.2**	31.9	48.9	37.1	25.5	**32.0**
Populations with mild and/or mild/moderate TBI by Glasgow Coma Scale*										
Studies with data (n)	4	2	2	1	**8**	1	0	1	4	**6**
Prevalence (%)	16.6	16.7	21.3	12.2	**17.1**	34.3	0	28.7	45.1	**39.1**
Populations with moderate and/or severe TBI by Glasgow Coma Scale*										
Studies with data (n)	0	0	0	0	**0**	0	1	3	5	**9**
Prevalence (%)	0	0	0	0	**0**	0	50.0	37.8	30.1	**32.9**

* Number of studies reporting data for those with mild TBI alone is insufficient to report weighted means.

Table 11. Validity of tools to diagnose depression after TBI

Author, Year Country Setting	Study Design N	Comparison and measures	Outcomes
Sliwinski et al. [90] 2006 US, other	Cross-sectional N=100	• BDI vs SCID • Validity measures, including sensitivity and specificity	• Correlation between the SCID and BDI was 0.30, p<0.05 • With specificity set at 0.80, the BDI correctly identified 36% of individuals diagnosed with depression via the SCID • With specificity set at 0.90, only 20% were correctly classified as depressed • A modified (six item) BDI was more strongly correlated with DSM-IV diagnosis (r=0.40, p<0.05), and sensitivity increased to 48% at 80% specificity and to 32% at 90% specificity
Fann et al. [112] 1995 US Trauma Center	Prospective Cohort N=135	• PHQ-9 vs SCID • Validity measures included sensitivity, specificity, PPV and NPV • ROC analysis identified optimal scoring algorithm	• Various scoring algorithms were used with the PHQ-9 • "Optimal" algorithm has sensitivity 0.93, specificity 0.89, PPV 0.63 and NPV 0.99.
Al-Adawi et al. 2007 [28] Oman, Tertiary Care Center	Cross-sectional N=68	• HADS vs CIDI (structured clinical interview for ICD-10 diagnosis) • Validity measures included sensitivity, specificity and ROC analysis	• Sensitivity of the depression subscale of HADS to identify patients considered depressed by clinical interview was 33.3%. Specificity was 100% (i.e., no false positives). • ROC analysis suggested that sensitivity can be increased with lower HADS cutoff • An "optimal" cutoff off of 4 produced a sensitivity of 53.8% and specificity of 75.9%

Three studies assessed the ability of various tools to screen for depression in individuals with TBI, relative to a structured clinical interview, which is accepted as the gold standard for diagnosing depression. Two of the studies were conducted in the United States, one at a trauma center[112] and another a community-based sample.[90] This second study was an analysis of individuals participating in a larger quality of life study focused on community integration of individuals with TBI. The third study was conducted in Oman at a tertiary care center.[28] The U.S. studies used as their gold standard the SCID, based on DSM-IV criteria, while the Oman study used the CIDI (also a structured clinical interview) that is based on ICD-10 criteria for diagnosis. Each evaluated the validity of a different tool: the BDI[90], PHQ-9[112] and HADS;[28] therefore, results cannot be synthesized across studies and are presented separately in the table and the text.

In their study of the BDI's ability to correctly identify depressed individuals, Sliwinski and colleagues selected 100 individuals randomly from a larger pool of 433 participating in a quality of life study. All participants had a brain injury that had occurred at least one year prior, were between the ages of 18 and 65, and were able to engage in a three to four hour interview. All participants were given both a SCID and a BDI, and sensitivity and specificity calculations were used to assess the ability of the BDI to identify the depressed individuals. Setting specificity at either 80 or 90 percent (reflecting the proportion of non-depressed individuals correctly

classified as non-depressed), they found low sensitivities (proportion of truly depressed individuals identified by the tool) of 36 and 20 percent, despite a statistically significant correlation (albeit low) between the tools of 0.30. After modifying the BDI to include six items that best discriminated between depressed and nondepressed individuals, sensitivity increased slightly, but did not exceed 48 percent.

Fann and colleagues recruited participants from a level one trauma center, with head injuries with a GCS score of less than or equal to 12. Participants were recruited prior to discharge and assessed every month for six months and then at eight, 10 and 12 months following injury. Participants were initially given the PHQ-9 over the phone, and invited to complete a SCID only if their PHQ-9 score met criteria for possible depression; thus restricting the analysis to a population with fairly high likelihood of depression. The investigators then assessed the ability of various algorithms for scoring the PHQ-9 to identify individuals with depression, using an ROC analysis to find the optimal criteria. The best algorithm, based on maximizing both sensitivity and specificity, resulted in a positive predictive value of 0.63 and a negative predictive value of 0.99. Sensitivity for this algorithm was 0.93 (0.74-1.00) and specificity was 0.89 (0.82-0.94).

Finally, Al-Adawi and colleagues studied 68 consecutive patients at a tertiary care center in Oman who had suffered TBIs, excluding individuals with a pre-injury psychiatric condition or other neurological history. They used a structured clinical interview based on the ICD-10 criteria for diagnosis as the gold standard, and assessed the ability of the HADS to correctly identify depressed individuals. Depressive disorder was diagnosed with clinical interview in 57.4 percent of the participants. Using ROC analysis to identify the best HADS criteria for depression, the maximum sensitivity and specificity achieved were 53.8 and 75.9 percent, respectively.

Huang and colleagues conducted SCIDs and the Zung depression scale on 70 consecutive patients from a physical rehabilitation hospital, but provide no diagnostic test characteristics by which to assess the results.[46]

With only three studies that included test characteristics available, each using a different screening tool, there is insufficient evidence to determine whether tools validated in other populations for screening depression appropriately identify individuals with depression after a TBI. Several studies were identified that compared various screening tools against one another, but none of these conducted a clinical interview to diagnose depression as a comparison.[31, 61, 65, 108] In the absence of a clinical diagnosis, it is difficult to assess the utility of these tools for identifying correctly depressed individuals. However, Bay and colleagues did use an expert consensus process to select subscale domains of three screening tools (NFI, POMS-D, CES-D) that correspond to the DSM-IV criteria for major depressive episode, and then found that the three tools were highly correlated ($r > 0.80$) in their identification of depressed individuals. Nonetheless, SCIDs were not actually done in the study.

This area of research represents a significant gap in the current literature. Given the wide range, and potentially high prevalence of depression after TBI, effective approaches to screening and diagnosis that can be deployed in large populations are needed. As studies are conducted to establish the prevalence of depression, sub-studies could be conducted focusing on establishing or comparing the validity and reliability of screening tools for this population.

KQ3. Prevalence of Concomitant Psychiatric Conditions

This section presents the results of our literature search and findings about the prevalence of concomitant psychiatric conditions in patients who develop depression after incurring a traumatic brain injury. We reviewed seven papers from six studies, of which all seven were of fair quality.

Concomitant psychiatric conditions that we included for review included: posttraumatic stress disorder (PTSD), other anxiety disorders, substance abuse, irritability/aggression, and any other named Axis I or Axis II disorders.

Content of the literature

We identified seven studies[13, 57, 59, 91, 96, 98, 110] from six populations that reported prevalence of concomitant psychiatric conditions within the population of depressed TBI patients,[13, 96, 98] or compared rates of co morbid conditions in those with and without depression.[57, 59, 91, 110] Papers that reported the overall prevalence of psychiatric conditions other than depression among the overall population of TBI patients with no data on their association with depression were excluded for this key question.

Study designs of the six studies (one study was represented in two papers) included four prospective cohorts,[13, 57, 59, 98, 110] one retrospective cohort[91] and one cross-sectional study.[96] All six studies were conducted in the United States. One was conducted at an academic medical center;[57] one at a rehabilitation center;[96] one in the community;[91] one was conducted at two hospitals within the same state;[59] and two were at trauma centers.[13, 98, 110] The most common condition studied in combination with depression was anxiety, which was assessed in four studies.[13, 59, 91, 96] Depression was diagnosed via clinical interview in most of the studies.[13, 57, 59, 91, 96, 98]

Summary of the literature on concomitant psychiatric conditions

The included studies reported relatively high rates of concomitant psychiatric conditions (8 to 93 percent of depressed participants had some concomitant condition), but because few presented these data separately for the depressed and non-depressed groups, few conclusions related specifically to this key question can be drawn. Nonetheless, anxiety appeared to be the most common comorbid condition. In the one study that compared rates of comorbid anxiety in patients with and without depression, it was significantly more common in the depressed group (76.7 versus 20.4 percent, $p<0.001$).[59]

The three studies that explicitly compare rates of concomitant psychiatric conditions in depressed and non-depressed patients are most useful for answering this key question.

In the first of these,[110] patients who were hospitalized with TBI of GCS severity ≤ 12 were assessed one to six months postinjury. Attempts were made to contact each patient monthly, but not all patients were reached every month. The overall cumulative incidence of both depression (per the PHQ-9) and PTSD (per the PCL-C) were calculated. While the overall incidence of PTSD was 11.3 percent for the cohort, the rate was 37 percent among the 27 individuals who also experienced depression, compared to none among those who did not. No other studies directly compared the proportion of depressed patients with and without PTSD.

Anxiety and aggression were measured in patients participating in a second prospective cohort in which participants were consecutively admitted patients at two hospitals.[59] The study compared outcomes among patients with closed head injury to those with multiple trauma, but no central nervous system involvement. Among the 91 TBI patients, 68 had sustained their injuries in a motor vehicle accident. Patients were followed up at three, six, and twelve months, at which time depression was assessed using a clinical interview and the HADS, and aggressive behavior was assessed with the Overt Aggression Scale. About one-third (33 percent) of patients had major depressive disorder (mood disorder with major depressive features). Over the course of followup, 23 of 30 (77 percent) of patients with major depressive disorder also had anxiety, compared with 9 of 44 (20.4 percent) of nondepressed patients (note: total N does not add up due to lack of complete data). Of note, PTSD was included with anxiety in this study, and was the defining psychiatric feature for seven of the 23 patients diagnosed with anxiety. Similarly, 17 of 30 (56.7 percent) depressed patients exhibited aggression, compared to 10 of 44 (22.7 percent) of nondepressed patients.

A cohort of 188 individuals with TBI who were enrolled in a larger study of mood disorders and psychosocial functioning after TBI was assessed twice over 12 months for depression and other psychiatric comorbidities.[57-58] The participants were all living in the community and had sustained their head injury within the past five years. They were recruited via telephone, and those who agreed to participate were assessed in person at study entry and 12 months later. In part, this study focused not only on the presence or absence of depression and other psychiatric conditions, but on the timing of the depression as it related to the presence of co-occurring psychiatric disorders. Therefore, individuals were subdivided into four groups for analysis: no depression at either time-point, resolved depression (present at study entry but not at 12 months), late-onset depression (present at 12 months but not at study entry) and chronic depression (present at study entry and 12 months). At study entry co-occurring psychiatric conditions were most frequent among those individuals who would have late onset depression (74 percent of late onset patients) and lowest among those in the chronic depression group (26 percent). At re-assessment, the presence of psychiatric conditions had increased in every group except those never diagnosed with depression, although in this group more than half of the individuals had depression at both time points. Among the psychiatric conditions examined, anxiety was most common at both study entry and 12 months (19 and 16 percent respectively). Psychiatric diagnoses before the TBI itself were common across all groups (56 percent of the overall population) with no statistically significant differences between groups.

The other two papers[13, 98] representing one study that used a prospective cohort design did not provide a measure of the incidence of psychiatric comorbidity in the non-depressed group. The authors report that 41 and 8 percent of depressed TBI patients had anxiety and bipolar disorder, respectively.[13, 98]

Finally, a retrospective cohort of community-dwelling individuals with TBI at least one year prior to interview[91] found that among pairs of concomitant psychiatric conditions, depression and anxiety combined was most common (25 percent), and that individuals with a pre-TBI Axis I diagnosis were most likely to experience coexisting diagnoses post-TBI ($p<0.03$). Four of 13 individuals with MDE in a cross-sectional study of 50 outpatients at a rehabilitation clinic also had anxiety disorder, as assessed by clinical interview.

All of the available studies reported a high rate of concomitant psychiatric conditions associated with depression after a TBI. Rates ranged from eight to 93 percent depending on the

particular psychiatric condition and the study population and design. Those studies that presented data on psychiatric conditions by depression status found higher rates among the depressed groups. None of the studies was able to ascertain directionality for the observed association. Anxiety disorders including GAD, PTSD, panic disorder, OCD, and specific phobias, were the most commonly reported conditions. Most studies grouped these conditions together and reported the overall prevalence of any anxiety disorder.

When the conditions were reported individually, GAD was most prevalent and affected from 31 to 61 percent of study participants in three papers.[13, 59, 96] PTSD was observed in 37 percent of depressed patients and none of those without depression.[110] Panic disorder was seen in 15 percent of patients with MDE, but not measured in those without depression.[96]

KQ4. Outcomes of Interventions for Treatment for Depression after TBI

To understand the treatment options for patients with TBI and subsequent depression, we sought publications that clearly documented the intervention, duration, and response to treatment.

Treatment outcomes in TBI

Using this approach we identified two publications[113-114] from two distinct study populations that specifically addressed a treatment intervention for individuals diagnosed with depression after a traumatic brain injury. Detailed summaries for both studies are included in Appendix C.

One of the treatment studies was conducted in the United States[113] and the second was in Canada.[114] Both were studies of medication, the first being an RCT of sertraline, while the second was an open-label case series of the effects of citalopram.

The study on sertraline was a double-blind placebo controlled trial, with block randomization, in which treatment was administered for 10 weeks.[113] Participants were at least six months post-TBI, and TBI included documented loss of consciousness or other evidence, such as pathology or imaging. Diagnosis of depression was established with DSM-IV criteria and a HAM-D score higher than 18. Dosage of sertraline was not fixed, and could be adjusted at two-week intervals, with a maximum dosage of 200 mg/d. Of 91 individuals screened, 52 were eligible and agreed to participate; 41 completed the study and contributed data to the analysis. Eight of the 11 participants who discontinued were excluded because of noncompliance with the treatment protocol. Generally speaking, participants in this study were middle aged, male and of lower SES (predominantly ≤ $20,000 annually). Time since injury ranged up to 30 years, and reasons for the TBI included assault (46.3 percent), fall (14.6 percent), gunshot wounds (2.4 percent) being hit by a falling object (2.4 percent) and motor vehicle accidents or pedestrian hit by a moving vehicle (34.2 percent). The primary outcome of interest was a change in depression status measured with the HAM-D. A positive response was considered to be a decrease of 50 percent, or a drop below 10 on the HAM-D. Of those that completed the study, 59 percent of the treated group and 32 percent of the control group had a positive response; the difference in response rates between the two groups was not statistically significant ($p = 0.08$).

Rapoport and colleagues,[114] studied the effect of citalopram on depressive symptoms after TBI, using an open-label, single arm (case series) design. The study was limited to individuals with mild to moderate TBI. Mild TBI was defined as loss of consciousness at time of injury of

20 minutes or less, an initial GCS of 13-15 and post traumatic amnesia of less than 24 hours. Moderate to severe TBI had a GCS of less than 13, a PTA greater than 24 hours or an abnormal CT image. Fifty-four of 65 patients attending the mild-to-moderate TBI clinic were diagnosed with major depression due to TBI, with a major depressive-like episode, using the depression module of the Structured Clinical Interview for DSM-IV Axis I disorders. All 65 patients began the study, however, 54 completers provided data for analysis. Although the study was intended to evaluate the effects of a six-week course of treatment, low response rates resulted in a study extension for some participants to 10 weeks. Therefore, although six week data were available for all 54 completers, 10-week data were available for 26 participants. Dosage of citalopram was titrated as deemed medically appropriate by the study physicians. The primary outcome measured was a change on the HAM-D score, with an improvement of 50 percent or more designated a positive response, and a score of less than eight defined as remission. In the six week data (n = 54), 27.7 percent were classified as responders and 24.1 percent were in remission. Among participants with data at 10 weeks, 46.2 percent were responders and 26.9 were in remission. Of the 11 individuals who dropped out of the study, six were in the intended six-week group and five were in the intended 10-week group. Ten of the eleven experienced an adverse event.

KQ5. Comparisons of Treatments

No studies addressed KQ5. It is discussed as a part of Future Research.

KQ6. Modifiers of Outcomes of Treatment

No studies addressed KQ6. It is discussed as a part of Future Research.

Grey Literature Results

Publications included in this review

A relevant pool of 56 potentially useful items were located following a series of Internet and relevant grey literature searches of United States government and military sources, nonprofit organizations, United States and international clinical trials registries, meeting proceedings, and dissertation databases. Selected resources were identified from the United States (one government report, one nonprofit white paper, five clinical trial protocols, one funding/grant opportunity, one systematic review, six funded projects, eight conference proceedings, nine dissertations), New Zealand (one guideline), Australia (two clinical trials), Europe (five conference proceedings – including one from Turkey), and Canada (three clinical trials, one conference proceeding, one dissertation).

Internet searches. The relevant retrieval from different Google® searches included one guideline, two reports, and one systematic review that in whole or in part, focus on treatment or screening for depression associated with TBI. A guideline from the New Zealand Guidelines group, not indexed in MEDLINE, provided guidance on treatment of depression in TBI that was based solely on expert opinion, thus contributing little to the literature for this topic. The RAND Corporation and IOM reports give a review of the current prevalence of depression, PTSD and TBI in military populations. Only the IOM report provided a review of the literature regarding

prevalence or the relationship between TBI and depression, while the RAND report provides a comprehensive overview of the literature for TBI, PTSD, and depression independently. These reports do provide a foundation for future research in the treatment of depression in the context of TBI, but add very little to the published literature summarized in this review.

A systematic review that had not been picked up in the original search of the TBI published literature provided a critical review of literature regarding pharmacologic, other biologic, psychotherapeutic, or rehabilitation treatment of depression after TBI. After a review of 658 articles retrieved from various bibliographic databases, 27 (13 pharmacological, six other biological, eight psychotherapeutic/rehabilitation intervention) articles were included in the review based on study inclusion/exclusion criteria and study abstract and full-text reviews. The study found a paucity of adequately powered and controlled studies in the literature to make conclusions on the best treatment modality for depression in TBI.

Funding opportunities & ongoing research. Nonpublished grey literature resources may indicate areas of future research for management of depression in TBI patients. Examples include a recent announcement regarding a military funding opportunity to support research in the treatment or prevention of depression or other mood disorders in TBI.[132] Also, six funded projects from NIH RePORTER and ten clinical trials from various clinical trials registries report current studies currently underway for treatment of depression in TBI patients. These projects will assess the impact of behavioral therapies;[133-141] supportive psychotherapy[142] and exercise;[143] transcranial magnetic stimulation[144] and drug interventions (e.g. sertraline, venlafaxine, and citalopram).[145-147] Several projects also focus on identification of risk factors for depression in the context of TBI.[148]

Meeting abstracts, proceedings, and dissertations. A significant pool of meeting abstracts, proceedings and dissertations were retrieved from the literature that focused on topics already covered in the published research. Overall, 14 conference proceedings and 10 dissertations were located that assessed treatment options for depression[149-152] and potential methods for characterizing or measuring development of depression in TBI.[141, 153-171] Examples of therapy modalities include use of nontraditional approaches, such as neurologic music therapy[149] and written emotional expression technique,[151] and medical approaches with methylphenidate and sertraline drug therapy.[150] Lack of reported data makes it difficult to identify or assess any impact of these treatments on depression in TBI patients. Additionally, the papers focusing on patient characteristics or modifiers that may affect outcome,[153-155, 157-159, 161-163, 165-166, 168, 170] disease progression,[152, 156, 164, 171] or rating scales[160, 167, 169] of depression in TBI patients provide very little data to make accurate assumptions of reported conclusions.

Summary and literature method critique. A review of the grey literature, government/non-profit reports and other unpublished resources did not retrieve much additional information to what had been found in the published and peer-reviewed literature. The majority of the high quality, relevant data comes from two large scale reports/white papers that mainly focus on the prevalence or the connection between depression and TBI. As was discovered from a review of published literature,[16] we noted very little data in the grey literature that assessed the impact of treatment for depression in TBI, although the pool of current clinical trial protocols and funded projects indicate growth in this area of the literature.

During the review of this material, we found some overlap between what was found in the published literature and the current search retrieval. Although we attempted to extract only unique or new data from the pool of grey literature sources, there may be some redundancy in

this section of the report given the nature of how this material is reported and maintained in data repositories and online databases.

Citations for all grey literature identified are in Appendix F.

Chapter 4. Discussion

This chapter summarizes the strength of the evidence to address our key questions and then presents methodologic considerations and a discussion of the findings for each of our six key questions. We conclude with a discussion of the status of research, limitations of the current literature, and our recommendations for future research priorities.

Strength of the Evidence

Strength of evidence is typically assigned to reviews of medical treatments after assessing four domains: risk of bias, consistency, directness and precision.[131] Although these categories were developed for assessing the strength of treatment studies, the domains apply also to studies of prevalence and screening. Available evidence for each key question was assessed for each of these four domains; the domains were combined qualitatively to develop the SOE for each key question.

We graded the body of literature for each key question and present those ratings as part of the discussion in Chapter 4. The possible grades were:

I. High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.

II. Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

III. Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.

IV. Insufficient: Evidence is either unavailable or does not permit a conclusion.

As a global assessment of this literature the evidence about prevalence and elevated risk of depression is moderate.

The strength of the evidence to inform when, with what tools, and in what settings screening for depression should occur after TBI is low. This assessment is based on lack of studies designed to specifically address these concerns that make explicit comparisons. The risk for bias is high since the data used was often cross-sectional, full populations were rarely delimited, and settings and populations may represent a biased portion of the spectrum of both the severity of TBI and of depression. As for prevalence, data are inconsistent across studies. Summary evidence is to a degree indirect. Though we included only studies for which the timing of administration of the screening or diagnostic tool was known and for which the tool was described, the studies overall were not designed for this use and estimates are imprecise.

Likewise understanding of psychiatric comorbidities is based on a small number of studies that do not provide consistency in conditions measured and are at risk of bias, resulting in low strength of evidence. Intervention studies included one RCT of good quality and one case series, therefore risk of bias was high, consistency unknown, and results lacked precision. The strength of evidence is insufficient for pharmacologic treatment of depression after TBI.

Principal Findings and Considerations

KQ1. Prevalence and Incidence of TBI and Depression

We identified 98 publications,[7, 12-14, 18-111] from 71 distinct study populations in which prevalence could be estimated.

We considered the SCID and other formal structured clinical interview protocols that map to the DSM and/or ICD codes to be the measures of depression that are most relevant to clinical care. Among studies that used a SCID or other structured protocol to reach a formal diagnosis of depression, the prevalence of depression after TBI ranged from 12.2 percent[53] to 76.7 percent[12]. If we focus on the subset of studies with both clearly operationalized criteria for TBI and use of the SCID, the range was 12.2 percent[53] to 54.0 percent[96].

Data are sparse to assess whether severity of injury influences risk of depression. Using structured interviews among those with mild or mild/moderate TBI populations, the overall prevalence of depression was 17. 0 percent compared to 32.2 percent in studies that enrolled or followed up populations of all severities. Too few studies isolate a sufficient number of those with mild TBI compared to those with moderate and/or severe injuries to make valid severity-based estimates. Likewise, stratification of prevalence by explanatory factors such as age, gender, area of brain injured, or mechanism of injury is not possible within the current body of literature.

No strong predictors of risk are available to tailor guidance or screening of those with TBI.

KQ2. Screening for Depression after TBI

Across all timeframes and using all depression measures, in studies with clear TBI definitions, the weighted average for prevalence of depression was 31.8 percent. Among those studies with repeated assessments and/or longer term followup, no clear pattern of expected natural history or peak prevalence emerged. Depression was more common among those with TBI than among normal comparison groups.

Three publications compared SCID to candidate tools for assessment of depression, the BDI, PHQ-9 and HADS.[28, 90, 112] None of the tools reported simultaneous sensitivity and specificity above 90 percent. With modification of the scoring algorithm as proposed by the authors, the PHQ-9 achieved a sensitivity of 93 percent, specificity of 89 percent, positive predictive value of 63 percent and negative predictive value of 99 percent. The BDI had poor sensitivity of 48 percent and 32 percent at specificities of 80 and 90 percent, respectively. The HADS provided 54 percent sensitivity and 76 percent specificity.

Therefore, no evidence provides a basis for targeting screening to one timeframe over another. Likewise, the literature is insufficient to determine whether tools validated in other populations for detecting depression appropriately identify individuals with depression after a TBI, or to choose among available tools.

KQ3. Prevalence of Concomitant Psychiatric Conditions

In general, the few papers that do specifically examine the prevalence of concomitant psychiatric conditions within the population of depressed TBI patients report high rates of such conditions within this population. When conditions were reported individually, General Anxiety Disorder (GAD) was most prevalent and affected from 31 to 61 percent of study participants in three papers.[13, 59, 96] PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and no patients without depression,[110] and panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression.[96] Consideration of potential for co-existing psychiatric conditions is warranted.

KQ4. Outcomes of Treatment for Depression after TBI

Only two publications[113-114] addressed a treatment for individuals diagnosed with depression after a traumatic brain injury. One of the treatment studies was conducted in the United States[113] and the second was in Canada.[114] Both were studies of medication, the first being an RCT of sertraline; the second, an open-label case series of the effects of citalopram. Of those that completed the sertraline study, 59 percent of the treated group and 32 percent of the control group had a positive response; the difference in response rates between the two groups was not statistically significant ($p = 0.08$). In the six week data on citalopram ($n = 54$), 27.7 percent were classified as responders and 24.1 percent were in remission. Among participants with data at 10 weeks, 46.2 percent were responders and 26.9 were in remission. Of the eleven individuals who dropped out of this case series, 10 had experienced an adverse event.

KQ5. Comparisons of Treatments

No studies were available to answer this key question.

KQ6. Modifiers of Outcomes of Treatment

No studies were available to answer this key question.

Future Research

State of the Literature

The amount of literature about traumatic brain injury is increasing rapidly, with the focus on the relationship between TBI and depression also growing. As is typical of advancing areas of research, early publications about TBI and depression have been predominantly cross-sectional, with little apparent consensus about measures or key covariates and a high degree of variability in quality of publications.

Prospective studies of sufficient size to enable multivariate modeling of predictors of outcome or analysis of outcome by factors such as severity are rare. Likewise studies that are prospective in the sense that they include repeated measures of depression are few. Often studies meet criteria for prospective investigation by enumerating patients at the time of injury and counting time elapsed until followup as the prospective component. However, with a single

measure of depression at one time of followup this data is in essence cross-sectional and cannot contribute to understanding the natural history of the onset and course of depression after TBI.

Achieving representative study populations is challenging and rarely achieved, because enumerating the entire population eligible for followup is hampered by the portion of the population who do not seek care for head injury. While studies in specialized settings like neuropsychiatric clinics or rehabilitation programs can be applicable to estimating risk in those settings they cannot be generalized to base the population of all those with injuries.

Overall, the content of the current literature is fair to poor with a preponderance of study designs that do not provide strong evidence. As a result the strength of the literature is low for understanding the predictors, natural history, treatment options, and modifiers of outcomes of depression that follows TBI. Strength is moderate for establishing that depression is common and exceeds the prevalence expected in the general population.

Concerning deficits in research methods. As a body of literature a number of concerning deficits were recurring. Fewer than twelve percent of included studies met criteria for good quality. For example, many publications lacked one or more of the following:

- Operational definitions using standard approaches to diagnosing and categorizing severity of TBI.
- Description of the method of enumerating potentially eligible TBI participants.
- Timeframe in which participants were accrued.
- Report of the proportion of potentially eligible individuals who could be contacted and those who agreed to enroll.
- Analysis of any difference between those reached and enrolled and those not reached and/or who declined enrollment.
- Analysis of drop out and loss to followup.
- Uniform time from injury at followup.
- Non-TBI comparison groups.
- Description of the validity and reliability of methods used to measure depression.
- Sufficient detail about the cut-offs used to assign categories of depression severity from screening scales.
- Collection of crucial covariates that should be investigated as candidate predictors or direct risk factors for developing depression after TBI such as other psychiatric co-morbidity, level of disability, cognitive function, and level of self-awareness.
- Collection of crucial covariates to assess potential confounding of the relationship between TBI and depression, for instance litigation status.
- Stratification of findings to help understand how characteristics like severity of injury or age contribute to depression risk
- Use of multivariate models in populations large enough to incorporate factors that confound and modify the relationship between TBI and depression risk.
- Masking of assessors to TBI status to prevent potential for over-diagnosing depression because TBI is thought to be associated with depression.
- Statement of hypotheses and power calculations.

Gaps in knowledge. Five of the six key questions for this report could not be adequately answered with existing literature, and the question about prevalence was only partially satisfied. The key questions were derived with expert and stakeholder input to define core knowledge for

which we should have information. The questions themselves can serve as an outline for critical areas in which knowledge is insufficient. Lack of studies to assess how best to identify and treat depression after TBI is disconcerting. High quality research is warranted across the spectrum of study designs and aims which includes:

- Collaborative studies in which multiple sites form networks to enumerate and followup large and more representative populations.
- Documentation of the natural history of onset and the course of depression after TBI.
- Investigation of the predictors of depression with emphasis on understanding etiology and better targeting of clinical resources.
- Direct comparison of screening tools and their yield in common clinical care settings for those with history of TBI including primary care practice.
- Intervention studies assessing the efficacy and effectiveness of the leading therapeutic modalities for depression.
- Head-to-head comparison of those found effective to assess comparative risks, benefits, and costs.
- Investigation of preventive interventions to decrease risk of onset of depression.
- Study of the value of educational interventions for those injured and their support networks to assist in detection of depression and in enhancing supports to mitigate negative effects on quality of life and function.

Conclusions

Overall, the content of the current literature is fair to poor with a preponderance of study designs that do not provide strong evidence. As a result the strength of the literature is low for understanding the predictors, prevalence, natural history, treatment options, and modifiers of outcomes of depression that follows TBI. Nonetheless, considerable evidence suggests depression after all forms and severity of TBI is common.

We find a concerning lack of high quality evidence to inform clinical-decision making for the one to two million individuals in the United States who experience traumatic brain injury each year. Lack of treatment studies focused on this populations is especially remarkable. Given how common, concerning and debilitating the combination of TBI and depression can be, a priority on promoting high-quality research in the United States is imperative.

References and Included Studies

1. Mann JJ, Apter A, Bertolote J, et al. Suicide Prevention Strategies: A Systematic Review. JAMA. 2005 October 26, 2005;294(16):2064-2074.
2. First MB, Frances A and Pincus HA. DSM-IV-TR Handbook of Differential Diagnois American Psychiatric Publishing, Inc; 2002.
3. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. J Head Trauma Rehabil. 1993;8:86-8.
4. Okie S. Traumatic brain injury in the war zone. N Engl J Med. 2005 May 19;352(20):2043-7.
5. Rutland-Brown W, Langlois JA, Thomas KE, et al. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil. 2006 Nov-Dec;21(6):544-8.
6. Crooks CY, Zumsteg JM and Bell KR. Traumatic brain injury: a review of practice management and recent advances. Phys Med Rehabil Clin N Am. 2007 Nov;18(4):681-710, vi.
7. Hoge CW, McGurk D, Thomas JL, et al. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med. 2008 Jan 31;358(5):453-63.
8. Department of Defense Deployment Health. Emerging Health Concerns: Traumatic Brain Injury. Washington, DC: Department of Defense; 2008 [updated 2008; cited 2008]; Available from: www.pdhealth.mil/TBI.asp#cg.
9. Rehabilitation of persons with traumatic brain injury. NIH Consens Statement. 1998 Oct 26-28;16(1):1-41.
10. Kim E, Lauterbach EC, Reeve A, et al. Neuropsychiatric complications of traumatic brain injury: a critical review of the literature (a report by the ANPA Committee on Research). J Neuropsychiatry Clin Neurosci. 2007 Spring;19(2):106-27.
11. O'Donnell ML, Creamer M, Pattison P, et al. Psychiatric morbidity following injury. Am J Psychiatry. 2004 Mar;161(3):507-14.
12. Varney NR, Martzke JS and Roberts RJ. Major depression in patients with closed head injury. Neuropsychology. 1987 May;1(1):7-9.
13. Jorge RE, Robinson RG, Starkstein SE, et al. Depression and anxiety following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 1993 Fall;5(4):369-74.
14. Holsinger T, Steffens DC, Phillips C, et al. Head injury in early adulthood and the lifetime risk of depression. Arch Gen Psychiatry. 2002 Jan;59(1):17-22.
15. Gordon WA, Zafonte R, Cicerone K, et al. Traumatic brain injury rehabilitation: state of the science. Am J Phys Med Rehabil. 2006 Apr;85(4):343-82.
16. Fann JR, Hart T and Schomer KG. Treatment for depression after traumatic brain injury: a systematic review. J Neurotrauma. 2009 Dec;26(12):2383-402.
17. Niogi SN, Mukherjee P, Ghajar J, et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol. 2008 May;29(5):967-73.
18. Hoofien D, Gilboa A, Vakil E, et al. Traumatic brain injury (TBI) 10-20 years later: a comprehensive outcome study of psychiatric symptomatology, cognitive abilities and psychosocial functioning. Brain Inj. 2001 Mar;15(3):189-209.
19. Whelan-Goodinson R, Ponsford J and Schonberger M. Association between psychiatric state and outcome following traumatic brain injury. J Rehabil Med. 2008 Nov;40(10):850-7.
20. Hawley CA and Joseph S. Predictors of positive growth after traumatic brain injury: a longitudinal study. Brain Inj. 2008 May;22(5):427-35.
21. Rao V, Spiro J, Vaishnavi S, et al. Prevalence and types of sleep disturbances acutely after traumatic brain injury. Brain Inj. 2008 May;22(5):381-6.
22. Lima DP, Simao Filho C, Abib Sde C, et al. Quality of life and neuropsychological changes in mild head trauma. Late analysis and correlation with S100B protein and cranial CT scan performed at hospital admission. Injury. 2008 May;39(5):604-11.
23. Bay E and Donders J. Risk factors for depressive symptoms after mild-to-moderate traumatic brain injury. Brain Inj. 2008 Mar;22(3):233-41.
24. Ruocco AC, Swirsky-Sacchetti T and Choca JP. Assessing personality and psychopathology after traumatic brain injury with the Millon Clinical Multiaxial Inventory-III. Brain Inj. 2007 Nov;21(12):1233-44.
25. Stalnacke BM. Community integration, social support and life satisfaction in relation to symptoms 3 years after mild traumatic brain injury. Brain Inj. 2007 Aug;21(9):933-42.
26. Keiski MA, Shore DL and Hamilton JM. The role of depression in verbal memory following traumatic brain injury. Clin Neuropsychol. 2007 Sep;21(5):744-61.
27. Sherer M, Evans CC, Leverenz J, et al. Therapeutic alliance in post-acute brain injury rehabilitation: predictors of strength of alliance and

impact of alliance on outcome. Brain Inj. 2007 Jun;21(7):663-72.
28. Al-Adawi S, Dorvlo AS, Al-Naamani A, et al. The ineffectiveness of the Hospital Anxiety and Depression Scale for diagnosis in an Omani traumatic brain injured population. Brain Inj. 2007 Apr;21(4):385-93.
29. Deb S and Burns J. Neuropsychiatric consequences of traumatic brain injury: a comparison between two age groups. Brain Inj. 2007 Mar;21(3):301-7.
30. Schofield PW, Butler TG, Hollis SJ, et al. Neuropsychiatric correlates of traumatic brain injury (TBI) among Australian prison entrants. Brain Inj. 2006 Dec;20(13-14):1409-18.
31. Bay E, Hagerty BM and Williams RA. Depressive symptomatology after mild-to-moderate traumatic brain injury: a comparison of three measures. Arch Psychiatr Nurs. 2007 Feb;21(1):2-11.
32. Marsh NV and Kersel DA. Frequency of behavioural problems at one year following traumatic brain injury: correspondence between patient and caregiver reports. Neuropsychol Rehabil. 2006 Dec;16(6):684-94.
33. Chiu WT, Huang SJ, Hwang HF, et al. Use of the WHOQOL-BREF for evaluating persons with traumatic brain injury. J Neurotrauma. 2006 Nov;23(11):1609-20.
34. Ghaffar O, McCullagh S, Ouchterlony D, et al. Randomized treatment trial in mild traumatic brain injury. J Psychosom Res. 2006 Aug;61(2):153-60.
35. Frenisy MC, Benony H, Chahraoui K, et al. Brain injured patients versus multiple trauma patients: some neurobehavioral and psychopathological aspects. J Trauma. 2006 May;60(5):1018-26.
36. Rapoport MJ, Herrmann N, Shammi P, et al. Outcome after traumatic brain injury sustained in older adulthood: a one-year longitudinal study. Am J Geriatr Psychiatry. 2006 May;14(5):456-65.
37. Chamelian L and Feinstein A. The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2006 Winter;18(1):33-8.
38. Koponen S, Taiminen T, Kurki T, et al. MRI findings and Axis I and II psychiatric disorders after traumatic brain injury: a 30-year retrospective follow-up study. Psychiatry Res. 2006 Apr 30;146(3):263-70.
39. Rapoport MJ, Kiss A and Feinstein A. The impact of major depression on outcome following mild-to-moderate traumatic brain injury in older adults. J Affect Disord. 2006 Jun;92(2-3):273-6.
40. Parcell DL, Ponsford JL, Rajaratnam SM, et al. Self-reported changes to nighttime sleep after traumatic brain injury. Arch Phys Med Rehabil. 2006 Feb;87(2):278-85.
41. Kashluba S, Casey JE and Paniak C. Evaluating the utility of ICD-10 diagnostic criteria for postconcussion syndrome following mild traumatic brain injury. J Int Neuropsychol Soc. 2006 Jan;12(1):111-8.
42. Gagnon J, Bouchard MA, Rainville C, et al. Inhibition and object relations in borderline personality traits after traumatic brain injury. Brain Inj. 2006 Jan;20(1):67-81.
43. Felde AB, Westermeyer J and Thuras P. Co-morbid traumatic brain injury and substance use disorder: childhood predictors and adult correlates. Brain Inj. 2006 Jan;20(1):41-9.
44. Kennedy RE, Livingston L, Riddick A, et al. Evaluation of the Neurobehavioral Functioning Inventory as a depression screening tool after traumatic brain injury. J Head Trauma Rehabil. 2005 Nov-Dec;20(6):512-26.
45. Evans CC, Sherer M, Nick TG, et al. Early impaired self-awareness, depression, and subjective well-being following traumatic brain injury. J Head Trauma Rehabil. 2005 Nov-Dec;20(6):488-500.
46. Huang DB, Spiga R and Koo H. Use of the Zung depression scale in patients with traumatic brain injury: 1 year post-injury. Brain Inj. 2005 Oct;19(11):903-8.
47. Mooney G, Speed J and Sheppard S. Factors related to recovery after mild traumatic brain injury. Brain Inj. 2005 Nov;19(12):975-87.
48. Koponen S, Taiminen T, Honkalampi K, et al. Alexithymia after traumatic brain injury: its relation to magnetic resonance imaging findings and psychiatric disorders. Psychosom Med. 2005 Sep-Oct;67(5):807-12.
49. McCauley SR, Boake C, Pedroza C, et al. Postconcussional disorder: Are the DSM-IV criteria an improvement over the ICD-10? J Nerv Ment Dis. 2005 Aug;193(8):540-50.
50. Levin HS, McCauley SR, Josic CP, et al. Predicting depression following mild traumatic brain injury. Arch Gen Psychiatry. 2005 May;62(5):523-8.
51. Rowland SM, Lam CS and Leahy B. Use of the Beck Depression Inventory-II (BDI-II) with persons with traumatic brain injury: analysis of factorial structure. Brain Inj. 2005 Feb;19(2):77-83.
52. Popovic V, Pekic S, Pavlovic D, et al. Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. J Endocrinol Invest. 2004 Dec;27(11):1048-54.

53. Rapoport MJ, McCullagh S, Shammi P, et al. Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2005 Winter;17(1):61-5.
54. Chamelian L, Reis M and Feinstein A. Six-month recovery from mild to moderate Traumatic Brain Injury: the role of APOE-epsilon4 allele. Brain. 2004 Dec;127(Pt 12):2621-8.
55. Brown SA, McCauley SR, Levin HS, et al. Perception of health and quality of life in minorities after mild-to-moderate traumatic brain injury. Appl Neuropsychol. 2004;11(1):54-64.
56. Koponen S, Taiminen T, Kairisto V, et al. APOE-epsilon4 predicts dementia but not other psychiatric disorders after traumatic brain injury. Neurology. 2004 Aug 24;63(4):749-50.
57. Hibbard MR, Ashman TA, Spielman LA, et al. Relationship between depression and psychosocial functioning after traumatic brain injury. Arch Phys Med Rehabil. 2004 Apr;85(4 Suppl 2):S43-53.
58. Ashman TA, Spielman LA, Hibbard MR, et al. Psychiatric challenges in the first 6 years after traumatic brain injury: cross-sequential analyses of Axis I disorders. Arch Phys Med Rehabil. 2004 Apr;85(4 Suppl 2):S36-42.
59. Jorge RE, Robinson RG, Moser D, et al. Major depression following traumatic brain injury. Arch Gen Psychiatry. 2004 Jan;61(1):42-50.
60. Franulic A, Carbonell CG, Pinto P, et al. Psychosocial adjustment and employment outcome 2, 5 and 10 years after TBI. Brain Inj. 2004 Feb;18(2):119-29.
61. Seel RT and Kreutzer JS. Depression assessment after traumatic brain injury: an empirically based classification method. Arch Phys Med Rehabil. 2003 Nov;84(11):1621-8.
62. Slaughter B, Fann JR and Ehde D. Traumatic brain injury in a county jail population: prevalence, neuropsychological functioning and psychiatric disorders. Brain Inj. 2003 Sep;17(9):731-41.
63. Tateno A, Jorge RE and Robinson RG. Clinical correlates of aggressive behavior after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2003 Spring;15(2):155-60.
64. Rapoport MJ, McCullagh S, Streiner D, et al. Age and major depression after mild traumatic brain injury. Am J Geriatr Psychiatry. 2003 May-Jun;11(3):365-9.
65. Seel RT, Kreutzer JS, Rosenthal M, et al. Depression after traumatic brain injury: a National Institute on Disability and Rehabilitation Research Model Systems multicenter investigation. Arch Phys Med Rehabil. 2003 Feb;84(2):177-84.
66. Rapoport MJ, McCullagh S, Streiner D, et al. The clinical significance of major depression following mild traumatic brain injury. Psychosomatics. 2003 Jan-Feb;44(1):31-7.
67. Bay E, Hagerty BM, Williams RA, et al. Chronic stress, sense of belonging, and depression among survivors of traumatic brain injury. J Nurs Scholarsh. 2002;34(3):221-6.
68. Koponen S, Taiminen T, Portin R, et al. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. Am J Psychiatry. 2002 Aug;159(8):1315-21.
69. Rapoport M, McCauley S, Levin H, et al. The role of injury severity in neurobehavioral outcome 3 months after traumatic brain injury. Neuropsychiatry Neuropsychol Behav Neurol. 2002 Jun;15(2):123-32.
70. McCauley SR, Boake C, Levin HS, et al. Postconcussional disorder following mild to moderate traumatic brain injury: anxiety, depression, and social support as risk factors and comorbidities. J Clin Exp Neuropsychol. 2001 Dec;23(6):792-808.
71. Levin HS, Brown SA, Song JX, et al. Depression and posttraumatic stress disorder at three months after mild to moderate traumatic brain injury. J Clin Exp Neuropsychol. 2001 Dec;23(6):754-69.
72. Powell J, Heslin J and Greenwood R. Community based rehabilitation after severe traumatic brain injury: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2002 Feb;72(2):193-202.
73. McCauley SR, Levin HS, Vanier M, et al. The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment. J Neurol Neurosurg Psychiatry. 2001 Nov;71(5):643-51.
74. Mooney G and Speed J. The association between mild traumatic brain injury and psychiatric conditions. Brain Inj. 2001 Oct;15(10):865-77.
75. Kersel DA, Marsh NV, Havill JH, et al. Psychosocial functioning during the year following severe traumatic brain injury. Brain Inj. 2001 Aug;15(8):683-96.
76. Kreutzer JS, Seel RT and Gourley E. The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. Brain Inj. 2001 Jul;15(7):563-76.
77. Bryant RA, Marosszeky JE, Crooks J, et al. Posttraumatic stress disorder and psychosocial functioning after severe traumatic brain injury. J Nerv Ment Dis. 2001 Feb;189(2):109-13.
78. Curran CA, Ponsford JL and Crowe S. Coping strategies and emotional outcome following traumatic brain injury: a comparison with orthopedic patients. J Head Trauma Rehabil. 2000 Dec;15(6):1256-74.
79. Vasterling JJ, Constans JI and Hanna-Pladdy B. Head injury as a predictor of psychological outcome

in combat veterans. J Trauma Stress. 2000 Jul;13(3):441-51.
80. Sherman EM, Strauss E, Slick DJ, et al. Effect of depression on neuropsychological functioning in head injury: measurable but minimal. Brain Inj. 2000 Jul;14(7):621-32.
81. Perlesz A, Kinsella G and Crowe S. Psychological distress and family satisfaction following traumatic brain injury: injured individuals and their primary, secondary, and tertiary carers. J Head Trauma Rehabil. 2000 Jun;15(3):909-29.
82. Deb S, Lyons I and Koutzoukis C. Neurobehavioural symptoms one year after a head injury. Br J Psychiatry. 1999 Apr;174:360-5.
83. Deb S, Lyons I, Koutzoukis C, et al. Rate of psychiatric illness 1 year after traumatic brain injury. Am J Psychiatry. 1999 Mar;156(3):374-8.
84. Gordon WA, Brown M, Sliwinski M, et al. The enigma of "hidden" traumatic brain injury. J Head Trauma Rehabil. 1998 Dec;13(6):39-56.
85. Sebit MB, Siziya S, Ndetei DM, et al. Study of psychiatric consequences of closed head injury at the Kenyatta National Hospital. East Afr Med J. 1998 Jun;75(6):332-5.
86. McCleary C, Satz P, Forney D, et al. Depression after traumatic brain injury as a function of Glasgow Outcome Score. J Clin Exp Neuropsychol. 1998 Apr;20(2):270-9.
87. Satz P, Zaucha K, Forney DL, et al. Neuropsychological, psychosocial and vocational correlates of the Glasgow Outcome Scale at 6 months post-injury: a study of moderate to severe traumatic brain injury patients. Brain Inj. 1998 Jul;12(7):555-67.
88. Satz P, Forney DL, Zaucha K, et al. Depression, cognition, and functional correlates of recovery outcome after traumatic brain injury. Brain Inj. 1998 Jul;12(7):537-53.
89. Gordon WA, Sliwinski M, Echo J, et al. The benefits of exercise in individuals with traumatic brain injury: a retrospective study. J Head Trauma Rehabil. 1998 Aug;13(4):58-67.
90. Sliwinski M, Gordon WA and Bogdany J. The Beck Depression Inventory: is it a suitable measure of depression for individuals with traumatic brain injury? J Head Trauma Rehabil. 1998 Aug;13(4):40-6.
91. Hibbard MR, Uysal S, Kepler K, et al. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil. 1998 Aug;13(4):24-39.
92. Kreuter M, Dahllof AG, Gudjonsson G, et al. Sexual adjustment and its predictors after traumatic brain injury. Brain Inj. 1998 May;12(5):349-68.
93. Kreuter M, Sullivan M, Dahllof AG, et al. Partner relationships, functioning, mood and global quality of life in persons with spinal cord injury and traumatic brain injury. Spinal Cord. 1998 Apr;36(4):252-61.
94. Kant R, Duffy JD and Pivovarnik A. Prevalence of apathy following head injury. Brain Inj. 1998 Jan;12(1):87-92.
95. Gomez-Hernandez R, Max JE, Kosier T, et al. Social impairment and depression after traumatic brain injury. Arch Phys Med Rehabil. 1997 Dec;78(12):1321-6.
96. Fann JR, Katon WJ, Uomoto JM, et al. Psychiatric disorders and functional disability in outpatients with traumatic brain injuries. Am J Psychiatry. 1995 Oct;152(10):1493-9.
97. Aloia MS, Long CJ and Allen JB. Depression among the head-injured and non-head-injured: a discriminant analysis. Brain Inj. 1995 Aug-Sep;9(6):575-83.
98. Jorge RE, Robinson RG, Starkstein SE, et al. Influence of major depression on 1-year outcome in patients with traumatic brain injury. J Neurosurg. 1994 Nov;81(5):726-33.
99. Linn RT, Allen K and Willer BS. Affective symptoms in the chronic stage of traumatic brain injury: a study of married couples. Brain Inj. 1994 Feb-Mar;8(2):135-47.
100. MacNiven E and Finlayson MA. The interplay between emotional and cognitive recovery after closed head injury. Brain Inj. 1993 May-Jun;7(3):241-6.
101. Jorge RE, Robinson RG, Arndt SV, et al. Depression following traumatic brain injury: a 1 year longitudinal study. J Affect Disord. 1993 Apr;27(4):233-43.
102. Jorge RE, Robinson RG and Arndt S. Are there symptoms that are specific for depressed mood in patients with traumatic brain injury? J Nerv Ment Dis. 1993 Feb;181(2):91-9.
103. Jorge RE, Robinson RG, Arndt SV, et al. Comparison between acute- and delayed-onset depression following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 1993 Winter;5(1):43-9.
104. Fedoroff JP, Starkstein SE, Forrester AW, et al. Depression in patients with acute traumatic brain injury. Am J Psychiatry. 1992 Jul;149(7):918-23.
105. Gass CS and Russell EW. MMPI profiles of closed head trauma patients: impact of neurologic complaints. J Clin Psychol. 1991 Mar;47(2):253-60.
106. Dunlop TW, Udvarhelyi GB, Stedem AF, et al. Comparison of patients with and without emotional/behavioral deterioration during the first

year after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 1991 Spring;3(2):150-6.
107. Mobayed M and Dinan TG. Buspirone/prolactin response in post head injury depression. J Affect Disord. 1990 Aug;19(4):237-41.
108. Kinsella G, Moran C, Ford B, et al. Emotional disorder and its assessment within the severe head injured population. Psychol Med. 1988 Feb;18(1):57-63.
109. Brooks N, Campsie L, Symington C, et al. The effects of severe head injury on patient and relative within seven years of injury. Journal of Head Trauma Rehabilitation. 1987;2(3):1-13.
110. Bombardier CH, Fann JR, Temkin N, et al. Posttraumatic stress disorder symptoms during the first six months after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2006 Fall;18(4):501-8.
111. Wade DT, King NS, Wenden FJ, et al. Routine follow up after head injury: a second randomised controlled trial. J Neurol Neurosurg Psychiatry. 1998 Aug;65(2):177-83.
112. Fann JR, Bombardier CH, Dikmen S, et al. Validity of the Patient Health Questionnaire-9 in assessing depression following traumatic brain injury. J Head Trauma Rehabil. 2005 Nov-Dec;20(6):501-11.
113. Ashman TA, Cantor JB, Gordon WA, et al. A randomized controlled trial of sertraline for the treatment of depression in persons with traumatic brain injury. Arch Phys Med Rehabil. 2009 May;90(5):733-40.
114. Rapoport MJ, Chan F, Lanctot K, et al. An open-label study of citalopram for major depression following traumatic brain injury. J Psychopharmacol. 2008 Nov;22(8):860-4.
115. Defense and Veterans Brain Injury Center Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings. Clinical Practice Guideline and Recommendations, December 22, 2006. 2006.
116. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA: Centers for Disease Control and Prevention; 2003.
117. Ivins BJ, Schwab KA, Warden D, et al. Traumatic brain injury in U.S. Army paratroopers: prevalence and character. J Trauma. 2003 Oct;55(4):617-21.
118. Warden D. Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil. 2006 Sep-Oct;21(5):398-402.
119. Langlois JA, Rutland-Brown W and Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006 Sep-Oct;21(5):375-8.
120. Busch CR and Alpern HP. Depression after mild traumatic brain injury: a review of current research. Neuropsychol Rev. 1998 Jun;8(2):95-108.
121. Graham DI and Lantos PL. Greenfield's Neuropathology, 7th Edition. 2002.
122. Wilk JE, Thomas JL, McGurk DM, et al. Mild traumatic brain injury (concussion) during combat: lack of association of blast mechanism with persistent postconcussive symptoms. J Head Trauma Rehabil. 2010 Jan-Feb;25(1):9-14.
123. Babin PR. Diagnosing depression in persons with brain injuries: A look at theories, the DSM-IV and depression measures. Brain Injury. 2003 Oct;17(10):889-900.
124. Alderfer BS, Arciniegas DB and Silver JM. Treatment of depression following traumatic brain injury. Journal of Head Trauma Rehabilitation. 2005 Nov-Dec;20(6):544-562.
125. Trivedi MH and Kleiber BA. Algorithm for the treatment of chronic depression. J Clin Psychiatry. 2001;62 Suppl 6:22-9.
126. Ereshefsky L. The Texas Medication Algorithm Project for major depression. Manag Care. 2001 Aug;10(8 Suppl):16-7; discussion 18-22.
127. Berney J, Favier J and Froidevaux AC. Paediatric head trauma: influence of age and sex. I. Epidemiology. Childs Nerv Syst. 1994 Nov;10(8):509-16.
128. Matchar DB, Myers ER, Barber MW, et al. Management of uterine fibroids. Evid Rep Technol Assess (Summ). 2001;Jan(34):1-6.
129. Schulz KF, Chalmers I, Grimes DA, et al. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. JAMA. 1994 Jul 13;272(2):125-8.
130. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12.
131. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2009 Jul 10.
132. Dept. of the Army -- USAMRAA. Psychological Health and Traumatic Brain Injury Advanced Technology/Therapeutic Devleopment Award. 2009 Jul 7, 2009;2010(Feb 9,).

133. University of Iowa NIoNDaSN. Treatment strategy to prevent mood disorders following traumatic brain injury. 2008 2009;2010(Feb 8).
134. University of Washington. Telephone and In-Person Cognitive Behavioral Therapy for Depression After Traumatic Brain Injury. 2007 October 1, 2007;2010(Feb 8).
135. Memorial Herman The Institute for Rehabilitation and Research (TIRR). Effectiveness of a Group Cognitive-Behavioral Intervention for Depression after TBI and Factors that Affect Response to Treatment. 2007 October 1, 2007;2010(Feb 8).
136. University of Washington. Phone cognitive behavioral therapy for depression after traumatic brain injury. 2008 2008;2010(Feb 8).
137. University of Illinois at Chicago. Neuropsychiatry of traumatic brain injury 2008 2008;2010(Feb 8).
138. Lakehead University Ontario Neurotrauma Foundation. Mindfulness-Based Cognitive Therapy Intervention to Treat Depression in Individuals with a Traumatic Brain Injury. In: ClinicalTrials.gov. [Internet]. 2008;2010 (Feb 8).
139. Toronto Rehabilitation Institute Ontario Neurotrauma Foundation Peel Halton Acquired Brain Injury Services. Improving Psychological Wellness After Acquired Brain Injury. In: ClinicalTrials.gov. [Internet]. 2009;2010 (Feb 8).
140. Monash University. The use of Motivational Interviewing and cognitive behavioural therapy to treat anxiety and/or depression following traumatic brain injury . In: Australian New Zealand Clinical Trials Registry. [Internet]. 2009;2010 (Feb 8).
141. Mauri MC, Colasanti A, Paletta S, et al. Post traumatic brain injury major depression and primary major depression: psychopathological and neuropsychological profiles. European Neuropsychopharmacology. [Meeting]. 2009 Sep;19(Suppl. 3):S389.
142. Mount Sinai School of Medicine U.S. Department of Education. Treatment of Post-TBI Depression Conditions. In: ClinicalTrials.gov. [Internet]. 2009;2010 (Feb 8).
143. University of Washington. The Effect of Exercise on Mood After Traumatic Brain Injury. In: ClinicalTrials.gov. [Internet]. 2008;2010 (Feb 8).
144. Bayside Health. TMS in the Treatment of the Sequelae of Closed Brain Injury. In: ClinicalTrials.gov. [Internet]. 2008;2010 (Feb 8).
145. University of Iowa, National Institute of Neurological Disorders and Stroke (NINDS);. Treatment Strategy to Prevent Mood Disorders Following Traumatic Brain Injury. In: ClinicalTrials.gov. [Internet]. 2008;2010 (Feb 8).
146. Virginia Commonwealth University, U.S. Department of Education. Pharmacological Intervention in Depression After Traumatic Brain Injury. In: ClinicalTrials.gov. [Internet] Bethesda (MD): National Library of Medicine (US); 2007 [updated 2007; cited 2010 Feb 8]; Available from: http://clinicaltrials.gov/ct2/show/NCT00205491.
147. Sunnybrook Health Sciences Centre, Ontario Mental Health Foundation. Depression and Traumatic Brain Injury. In: ClinicalTrials.gov. [Internet]. 2008;2010 (Feb 8).
148. Johns Hopkins University. Post traumatic brain injury (TBI) depression. 2008 2008;2010(Feb 8).
149. Colasanti A, Mauri MC, Paletta S, et al. Primary major depression versus post-traumatic brain injury major depression: psychopathological and neuropsychological differences. European Neuropsychopharmacology. [Meeting]. 2008 Aug;18(Suppl. 4):S582-S583.
150. Buzzi MG, Bivona U, Matteis M, et al. Cognitive and psychological patterns in post-traumatic headache following severe traumatic brain injury. Cephalalgia. [Meeting]. 2003 September;23(7):672.
151. Wegner RC. Spirituality and religion as predictors of mood and quality of life following traumatic brain injury; 2008.
152. Statman SH. The evolution of depression over the first two years post head trauma. Dissertation Abstracts International. 1989;49(7-B).
153. Thaut MH, Gardiner JC, Holmberg D, et al. Neurologic Music Therapy Improves Executive Function and Emotional Adjustment in Traumatic Brain Injury Rehabilitation. In: DallaBella S, Kraus N, Overy K, et al., editors. Neurosciences and Music III: Disorders and Plasticity: Blackwell Publishing; 2009. p. 406-416.
154. Mauri MC, Colasanti A, Natoli A, et al. Psychiatric and neuropsychological sequelae of TBI: a case-control, longitudinal study. International Journal of Neuropsychopharmacology. [Meeting]. 2008 Jul;11(Suppl. 1):308.
155. Hou J-GG and Lai E. Previous traumatic brain injury may be a risk factor of mood disorders in Parkinson's disease. Neurology. [Meeting]. 2008 Mar 11;70(11, Suppl. 1):A438.
156. Lee H, Kim S, Kim J, et al. Comparing effects of methylphenidate, sertraline and placebo on depressive symptoms and psychomotor function in patients with traumatic brain injury. International Journal of Neuropsychopharmacology. [Meeting]. 2004 Jun;7(Suppl. 2):S274.
157. Anderson SS. The effect of written emotional expression on depression following mild traumatic brain injury: A pilot study. Dissertation Abstracts

International: Section B: The Sciences and Engineering. 2009;69(9-B).
158. Shepherd JG, Jr. Coping style as mediator of health-related quality of life and depression after an acquired brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2007;68(2-B).
159. Jordan BD, Glass E and Ortega-Verdejo K. Assessment of neuropsychiatric symptoms in patients with traumatic brain injury. Neurology. [Meeting]. 2002 April 9;58(7 Supplement 3):A357.
160. Van Den Eeden SK, Tanner CM, Popat RA, et al. The risk of Parkinson's disease associated with head injury and depression: A population-based case-control study. Neurology. [Meeting]. 2000 April 11;54(7 Supp. 3):A347.
161. Holtzer R, Burright RG and Donovick PJ. Depression and brain injury history of psychiatric patients. Society for Neuroscience Abstracts. [Meeting]. 1998 1998;24(1-2):740.
162. Warden DL, Dougherty DS, Quintero-Sheeley E, et al. Psychotic symptoms following moderate traumatic brain injury. Neurology. [Meeting]. 1994 1994;44(4 SUPPL. 2):A401.
163. Rao N. Suicide after successful rehabilitation of traumatic brain injury. Archives of Physical Medicine and Rehabilitation. [Meeting]. 1991;72(10):818.
164. Van Mier H, Hulstijn W, Tromp E, et al. Fine motor performance in closed head injury and depression. Society for Neuroscience Abstracts. [Meeting]. 1990;16(2):1317.
165. O'Brien KP. Relationship of psychosocial and physical dysfunction to emotional adjustment after traumatic brain injury. Journal of Clinical and Experimental Neuropsychology. [Meeting]. 1988;10(1):41-42.
166. Fenimore EA. Depression following traumatic brain injury and the Hamilton Depression Rating Scale. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2006;67(3-B).
167. Bay EH. Chronic stress, cortisol regulation, interpersonal relatedness, cognitive burden, and depressive symptoms among community-dwelling survivors of brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2002;62(10-B).
168. Sinacori DR. Depression in a brain-injured sample: An investigation of indicators on the Rorschach and MMPI-2. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2000;60(8-B).
169. Ruttan LA. Depression and neuropsychological functioning in mild traumatic brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 1998;59(5-B).
170. Burg JS. Psychiatric treatment outcome following traumatic brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 1997;57(12-B).
171. Mervak TA. Physical and psychological factors in depression following closed head trauma. Dissertation Abstracts International. 1980;40(12-B, Pt 1).

List of Acronyms/Abbreviations

[la]/LA	language
[mh:noexp]	does not include MeSH terms found below this term in the MeSH tree
[mh]	Medical Subject Heading
[pt]/PT	Publication type
[tw]	Text word
ab.	Abstract word
ABI	Acquired Brain Injury
AES-S	Apathy Evaluation Scale-Self Rated
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BHS	Becks Hopelessness Scale
BIS	Brain Injury Scale
BSI	Brief Symptom Inventory
CAQ	Clinical Analysis Questionnaire
CES-D	Center for Epidemiologic Studies Depression Scale
CHI	Closed head injury
CIDI	Composite International Diagnostic Interview
CiOP	Changes in Outlook Questionnaire
CIQ	Community Integration Questionnaire
CIRS	Cumulative Illness Rating Scale
CIS-R	Clinical Interview Schedule-Revised
CNS	Central nervous system
COF	Causes of Fatigue Questionnaire
COS	Community Outcome Scale
CPCS	Checklist of Postconcussion Symptoms
CT	Computed tomography
DASS	Depression Anxiety Stress Scales
DAST	Drug Abuse Screening Test
DE	Descriptors/Descriptors assigned to citations
DIS-III-A	The Diagnostic Interview Schedule Version A
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EBIQ	European Brain Injury Questionnaire
FAM	Functional Assessment Measure
FIM	Functional Independence Measure
FSS	Fatigue Severity Scale
GAF	Global Assessment of Functioning
GCS	Glasgow Coma Scale
GHQ	General Health Questionnaire
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale Extended

GSW	Gunshot wound(s)
HADS	Hospital Anxiety and Depression Scale
HAMD	Hamilton Rating Scale for Depression
HAS	Hamilton Anxiety Scale
HIBS	Head Injury Behavior Rating Scale
HSCL-25	Hopkins Symptom Checklist
HTQ	Harvard Trauma Questionnaire
ICD-10	International Classification of Disease version 10
IDPESQ	Indice de detresse psychologique de l'Enquete Sante Quebec (French adaptation of the Psychiatric Symptom Index)
ISS	Injury Severity Scale
K-10	Kessler Psychological Distress Scale
kw/KW	Key words
Lg.	language
LOC	Loss of Consciousness
LSI-A	Life Satisfaction Index I-A
MADRS	Montgomery and Asberg Depression Rating Scale
MASQ	Mood and Anxiety Symptom Questionnaire—Short Form
MCMI-II/III	Millon Clinical Multi-Axial Inventory (version 2/3)
MDE	Major depressive episode(s)
MeSH	Medical Subject Heading
mg/dL	Milligram per deciliter
MMPI-2	Minnesota Multiphasic Personality Inventory version 2
MPAI	Mayo-Portland Adaptability Inventory
NEOPI-R	NEO Personality Inventory-Revised
NFI-Dep	Neurobehavioral Functioning Index Depression Subscale
NPI	Neuropsychiatric Inventory
NRS-R	Neurobehavioral Rating Scale-Revised
PAI	Personality Assessment Inventory
PCS	Postconcussion Syndrome
PHQ-9	Patient Health Questionnaire-9
PIM	Participation and Independence Measure
PO	population
POMS	Profile of Mood States
PRIME-MD	Primary Care Evaluation of Mental Disorders
PSE	Present State Examination
PSS	Perceived Stress Scale
PTA	Post-traumatic Amnesia
QoL	Quality of life
RDS	Referral Decision Scale
RPCQ	Rivermead Post-Concussion Disorder Questionnaire
SCAN	Schedules for Clinical Assessment in Neuropsychiatry

SCID	Structured Clinical Interview for DSM-IV
SCL 90	Symptom Checklist 90
SCL-20	Hopkins Symptom Checklist depression subscale
SF-12 v2	12-Item Short Form Health Survey-Version 2
SF-36	36-Item Short Form Survey Instrument
SIP	Sickness Impact Profile
TBI	Traumatic Brain Injury
ti.	Title word
VAS-D	Visual Analog Scale - Depression
VAS-F	Visual Analog Scale - Fatigue
WHOQOL-BREF	World Health Organization Quality of Life Questionnaire
WSRS	Wimbledon Self-Report Scale
ZDS	Zung Depression Scale
ZSDS	Zung Self-rating Depression Scale