Comparative Effectiveness Review
Number 25

Effective Health Care Program

Traumatic Brain Injury and Depression

Executive Summary

Introduction

We do not know the extent to which 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 it can deplete the mental energy and motivation needed for both recovering from the depression itself and adapting to the physical, social, and emotional consequences of trauma with brain injury. 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. Clinicians, caregivers, and patients lack formal evidence to guide the timing of depression screening, which tools to use for screening and assessment, treatment choices, and assessment of treatment success.

Importance of Depression

Depression is defined by criteria that 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.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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Effective Health Care

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, and causes self-doubt and difficulty taking action, all of which can delay recovery from TBI. The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, (DSM-IV-TR)[2] defines 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.

The disturbances may also occur following TBI due to other circumstances, such as pain that disrupts sleep, which may mask the recognition that the sleep disturbance is also a part of a burgeoning depression. Depression may be financially costly in undermining physical therapy efforts, treatment compliance in general, and rehabilitation planning and efforts. 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 TBI

TBI occurs when external force from an event such as a fall, sports injury, 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 or 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]

TBI is responsible for roughly 1.2 million emergency department visits each year, with 1 in 4 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 at all, or they seek care in other settings. The Centers for Disease Control and Prevention estimates that up to 75 percent of TBIs are 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. More than 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 and a concomitant rise in TBI that is more often moderate to severe than mild.[4] The military confirms that more than 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 TBI 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 percent 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 it remains undiagnosed or affects 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

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 the 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 provided 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 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 decisionmaking. This review is focused on pragmatic aspects of these concerns.

Key Questions

In preparing this report, we have addressed the following key questions (KQs):

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, post-traumatic stress disorder (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 psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and 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, preexisting 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, and the Published International Literature on Traumatic Stress 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. They resolved differences through discussion, review of the publications, and arrival at 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 overrepresent 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 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 reported 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.

Results

Literature search yield. As a result of the search, 2,015 nonduplicate articles were identified. One hundred fifteen articles were included in the review, representing 81 distinct populations, with 112 articles pertaining to KQ1, 113 to KQ2, 9 to KQ3, 2 to KQ4, and none identified for KQ5 or KQ6. Detailed reasons and process for exclusions are described in the full report.

KQ1. Prevalence of Depression After Traumatic Brain Injury

Content of literature. We identified 112 publications[7,12-14,18-125] from 79 distinct study populations. Thirty-eight of the 79 were in the United States, 12 in Canada, 12 in Europe, 9 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 = 33), including those that specifically noted trauma center status (n = 10), and rehabilitation programs (n = 19). 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 = 38) using closed head injury in concert with Glasgow Coma Scores (GCS). American Congress of Rehabilitation Medicine criteria were common (n = 13), as were ad hoc operational definitions (n = 12) and failing to clearly define criteria (n = 12). 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-three 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 assessments 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 = 29). Among written or administered tools, the Beck Depression Inventory (BDI; n = 13), Hospital Anxiety and Depression Scale (HADS; n = 11), and Center for Epidemiologic Studies Depression Scale (CES-D; n = 8) were most common. A wide variety of other measures and customized uses of subscales (n = 62) were also used.

Prevalence estimates. We have considered the Structured Clinical Interview for DSM-IV (SCID) and other formal structured clinical interview protocols that map to the DSM and/or International Classification of Diseases 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 use of the SCID or other clinical interview and clearly operationalized criteria for TBI, 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 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 20.3 percent compared with 32.5 percent in studies that enrolled or followed up populations of all severity. Too few studies isolated 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.

Fourteen studies in 13 distinct study populations report results from multivariate models to identify predictors or risk factors for depression after TBI.[13-14, 23, 38, 50, 64, 78, 99, 103, 118-121, 125] Age was reported in a large United States cohort (n = 559) to be an independent risk factor for depression among both those with and without prior depression. In this study, which reflects the full spectrum of severity of TBI, risk decreased with increasing age, such that those age 60 and older were at lowest risk.[125] In another study aiming at predicting risk, when age was grouped with other factors, the combination of older age at injury, CT scan with documented intracranial lesion, and higher 1-week CES-D scores, were sensitive (93 percent) though not specific (62 percent) for identifying those with mild TBI who were depressed by 3 months after their injury.[50] One group has found that women have higher risk (relative risk [RR] = 1.27; 95 percent confidence interval [CI]: 1.07, 1.52) of new but not recurrent depression after TBI after adjusting for other risk factors.[125]

Severity of TBI is not clearly linked with risk. In the sole model that assessed GCS scores, coma length, and duration of post-traumatic amnesia, none of the factors were associated with depression or its severity.[118] Another group using the Injury Severity Score also found no association between severity and prevalence of depression.[121]

History of alcohol and substance abuse increase risk.[14,64,125] Pain, involvement in litigation related to the injury, and perceived stress have been reported as risk factors among those entering rehabilitation care and in prospective cohorts.[23,121] 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 that "availability of a confidant" reduced risk of depression,[78] and another reported that years married were inversely related to risk, while presence and degree of cognitive disability, motor disability, and social aggression elevated risk.[99] Concepts related to resilience or personality traits have not been widely investigated, but scores on the Adult Hope Scale ($p < 0.005$) and the Life Orientation Test-Revised ($p < 0.05$), a measure of dispositional optimism, are both found to contribute independently to predicting depression and its severity as measured by the BDI in a small Israeli study (n = 65).[119] History of depression has been documented as a substantive risk for having depression at followup (RR = 1.54; 95 percent CI: 1.31, 1.82), as was depression at the time of the injury (RR = 1.62; 95 percent CI: 1.37, 1.91).[125]

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

yields inconsistent results. In aggregate for all those with TBI, onset of major depression within 3 months of injury has been reported to be sevenfold as common (95 percent CI: 1.36 to 43.48) among those with abnormal CT scans after injury compared with normal imaging.[50] Focusing on locations of injury, Jorge and colleagues[13,103] have replicated their findings in several CT scan-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 magnetic resonance imaging (MRI) near the time of injury, the findings from CT scan 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. In a study of political prisoners, up to 50 years after injury, TBI-associated cerebral cortical thinning in the left superior frontal and bilateral superior temporal cortex, as assessed by MRI, was associated with depression, and similar effects were not seen in prisoners without a history of TBI with respect to depression risk.[118]

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 27 percent met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 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 1137[12-14,18-126] publications in 79 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 1 year and beyond, both categories of assessments converge around 30 percent (27.4 percent with SCID and 33.2 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. Five publications compared SCID to candidate tools for assessment of depression, the BDI,[90,115] Patient Health Questionnaire (PHQ-9),[126] and HADS.[28,117] None of the tools reported simultaneous sensitivity and specificity above 90 percent. One study identified different optimal cutoffs of the BDI-II; maximum sensitivity of 87 percent and specificity of 79 percent were obtained with cutoffs of 19 for participants with mild TBI, and 35 for those with moderate or severe TBI. 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 (Neurobehavioral Functioning Index , Profile of Mood States Depression Scale, 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 TBIs. Nor does the literature support any one tool over the others.

KQ3. Prevalence of Concomitant Psychiatric Conditions

Content of literature. We identified nine publications[13,57,59,91,96,98,110,117,125] in eight populations that reported prevalence of concomitant psychiatric conditions within the population of depressed TBI patients,[13,96,98,117] or compared rates of comorbid conditions in those with and without depression.[57,59,91,110,125] 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 five prospective cohorts,[13,57,59,98,110,125] one retrospective cohort,[91] and two cross-sectional studies.[96,117] Seven studies were conducted in the United States[13,57,59,91,96,98,110,125] and one in Australia.[117] 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] one at a tertiary care center,[117] and three at trauma centers.[13,98,110,125] 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]

Coexisting psychiatric conditions. Eight percent to 93 percent of depressed participants had one or more concomitant conditions. Anxiety was the most commonly detected coexisting condition. In the studies that compared rates of comorbid anxiety in those with and without depression, it was significantly more common in the depressed group (76.7 percent vs. 20.4 percent in one study; 60 percent vs. 7 percent in the second).[59,125]

The recruitment phase of a clinical trial for sertraline to treat major depressive disorder was described in the largest study, and included 1-year followup of 599 participants, all of whom had GCS scores of ≤12.125 Depression was assessed with a structured interview based on the PHQ-9, and assessment for anxiety disorders also used modules of the PHQ. The 1-year cumulative incidence of Major Depressive Disorder (MDD) in this population was 53.1 percent. During this first year following injury, individuals with MDD had substantially higher rates of a concomitant anxiety disorder than did participants without MDD (60 percent vs. 7 percent: RR, 8.77; 95 percent CI, 5.56 to 13.83).

Assessing depression with the PHQ-9, and PTSD with the PTSD Checklist-Civilian, 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] One-third of patients had major depressive disorder (mood disorder with major depressive features). Over the course of followup, 23 of 30 (76.7 percent) patients with major depressive disorder also had anxiety, compared with 9 of 44 (20.4 percent) nondepressed patients. Of note, PTSD was included with anxiety in this study, and was the defining psychiatric feature for 7 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) 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, coexisting 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 reassessment, 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, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers.[13,59,96,125] PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in 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 coexisting psychiatric conditions is warranted.

KQ4. Outcomes of Treatment for Depression After TBI

Content of literature. Only two publications[127-128] addressed a treatment for individuals diagnosed with depression after a traumatic brain injury. One of the treatment studies was conducted in the United States[127] and the second was in Canada.[128] Both were studies of antidepressant efficacy, the first being a randomized controlled trial of sertraline, and 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.[127] Participants were at least 6 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 Hamilton Rating Scale for Depression (HAM-D) score higher than 18. Dosage of sertraline was not fixed and could be adjusted at 2-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 who 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[128] 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 score of 13–15, and post-traumatic amnesia (PTA) of less than 24 hours. Moderate to severe TBI had a GCS score of less than 13, a PTA greater than 24 hours, or an abnormal CT image. The study intended to evaluate the effects of a 6-week course of treatment in 54 patients; however, low response rates resulted in a study extension for 26 participants to 10 weeks. Therefore, although 6-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 8 defined as remission. In the 6-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, 6 were in the intended 6-week group and 5 were in the intended 10-week group. Ten of the 11 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 decisionmaking for the 1 to 2 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.

Full Report

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