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The Assessment and Treatment of Individuals with History of Traumatic Brain Injury and Post-Traumatic Stress Disorder: A Systematic Review of the Evidence

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Prepared by:

Minneapolis Veterans Affairs Medical Center
Minnesota Evidence Synthesis Program
Center for Chronic Disease Outcomes Research
Minneapolis, MN

Investigators:

Principal Investigator
Kathleen Carlson, PhD

Co-Investigators

Shannon Kehle, PhD
Laura Meis, PhD

Research Associates

Nancy Greer, PhD
Rod MacDonald, MS
Indulis Rutks, BA

Director

Timothy J. Wilt, MD, MPH

PREFACE

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HSR&D provides funding for four ESP Centers. Each Center has an active and publicly acknowledged VA affiliation and also serves as an Evidence Based Practice Center (EPC) supported by the Agency for Healthcare Research and Quality (AHRQ). The Centers will each generate three evidence syntheses annually on clinical practice topics of key importance to VHA leadership and policymakers. A planning committee with representation from HSR&D, Patient Care Services (PCS), Quality Enhancement Research Initiative (QUERI), Office of Quality and Performance (OQP), and the VISN Clinical and Quality Management Officers, has been established to identify priority topics and key stakeholder concerns and to ensure the quality of final reports. Comments on this evidence report are welcome and can be sent to Susan Schiffner, ESP Program Manager, at Susan.Schiffner@va.gov.

This report is based on research conducted by the Minneapolis Veterans Affairs Medical Center, Minnesota Evidence Synthesis Program, and the Center for Chronic Disease Outcomes Reasearch under contract to the Department of Veterans Affairs. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs.

This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. The Department of Veterans Affairs endorsement of such derivative products may not be stated or implied.

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INTRODUCTION

Traumatic brain injury (TBI) has been defined as trauma to the head that results in a decreased level of consciousness, amnesia, other neurologic or neuropsychologic abnormalities, skull fractures, intracranial lesions, or death.[1] TBI can be caused by penetrating trauma or by blunt force, including acceleration/deceleration forces that cause the brain to collide with the skull.[1] Blunt force TBI is typically classified by level of severity, most commonly differentiated as mild, moderate, or severe. The vast majority of civilian patients that are hospitalized for TBI are diagnosed with mild TBI (mTBI).[2] While a similar ratio specific to soldiers or veterans is not readily available, mTBI is also prevalent in this population.[3] Personnel engaged in the current military operations, Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF), are sustaining mTBI at unprecedented rates.[4] One commonly referenced report estimated that nearly 20%, or 300,000, OEF/OIF veterans had sustained a TBI during deployment,[5] many of these being mTBI. There has been much political and media interest in the rates of mTBI associated with the current conflicts. While most of those who sustain mTBI do not experience ongoing symptoms, a minority of individuals will experience some psychosocial, mental, and/or physical health problems.[6,7] Thus, there is major concern across veteran healthcare providers, particularly the U.S. Department of Veterans Affairs (VA) and Department of Defense (DoD), regarding the identification and care of mTBI.

Post-traumatic stress disorder (PTSD) is a highly prevalent and pernicious mental health problem with significant costs to the individual and society. It is an anxiety disorder characterized by avoidance behaviors, physiological hyperarousal, and re-experiencing symptoms following exposure to a traumatic event.[8] Population-based epidemiologic studies have shown that nearly 56% of people will experience a psychologically traumatic event, and between 8-12% of individuals will meet criteria for PTSD during their lifetimes.[9,10] United States (U.S.) military veterans' risk of developing PTSD is higher than the risk in the general U.S. population. The lifetime prevalence of PTSD among Vietnam veterans is estimated to be 19%.[11] Similar patterns are being observed among OEF/OIF soldiers and veterans. A study by Hoge and colleagues found that exposure to traumatic events was extremely high among OIF soldiers and Marines, with 93% to 97% having been shot at and approximately 95% having seen human remains.[12] Screening data from OIF soldiers suggest that approximately 17% of active duty soldiers and 25% of reserve soldiers may meet criteria for PTSD three to six months post-deployment.[13] Studies have found that veterans with PTSD have significant impairments in social and occupational functioning and quality of life.[14-18]

VA and DoD healthcare providers are now facing a large population of OEF/OIF veterans who have sustained TBI, particularly mTBI, and also suffer from PTSD.[19] However, the long-term health outcomes of individuals who have received diagnoses of both TBI and PTSD (TBI/PTSD), especially mTBI and PTSD (mTBI/PTSD), are poorly understood. There is concern that current evidence-based practices to define, identify, and treat mTBI and PTSD may be less accurate and/or effective when the conditions co-occur. Thus, there is a need to develop an evidence base and identify best practices for patients with this co-diagnosis. The objective of this evidence synthesis report was to systematically review and summarize the published literature that addresses the epidemiology, assessment, and treatment of adults with mTBI/PTSD.

While the epidemiologic review compares prevalence estimates of PTSD across all TBI severity levels, so as to examine any potential differences in prevalence by TBI severity, the assessment and treatment sections of this report were focused on mTBI because of the growing concerns related to this injury in the U.S. military population. We emphasized results most relevant to U.S. military personnel and veterans.

BACKGROUND

Because of the dramatic rise in the number of veterans who have sustained TBI and psychological trauma, there has been a recent spike in the literature pertaining to the overlap between the two conditions. There has been scientific debate about whether or not the history of TBI may preclude the development of PTSD.[20,21] This debate stemmed mainly from the fact that PTSD by definition involves re-experiencing of traumatic events, while TBI frequently involves amnesia for the traumatic event and, thus, no memories to re-experience. For example, a study by Sbordone and Liter found that all PTSD patients were able to provide a highly detailed recollection of events occurring within 15 minutes of the traumatic event, compared with none of the patients who had sustained TBI.[21] These authors suggested that history of TBI and development of PTSD are mutually exclusive events. However, since the time of their report, there has been continued documentation of PTSD developing in individuals with history of TBI, and co-occurring TBI/PTSD symptoms, across a variety of populations and TBI severity levels.[24-26] Thus, it is generally accepted that the two conditions can and do co-occur.

More recently, however, researchers have proposed that symptoms often attributed to mTBI could instead be due to PTSD and other mental health problems.[22,23] Hoge et al. found that, after statistical adjustment for PTSD and depression, soldiers' mTBI history (assessed three to four months after return from deployment) no longer had a statistically significant association with physical health symptoms with the exception of headaches.[22] The results of this study may reflect the normal healing process generally experienced after mTBI. It is estimated that approximately 90% of mTBI cases follow a predictable course of recovery and do not experience long-term residual symptoms requiring treatment.[6,7] A small minority of individuals may experience ongoing mTBI-related psychosocial, mental, and/or physical health problems; however, a 2008 Institute of Medicine (IOM) report on the long-term consequences of TBI cited insufficient evidence of associations between mTBI and neurocognitive deficits or limitations in psychosocial functioning.[24] Hoge et al. have suggested that definitions frequently used for both screening and eventual diagnosis of mTBI, especially in the presence of suspected PTSD, are methodologically inadequate, not validated, prone to bias, and potentially result in misattributing a chronic health condition to a large group of individuals.[23] They particularly draw comparisons and distinctions between mTBI versus moderate and severe TBI as noted in the table below.[23] Hoge et al. urge use of an approach that would "establish case definitions and evaluation tools that fulfill criteria for causation; have clinical validity and do not lead to misattribution; ensure that screening does not include nonspecific questions, is conducted near the time of injury, and maintains independence of variables; use communication strategies that promote expectations of recovery; apply knowledge from studies on the relationship between compensation and persistent post-concussive symptoms to ensure that disability regulations do not generate disability; … [develop and evaluate] evidence-based step-care and collaborative care models; and reduce the

impact of flawed assumptions, conformity to consensus processes, and lack of scientific rigor on health policies and outcomes."[23] While the viewpoints by Hoge et al. are disputed for clinical purposes,[28] it is noteworthy that some of their suggestions, such as stricter standardization of case definitions, would result in higher quality evidence for scientific purposes, upon which practice guidelines specific to patients with mTBI/PTSD could be based.

Comparison of Mild TBI with Moderate and Severe TBI*

Variable	Mild TBI (Concussion)	Moderate and Severe TBI
Clinical definition	Loss of consciousness lasting <30 minutes, any alteration of consciousness, or post-traumatic amnesia lasting <24 hrs; some definitions include Glasgow Coma Scale score of 13 to 15	Loss of consciousness lasting ≥ 30 minutes to prolonged coma, post-traumatic amnesia lasting ≥24 hr up to permanently, or Glasgow Coma score as low as 3
Focal neurologic signs	Usually none or transient	Frequently present
Neuroimaging with CT or MRI	Usually negative	Diagnostic
Natural History	Full recovery is usual; there is lack of consensus on the natural history of concussion and post-concussive symptoms	Natural history and recovery are directly related to the severity of the injury and functional neuroanatomy
Case definitions and specificity of injury sequelae	Case definitions of post-concussive syndrome have low reliability and validity and show poor correlation with one another; there are high rates of these symptoms in healthy populations and high rates of "post-concussion syndrome" after non-head injuries	Injury sequelae are not debated
Predictors of persistent symptoms or disability	Psychological factors (e.g., depression, anxiety, or PTSD), compensation and litigation, and negative expectations and beliefs are the strongest risk factors	Directly related to injury characteristics
Neurocognitive testing	Often inconclusive beyond the period of acute injury	Essential and valuable component of on-going clinical care
Neuronal-cell damage	Metabolic and ionic processes caused by axonal twisting or stretching; these can lead to secondary disconnection	Combination of cellular disruption directly related to injury and metabolic, vascular, and ionic processes
Epidemiologic evidence of causation between injury and sequelae	Inconsistent and debated	Not debated

*CT denotes computed tomography, MRI magnetic resonance imaging, PTSD post-traumatic stress disorder and TBI traumatic brain injury.

Note: Table adapted from Hoge et al.[23]

There seems to be little convergent data on the prevalence, health outcomes, and treatment of TBI/PTSD. Previous reviews have highlighted the widely variable rates of overlap between diagnosis of TBI and PTSD.[29-31] For example, McMillan reported that the prevalence of cases with both diagnoses ranged across studies from 1% to more than 50%,[29] while Kim et al. similarly reported a range from 3% to 59%.[30] Discrepancies in the reported epidemiology of TBI/PTSD may be due to differences in the true prevalence of these conditions specific to different types of trauma, levels of trauma severity, and/or baseline characteristics of the study population. Additionally, as indicated above, the methods of case ascertainment, that is, the methods, criteria, and cut-offs used to epidemiologically define and study TBI and/or PTSD "cases," can vary widely.[32] It is important to examine reported prevalence of TBI/PTSD across these potentially significant sub-categories (severity, etiology, study population, and case ascertainment) to gain a better understanding of the overlap between the two conditions.

Determining the etiology of presenting problems in individuals who have a history of mTBI as well as probable current PTSD may be complicated. While mTBI is considered a historical diagnosis and should not require the presence of current symptoms for a diagnosis to be assigned, this understanding may not be shared across all clinical disciplines that encounter mTBI patients. A number of symptoms and associated problems are common to both mTBI and PTSD. These symptoms include sleep disturbance, fatigue, depressed mood, concentration and memory problems, irritability, and reduced cognitive processing speed.[26] As noted by Hoge et al., PTSD and depression may be important confounders of problems seemingly associated with an mTBI event or other physical health problems.[22] Problems due to mTBI can also obstruct patients' abilities to verbalize and describe symptoms of either condition.[33] Research has also suggested that the presentation of PTSD symptoms may actually vary among individuals with and without a history of mTBI, such that different constellations of symptoms are more prominent among those with a history of brain injury (e.g., dreams, nightmares, and hyperarousal) than among those without history of brain injury (e.g., intrusive recollections).[34] Additionally, the presence of other problems that commonly occur with both conditions (e.g., alcohol use, depression) may interfere with attempts to develop and complete an accurate diagnostic profile.[33]

It remains unknown how well diagnostic instruments currently used for assessing history and symptoms of mTBI or PTSD perform in individuals with both conditions. Without this understanding, including how rates of co-occurrence vary with different approaches to assessment, conclusions regarding the true presence and extent of overlap between mTBI and PTSD cannot be reached. Additionally, as each condition could yield alternative explanations for symptomology, accurate and differential diagnosis provides important implications for treatment. For example, avoidance of previous activities can be due to either symptoms of PTSD or the development of mTBI-related cognitive deficits. Intrusive thoughts can be explained through attempts by the patient to fill memory gaps caused by mTBI or through symptoms of PTSD.[26,35] As a result, developing and evaluating appropriate treatment recommendations remains tied to accurate assessment and diagnosis of both mTBI and PTSD.

Efficacious treatment for individuals with mTBI/PTSD is of importance to VA and DoD as well as the private healthcare sector. Initial data suggest that a large number of veterans with history and/or diagnoses of both mTBI and PTSD are presenting for treatment; one study examining

outcomes and service utilization of OIF veterans one-year post-deployment found that 65% of those with mTBI/PTSD reported seeking treatment for concerns related to reintegration.[19] Fortunately, there are a number of efficacious psychological and pharmacological treatments for PTSD. The treatments with the strongest evidence are cognitive-behavioral psychotherapies. Effect sizes for cognitive-behavioral treatments, such as prolonged exposure therapy and cognitive processing therapy, range from medium to very large when compared to no-treatment conditions, and from small to large when compared to other psychological or psychiatric treatments.[36] Among veterans, high quality studies have shown that 40% to 50% of patients no longer meet criteria for PTSD following either prolonged exposure or cognitive processing therapy.[37,38] Preliminary data also suggest that such therapies will be helpful for OEF/OIF veterans. A small, ongoing trial of prolonged exposure among OEF/OIF veterans has shown a 50% reduction in PTSD symptoms following treatment.[39] Data regarding the treatment of mTBI symptoms are less robust than the evidence for treatment of PTSD; however, there is evidence that providing psychoeducation regarding the typical sequelae, expected course of recovery, and compensatory strategies soon after injury may be effective in facilitating the return to premorbid functioning.[40,41] The VA and DoD have recommended early education as a treatment of choice for those with a history of mTBI.[6]

While efficacious treatments for both mTBI symptoms and PTSD exist, patients presenting with both a history of mTBI and PTSD may need unique therapies. Patients with both conditions may experience a differential response to standard treatments compared to those with only mTBI history or PTSD. Bryant and Hopwood have identified mechanisms by which mTBI symptoms may interfere with evidence-based treatments for PTSD.[20] They note that physical pain, which frequently occurs after mTBI,[42] may limit the extent to which patients can engage in empirically supported treatments that involve in-person exposure to anxiety producing situations. They additionally note that cognitive limitations may make it necessary to modify cognitive-behavioral therapies, and that emotion regulation and impulse control problems may complicate the use of exposure techniques. It is unknown whether or how PTSD may conversely interfere with treatment of patients who have developed symptoms due to mTBI.

This review seeks to summarize the literature published between 1980 and June, 2009 that is specific to the epidemiology of TBI/PTSD, and to the assessment and treatment of mTBI/PTSD. It is important to note that, consistent with its definition, we have conceptualized "TBI" as a historical event and do not require the presence of current symptoms to enumerate TBI cases. However, even though a clinical interview is necessary to render a confirmed TBI diagnosis, we have included in this evidence review studies in which survey-based screening measures were used to enumerate both "probable TBI" history and current "probable PTSD." Additionally, we have included studies that were based on data from the VA's post-deployment screening program, in which "symptomatic probable TBI" cases are identified based on historical TBI-related events plus current symptoms potentially attributable to a TBI. We have been careful to specify studies based on screening versus clinical cases when possible.

METHODS

TOPIC DEVELOPMENT

This topic was nominated by the Center for Chronic Disease Outcomes Research, Minneapolis VA Medical Center, in consultation with the Polytrauma/Blast-related Injuries QUERI and the VA Evidence Synthesis Program. The key questions and scope of this review were refined based on input from Technical Advisory Panel members Matthew Friedman, MD, Robin Hurley, MD, Nancy Bernardy, PhD, and Katherine Helmick, MS, CNRN, CRNP.

The final key questions were:

1) What is the observed prevalence of comorbid TBI and PTSD? Does the reported prevalence vary by study population, trauma etiology, TBI severity, or methods of case ascertainment?

2a) What is known about the relative accuracy of diagnostic tests used for assessing mTBI when comorbid with PTSD?

2b) What is known about the relative accuracy of diagnostic tests used for assessing PTSD when comorbid with mTBI?

3a) Are there psychosocial or pharmacological therapies used for treatment of mTBI and PTSD simultaneously?

3b) Are therapies for treatment of mTBI effective when mTBI is comorbid with PTSD? Is there evidence of harms?

3c) Are therapies for treatment of PTSD effective when PTSD is comorbid with mTBI? Is there evidence of harms?

SEARCH STRATEGY

A study search coordinator developed the search strategy with input from the principal investigators (Appendix A). We searched PubMed, PsycINFO, and REHABDATA databases for articles published from 1980 to June, 2009. The search was limited to studies involving human subjects and published in English. Reference lists from studies related to the key questions were searched for additional research studies. TBI was operationalized as a history of confusion, disorientation, or loss of consciousness resulting from a force to the head.[43] Included studies must have enrolled participants with a self-reported history of probable TBI, or diagnosed TBI history, regardless of the presence of current TBI-related symptoms. PTSD was operationalized as the development of symptoms characterized as Post-traumatic Stress Disorder by the Diagnostic and Statistical Manual (DSM-III, DSM-III-R, DSM-IV, or DSM-IV-TR).[44-47] Included studies must have had participants with DSM-III or DSM-IV diagnoses of or positive screens for PTSD as determined through semi-structured interview, clinical diagnosis of PTSD, or scores exceeding cutoffs indicating probable diagnosis of PTSD on self-report inventories.

A description of the search strategy used to identify ongoing and unpublished research studies is presented in the Active Research section below.

STUDY SELECTION

Titles and abstracts (when available) from all references identified in the literature search process were reviewed by a study investigator (KC, SK, LM). The initial screening was designed to identify peer-reviewed, English language articles published after 1980 that included an adult population with probable or diagnosed history of TBI and probable or diagnosed PSTD and were related to one or more of the key questions or that might provide background information. Studies of all design types were considered. Full-text versions of articles that potentially met these criteria were then obtained for further review. We excluded studies if they included more than 10% of subjects less than age 18 years, did not enroll individuals with a history of probable TBI or probable or diagnosed PTSD, or did not present results in a manner that addressed the key questions. Studies that did not meet inclusion criteria for key questions but were considered of special relevance because they were of high methodologic quality or provided evidence potentially, but not directly, relevant to the key questions were included as secondary results.

DATA ABSTRACTION

A content expert abstracted data onto standardized forms (Appendix B) from each article that met the study selection criteria. Results were reviewed with another member of the research team. For Key Question #1, we abstracted the study setting and overall population (e.g., military, veteran, civilian), as well as population demographics (gender, age, race/ethnicity, education level, disability seeking status, presence of pain or mental health disorders other than PTSD), trauma etiology (e.g., combat, terror, motor vehicle, assault), severity of TBI (mild, moderate, severe, and how defined), number of and time since trauma(s), and method(s) used to ascertain, define, and enumerate TBI and PTSD cases (administrative data, self-report, clinical screening, structured interview, neuropsychiatric evaluation). Numerator (TBI/PTSD) and denominator (total study population) data were collected to allow reporting of prevalence by study population. We included studies that assessed for PTSD in patients with a reported history of TBI as well as studies that assessed for both TBI and PTSD across more heterogeneous patient populations.

We attempted to address Key Question #2 using established methods as outlined by Bossuyt et al.[47] and Leeflang et al.[48] Population, trauma, and case assessment data were abstracted as defined for Key Question #1. In addition, if reported, we noted the operationalized cut-off scores for tests used to diagnose mTBI and/or PTSD (including screening instruments, clinical interviews, neuropsychological batteries), the names of diagnostic reference tests used for comparison, and the operationalized cut-off scores for these reference tests. Other data we sought to abstract included whether those administering tests for mTBI or PTSD were blinded to results of the other assessment methods, the time interval between administration of the tests, whether treatments were received between tests, and the methods used to calculate or compare the diagnostic accuracy and statistical uncertainty. We attempted to determine if comparator test findings would lead to reclassification of disease/injury presence or treatment versus the control diagnostic test. We sought to examine variability in reports of diagnostic accuracy by population subtype.

For Key Question #3, we included only studies in which at least 80% of the participants were

diagnosed with both mTBI and PTSD or the outcomes were stratified for those with both diagnoses. We sought to abstract results from studies of psychological or pharmacological therapies that simultaneously targeted symptoms of mTBI and PTSD or from studies that treated only one of the conditions in individuals with both conditions. Because we expected to identify few studies that would include either a wait-list control or other comparison group, we included studies of treatment outcomes without a comparison group. The outcomes of interest were PTSD symptomology (self-report or clinician-assessed), mTBI symptomology (self-report or objective performance measures), functional status/ability, pain, and quality of life. When data were available, outcomes at baseline, post-treatment, short (one- to six-months), medium (six-months to one year), and long-term (greater than one year) follow-up were recorded. Harms that occurred due to administering a treatment designed for only one of the conditions to a participant with mTBI/PTSD were documented as were the characteristics of the study setting (e.g., veteran or community hospital).

QUALITY ASSESSMENT

We attempted to rate the quality of randomized controlled trials, cohort studies, and case-control studies as good, fair, or poor based on criteria specific to the study design type.[49] Cross-sectional studies, case series, and case reports were considered of low methodologic quality. We assessed studies for applicability to U.S. OEF/OIF veterans. Evidence tables were organized by key questions and conclusions were drawn based on qualitative syntheses of the evidence. We also sought to evaluate the overall quality of the evidence for each main outcome as proposed by the GRADE Working Group.[50]

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by key question, intervention, or clinical condition, as appropriate. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question or clinical topic, and drew conclusions based on qualitative synthesis of the findings. We did not conduct pooled analyses due to marked heterogeneity in study design, cohort creation, patient demographic characteristics, trauma type, etiology, assessment methodology, and disease/injury definition. We report individual study results and summarize findings across these key variables.

ACTIVE RESEARCH

We identified ongoing and/or unpublished funded research related to the key questions by searching the VA HSR&D research database (http://www.hsrd.research.va.gov/research), the Computer Retrieval of Information on Scientific Projects (CRISP) database (http://crisp.cit.nih.gov/crisp), the Clinical Trials database (http://www.clinicaltrials.gov), the *meta*Register of Controlled Trials (http://www.controlled-trials.com/mrct), and the Department of Defense Congressionally Directed Medical Research Program (CDMRP) database. We contacted the HSR&D Program Managers for Long Term Care and Mental Health; individuals associated

with the National Center for PTSD; the Physical Medicine and Rehabilitation TBI/Polytrauma Program; the Polytrauma/Blast-Related Injuries QUERI; the War Related Illness and Injury Study Center (WRIISC); and key authors in the field. Members of our Technical Advisory Panel and the Polytrauma/Blast-related Injuries QUERI provided additional contacts. Individuals were contacted once by e-mail and asked to provide a brief protocol or to complete a survey to capture information about related research projects. This survey was adapted from a survey used by the Oregon Evidence-based Practice Center in a systematic review of pain in patients with polytrauma.[51] There was no further attempt to contact individuals who did not respond to our initial e-mail request.

PEER REVIEW

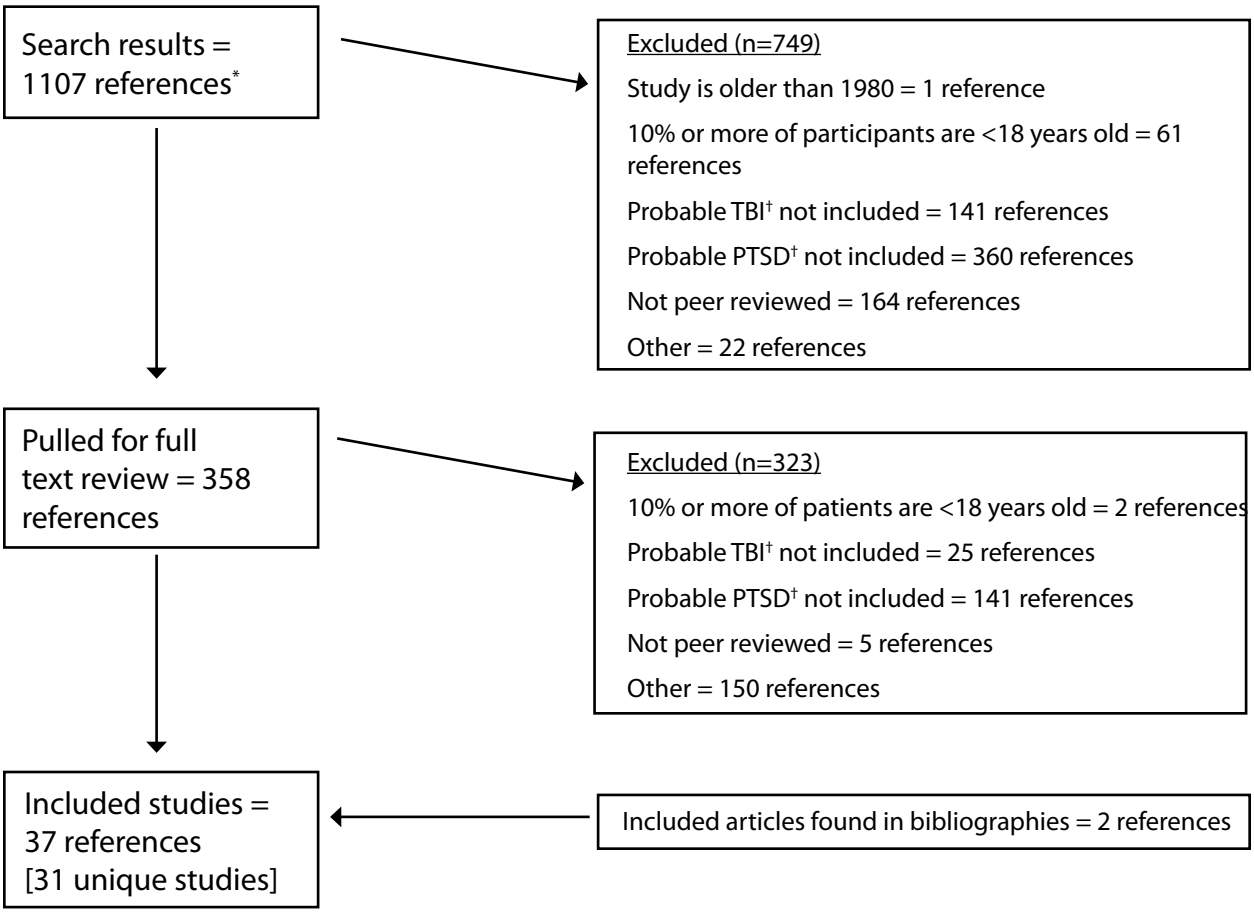
A draft version of this report was sent to peer reviewers that included members of our Technical Advisory Panel; participants in the VA consensus conference on practice recommendations for treatment of veterans with mTBI, PTSD, and pain; and Dr. Charles W. Hoge, Director of the Division of Psychiatry and Neuroscience at Walter Reed Army Institute of Research. Peer reviewer comments were compiled, responses were prepared (Appendix C), and resulting edits were incorporated into the final version of this report.

RESULTS

LITERATURE FLOW

The combined library contained 1107 citations, of which we reviewed 358 articles at the full-text level. From those 358 articles, we identified 31 unique studies (described in 37 references) that addressed the key questions (Figure 1). Studies were excluded because they were published prior to 1980, included more than 10% of participants less than age 18 years, did not enroll individuals with history of probable TBI or probable PTSD, or did not present results in a manner that addressed the key questions. A study by the RAND Corporation was included under primary results (not depicted in diagram). The RAND study assessed both probable TBI history and PTSD in a large, presumably nationally-representative sample of U.S. military personnel. While it was not published in a peer-reviewed journal, the report was peer-reviewed, published by the RAND Corporation, and is available on the RAND website.[5] An additional five studies were included under secondary results (not depicted in flow diagram).

Figure 1. Published data search and selection



*Search results from PubMed (700), PsycInfo (552) and REHABDATA (123) were combined, removing duplicate entries (268).
† "Probable" TBI and PTSD are defined on page 6 and include positive "screens" based on self-report measures as well as clinical diagnoses.

Key Question #1.

What is the observed prevalence of comorbid TBI and PTSD? Does the reported prevalence vary by study population, trauma etiology, TBI severity, or methods of case ascertainment?

Summary of Findings

There were 31 unique studies that reported prevalence of TBI/PTSD. We also included a telephone survey of a national sample of OEF/OIF veterans conducted by the RAND Corporation that was peer reviewed and published electronically on their website yielding a total of 32 unique studies. Studies varied considerably by design, population, trauma etiology and severity, presence of pain or mental health disorders other than PTSD, methods and timing of case ascertainment, and definitions of disease/injury and severity. Additionally, while clinically relevant baseline characteristics were sometimes reported, prevalence of TBI/PTSD was rarely stratified by these variables. Therefore, results could not be pooled across studies, few patterns could be discerned, and reliable outcome estimates could not be obtained for key patient groups. A few studies uniquely enrolled or excluded subjects with a particular characteristic (e.g., men; military veterans). We attempted to separately describe findings from studies that were unique to the military or veteran population.

Study Details (Table 1; Appendix D)

Description of studies reporting prevalence of TBI/PTSD

Thirty-one unique published studies meeting inclusion criteria and enrolling between 10 and 2525 participants (majority less than 200) reported prevalence of TBI/PTSD among participants.[21,22,52-81] Additionally, the study by the RAND Corporation, which enrolled 1965 participants, reported prevalence of TBI/PTSD.[5] The two largest of the published studies and the RAND report involved U.S. military personnel.[5,22,55] A summary of characteristics across published studies is presented in Table 1. Details on study design, population characteristics, assessment methods, and prevalence data for each of the published studies and, separately, the RAND study, are tabulated in Appendix D (Tables 1 and 2).

Study design and location

Many studies were single center and nearly all assessed TBI/PTSD status in patients who had been previously hospitalized or received care in an emergency room specifically related to their trauma. Because individuals who have experienced a TBI, especially mTBI, or who have PTSD may not present to medical facilities for TBI/PTSD-related symptoms, findings from most of the identified studies may not provide accurate population estimates (even for military veterans) for the prevalence of both conditions, particularly mTBI/PTSD. One study (n=144) utilized a case-control design;[56] the remaining were mostly cohort or cross-sectional studies. One small case series enrolled ten subjects.[65] The majority of studies were conducted in the U.S. (n=16),[21,22,52-55,57,58,63,67,71-74,79,81] followed by the United Kingdom (n=6),[61,62,64,77,78,80] Australia (n=4),[59,68-70] Israel (n=3),[56,60,66] and Denmark (n=1).[76] The RAND report described a cross-sectional U.S. national telephone survey of OEF/OIF veterans.[5]

Patient demographic characteristics

Eight of the American studies and the RAND report evaluated U.S. military personnel.[5,22,52-55,73,79,81] In 24 of the 29 studies reporting gender, the majority of subjects were male (ranging from 53% to 100%). One U.S. study evaluating veterans was exclusive to males.[73] Among the 27 studies reporting mean age, ages averaged between 30 and 40 years; two studies had mean ages greater than 50 years.[73,79] Among the seven studies reporting race, most subjects were white (range 16% to 92%).[57,58,63,67,71,72,79] One study (n=200) included mostly non-white subjects (84%).[67] Most U.S. subjects had at least a high school education. The RAND study evaluated a military active duty and veteran population that was mostly male (89%), mostly white (66%), and had a median age of 30.[5]

TBI severity

Twenty-four studies[21,22,52,53,55,56-61,63,65,67-70 ,73,75-81] included subjects with a history of mTBI, 12 exclusively.[21,22,52,53,55,59-61,68-70,76] The percentage of subjects who experienced a moderate TBI ranged from 10% to 40% in 10 studies[56-58,65,67,73,75,78-80] and 100% in one study.[74] The percentage of subjects who experienced a severe TBI ranged from 5% to 62% in eight studies[56-58,65,78-81] and 100% in three studies.[62,64,66] Only two studies did not report levels of TBI severity.[71,72] The RAND study did not measure information pertinent to TBI severity.[5] However, by virtue of the study population, and the substantial proportion of respondents reporting they had received no medical care related to a TBI, the majority of individuals reporting a history of TBI were likely to have incurred mTBI.

TBI etiology

Injuries related to combat (blast and non-blast sources) accounted for most of the trauma in the studies of U.S. military personnel.[22,52-55,73,79,81] Combat-related trauma was reported exclusively in five of the eight U.S. studies involving soldiers and veterans.[52-54,73,81] Combat injury was noted in only one study outside the U.S., accounting for 25% of trauma cases in an Israeli study.[66] Trauma resulting in TBI due to motor vehicle crashes (MVC) was reported in 22 studies, ranging from 17% to 100% of the cases.[21,22,55,56-58,60-62,64-72,74,77,78,80] Five of the studies included only trauma due to MVCs.[61,65,69,70,72] Trauma due to assaults (range 3% to 58%) was reported in 10 studies[57,62,64,67,68,71,74,75,78,80] and trauma due to falls (range 8% to 39%) was also reported in 10 studies.[21,22,55,56,58,62,64,74,78,80] The case-control study, conducted in Israel, compared trauma due to terror (blast or gunshot) to non-terror trauma, mainly as a result of MVCs.[56] The RAND study did not precisely identify TBI etiology.[5] The survey asked respondents about TBI-related events that occurred while deployed.

Presence of pain or mental health disorders other than PTSD

Pain, including headaches, was reported in five studies (11% to 100% of participants).[22,53,68,69,76] Few studies reported the prevalence of any mental health disorders other than PTSD. Depression (or depressive symptoms) was the most commonly reported mental health condition, reported in nine studies.[22,57,63,65-67,71,75,80] Prevalence was less than 50% in most studies. One case series study involved participants (n=10) of which 90% had been diagnosed with obsessive-compulsive disorder.[65] Substance use disorder was reported in three studies, ranging from 14% to 42% of participants,[63,71,73] followed by anxiety disorders other than PTSD (9% to 60% of participants) reported in four studies,[57,63,71,80] and panic disorder (14% of participants) reported in one study.[71]

A major purpose of the RAND study was to assess the prevalence of depression in the OEF/OIF veteran population. Approximately 14% of the study population was deemed to have probable major depressive disorder.[5]

Definitions and ascertainment methods

Studies varied widely in their operational definitions of TBI and PTSD and the methods and timing of assessment. Methods of case ascertainment included medical records review, clinical interviews, varying scores on the Glasgow Coma Scale, self report of loss of consciousness and/or altered mental status, and receiving treatment for a head injury at a hospital. Several studies based case inclusion criteria on positive responses to TBI and/or PTSD screening measures. For example, a single cross-sectional administrative database study of 126 veterans (gender, race, and age not reported) used a positive screen on the VA 4-item TBI screening instrument to enroll participants.[53] In this study, the prevalence of TBI/PTSD was determined by assessing the percentage of individuals reported to have a probable history of TBI based on this instrument who also scored >50 on the self-reported Post-traumatic Stress Disorder Checklist (PCL). The RAND study similarly used screening instruments to assess history of TBI (the Brief Traumatic Brain Injury Screen [BTBIS]) and PTSD (PCL-Military Version [PCL-M]).[5] The time since trauma when assessments were conducted was frequently not reported. However, three longitudinal studies followed hospital TBI cohorts over time and assessed for PTSD at various reported time points since injury.[58,61,70]

Table 1. Summary of study characteristics for n=31 published unique studies reporting prevalence of TBI/PTSD

Characteristic	Range (# of participants, percents, or means)	# of studies reporting
Range of enrolled subjects	10 to 2525	31
Range of enrolled subjects in studies in which all subjects were U.S. veteran and/or active duty	43 to 2525	8
Mean age	25 to 52	27
Gender, female - %	0 to 83	29
Race, white - %	16 to 92	7
Race, non-white - %	6 to 84	7
Education, less than high school graduate - %*	3 to 48	4
Education, high school graduate or more - %*	34 to 85	5
Education, any college - %*	25 to 49	3
TBI severity (Studies not reporting TBI severity n=8)		
TBI, mild - %	19 to 100 (*11 studies 100%*)	21
TBI, moderate - %	10 to 100 (*1 study 100%)*	12
TBI, severe - %	17 to 100 (3 *studies 100%*)	12
Trauma etiology (Studies not reporting etiology n=4)		
Motor vehicle crashes - %	17 to 100 (*6 studies 100%*)	22
Assaults - %	3 to 58	11
Falls - %	8 to 39	11
Combat-related injuries - %	25 to 100 (*4 studies 100%*)	8
Work-related injuries - %	3 to 15	4
Sports/leisure-related injuries - %	14, 28	2
Terror-related injuries - %	50	1
Other/not defined	14 to 30	5
Presence of pain or mental health disorders other than PTSD (Studies not reporting n=17)		
Pain, including headaches - %	11 to 100 (*1 study 100%*)	5
Depression and/or depressive symptoms - %	9 to 90	8
Substance use disorders - %	14 to 42	3
Anxiety disorders other than PTSD or anxiety symptoms unspecified - %	9 to 60	3
Obsessive-compulsive disorder - %	15, 100 (*1 study 100%)*	2
Panic - %	14	1
Depression and anxiety disorders unspecified - %	71	1
Study type		
Cohort	28 to 307	14
Case-control	144	1
Cross-sectional	43 to 2525	15
Case series	10	1

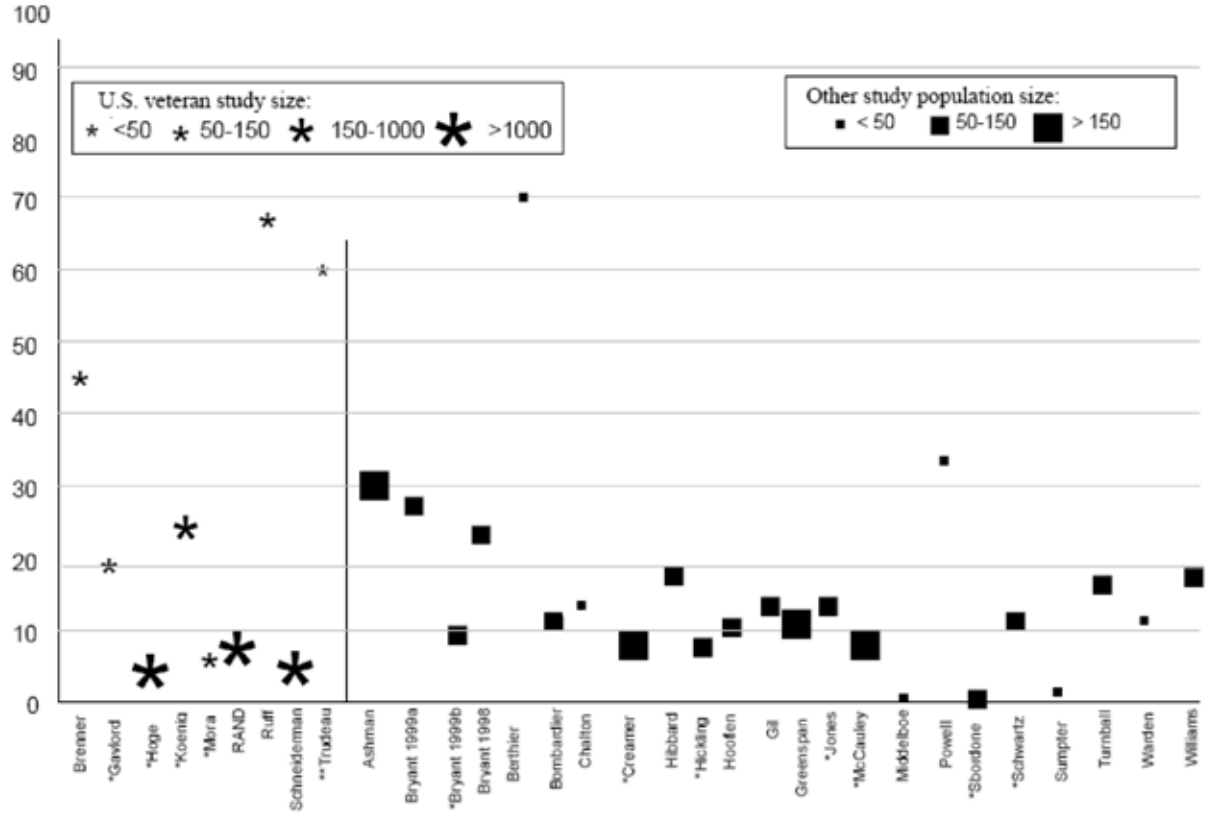
* U.S. only

Prevalence of TBI/PTSD (Figures 2 and 3; Appendix D)

Reported prevalence of TBI/PTSD across study populations

Figure 2 displays the range of reported TBI/PTSD prevalence levels across study populations; studies involving U.S. military populations are listed first. As shown, the range of TBI/PTSD prevalence was broad (from 0% to 70%). Across all 31 published studies, plus the RAND study, the majority (n=22) reported prevalence levels of 20% or less. The few studies with values of 50% or more were small and/or had highly non-representative study populations (e.g., patients with obsessive-compulsive disorder).[53,65,73] Among the U.S. military/veteran studies, the three largest, most representative studies reported TBI/PTSD prevalence between 5% and 7%.[5,22,55] Each of these studies used similar self-report screening measures to assess both history of mTBI and current PTSD; thus, these numbers do not reflect actual diagnoses of mTBI or PTSD, which is almost certainly lower than the prevalence estimates based on the reported initial screening results. Among the four largest non-military studies, prevalence ranged from 8% to 30%.[58,59,63,67] Two of these studies involved populations that were comprised entirely of individuals with a history of TBI.[58,63] The other two involved clinic/hospital cohorts, identified diagnoses that were mostly mild and moderate TBI, and assessed for PTSD using a structured clinical interview (e.g., Clinician-administered PTSD Scale [CAPS], Structured Clinical Interview for the DSM-IV [SCID]) which are considered to be more stringent than the frequently used self-report PTSD screening measures (e.g., PTSD Checklist [PCL], Impact of Events Scale [IES]). Both of these studies reported TBI/PTSD prevalence of 8% in their study populations.[59,67]

Figure 2. Prevalence of TBI/PTSD across study populations



* Study populations included participants with and without TBI history. Unless indicated, all other study populations were comprised exclusively of participants with TBI history.
** Study population was comprised exclusively of participants with PTSD.

Reported prevalence of TBI/PTSD by level of TBI severity

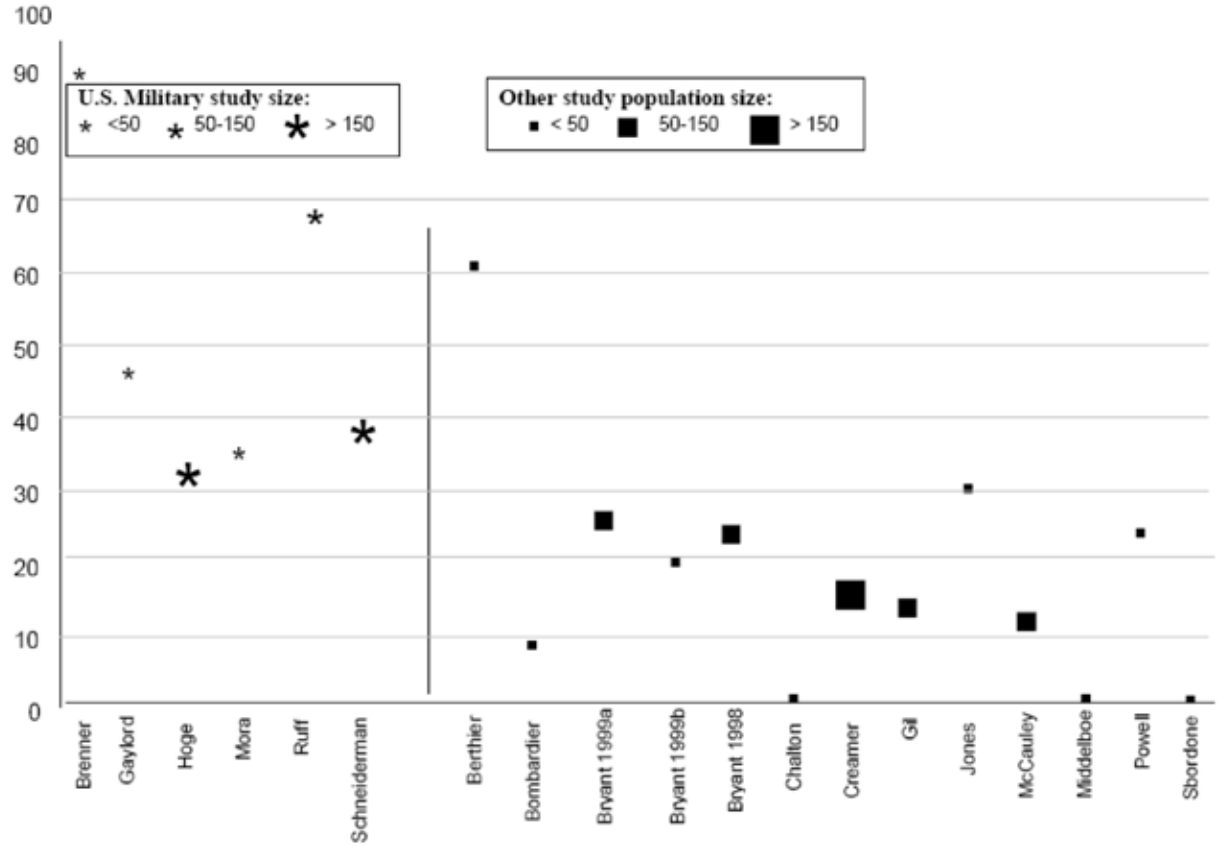
Prevalence of TBI/PTSD may differ by TBI severity. In the studies that involved study populations that were homogenous by TBI severity, or that reported PTSD prevalence stratified by TBI severity, prevalence of PTSD ranged from 0% to 89% in participants with a history of mTBI,[21,22,52,53,55,57,59-61,65,67-70,75,76,79-81] 8% to 55% for those with a history of moderate TBI,[57,65,67,74,75,79,80] and 0% to 19% for those with a history of severe TBI.[57,61,64-66,79,80] Because the emphasis of this evidence review was on mTBI, we were particularly interested in prevalence of PTSD among individuals with a history of mTBI. Figure 3 depicts the prevalence of mTBI/PTSD across studies, again listing studies of U.S. military and veteran populations first. It is important to emphasize the different denominator used in the prevalence values reported in Figure 3 (# with mTBI/PTSD / # of individuals with mTBI) in contrast to Figure 2 (# with TBI/PTSD / # of individuals in study *with or without* TBI).

Two points should be noted when examining the studies in this way. First, when restricting the denominator to individuals with a positive history of mTBI, we are asking a slightly different question about prevalence. In Figure 2, we examine prevalence of TBI/PTSD across entire study populations while, in Figure 3, we examine prevalence of PTSD in individuals with a history of mTBI. Both questions were of interest for this review. However, when examining prevalence

of PTSD among individuals with a history of mTBI, the reported prevalence values tend to be higher, which could be due to differential exposure among these individuals or other selection biases. Note that some values in Figure 3 are the same as in Figure 2 because these studies involved populations in which all participants had a history of mTBI.[21,22,52,53,55,59,60,61,68,69,70,76]

Second, the prevalence of PTSD in U.S. military/veteran study populations with a history of mTBI tends to look somewhat higher than prevalence of PTSD in the civilian study populations; however, the assessment methods varied and could account for these differences. The two large U.S. military studies reported PTSD prevalence levels of 33% and 39% among those with a history of mTBI.[22,55] These values are consistent with the findings of the RAND study, which reported a PTSD prevalence of 34% among those with history of TBI (note that the RAND study was not exclusive to mTBI though likely predominantly identified mTBI).[5] Each of these studies used similar self-report screening measures for both mTBI and PTSD; thus, these numbers do not reflect actual diagnoses of mTBI or PTSD. In contrast to these studies, the largest of the civilian studies reported PTSD prevalence between 12% and 27%.[59,60,67,68,70] While lower than prevalence values in the military/veteran studies, all five of these studies involved patients specifically treated for trauma in a hospital or clinic and utilized a structured clinical interview to assess PTSD. No studies provided estimates of mTBI/PTSD prevalence in civilians who were not specifically treated in a hospital or clinic for TBI.

Figure 3. Prevalence of PTSD among study participants with a history of mTBI



Reported prevalence of TBI/PTSD by trauma etiology

In addition to variation by TBI severity, prevalence of TBI/PTSD would be expected to vary by important exposure characteristics including type of trauma, time since trauma exposure, and number of trauma exposures. Most studies described populations with diverse trauma sources. To examine potential differences in TBI/PTSD prevalence by military versus non-military etiologies, we compared studies that reported prevalence of PTSD in populations with TBI, if they: 1) reported prevalence explicitly by etiology; or 2) reported prevalence in populations in which ≥75% had a single etiology. The following table lists these studies organized by military and non-military etiology. We use the term 'military' and further describe the percent by etiology of blast or burn (presumed combat) because in some instances military trauma may not be due to direct combat injuries (e.g., non-combat motor vehicle crashes). All the military-related studies identified in this table, except Koenigs et al.,[54] involved personnel serving in OEF/OIF.

Table 2. Prevalence of PTSD among individuals with TBI, by trauma etiology

Author, year	Injury etiology	TBI severity	% of TBI subjects with PTSD
Military-related Injuries			
Gaylord et al., 2008[52]	Military, blast and burn (100%)	Mild 100%	45%
Hoge et al., 2008[22]	Military, blast (75%)	Mild 100%	33%
Koenigs et al., 2008[54]	Military (100%)	Penetrating 100%	32%
Mora et al., 2009[81]	Military, blast and burn (100%)	Mild 95% Severe 5%	35%
RAND, 2008[5]	Military (100%)	Not Reported	34%
Ruff et al., 2008[53]	Military, blast (100%)	Mild 100%	66%
Non-military injuries*			
Bryant et al., 1998[70]	Motor Vehicle Crashes (MVC) (100%)	Mild 100%	24%
Bryant et al., 1999b[71]	MVC (100%)	Mild 100%	20%
Gil et al., 2005[60]	MVC (84%)	Mild 100%	14%
Hickling et al., 1998[72]	MVC (100%)	Not reported	56%
Jones et al., 2005[61]	MVC (100%)	Mild 100%	32% at time 1 19% at time 2
Schwartz et al. 2007[56]	MVC (82%)	Mild 32% Moderate 21% Severe 47%	42%

* Excluded 1 study reporting TBI/PTSD among a population of patients with obsessive-compusive disorder (Berthier et al., 2001)[65]

This table contains data points similar to those in Figure 3 except that all levels of TBI severity are included. Of note is that other potentially important parameters also varied considerably (e.g., study size and representativeness, PTSD assessment method, time since trauma exposure). Not taking into account the potential effects of these other variables, the prevalence of TBI/PTSD ranged from 32% to 66% in individuals with military-related TBI.[5,22,52-54,81] The prevalence of TBI/PTSD ranged from 14% to 56% in individuals with non-military injuries.[56,60,61,69,70,72] As opposed to the studies in which subjects had a history of military-related TBI, all of which reported PTSD prevalence greater than 30%, four of the seven reports involving subjects with non-military injuries reported values less than 30%.[60,61,69,70] Whether this is an epidemiologically important difference is not certain, as other study parameters may have simultaneously affected results.

Reported prevalence of TBI/PTSD by time since trauma

Similar to trauma type, time since trauma was widely variable across studies and even within studies. Across this group of studies, the potential effect of time since trauma on TBI/PTSD prevalence would best be described in three longitudinal studies enrolling patients with a TBI and assessing for PTSD at different time points post-injury. Unfortunately, no patterns could be discerned. Jones et al. identified PTSD in 32% of patients with TBI history at six weeks post-injury, and in 19% at three months post-injury.[61] Greenspan et al. identified PTSD in 11% of patients with TBI history at six months post-injury, and in 16% at twelve months post-injury.[58] Bryant and Harvey reported PTSD in 24% of patients with TBI history at six months post-injury, and 22% at two years post-injury.[70]

Reported prevalence of TBI/PTSD by methods of assessment

Studies varied in terms of how a positive screen or diagnosis for PTSD was defined and in how TBI was assessed and defined. Methods of PTSD assessment included structured interviews, self-report instruments, and non-standardized diagnoses by clinicians. Overall, within studies utilizing structured interviews (e.g., CAPS and SCID) to assess PTSD, prevalence of TBI/PTSD ranged from 3% to 70% across study populations.[54,59,60,62,63,65,67-72,74,78-80] For studies utilizing self-report instruments (e.g., PCL and IES), prevalence of TBI/PTSD ranged from 5% to 66%.[5,22,52,53,55,57,58,64,76,81] One study reported a 10% prevalence of diagnosed TBI/PTSD using the PTSD Inventory; however, it was unclear whether the instrument was used as a self-report instrument or as a structured interview.[66] Finally, one study did not articulate how PTSD was defined or diagnosed; this study reported no cases of PTSD among patients with a history of TBI.[21] Structured clinical interviews, particularly the CAPS, are considered the gold-standard for PTSD assessment and diagnosis. The studies that used the CAPS to assess PTSD identified prevalence levels of TBI/PTSD ranging from 3% to 38%.[59,60,62,72,78,80] Among the studies using the SCID, prevalence ranged from 8% to 44% across entire study populations.[54,63,65,67,71,79]

Self-report measures, including instruments used for screening, are considered less valid methods for PTSD assessment. Studies that utilized the PTSD Checklist (PCL) to assess for PTSD used different score thresholds to define the presence of PTSD. Studies did not present results in a fashion that would allow for calculation of prevalence at a single common value. The prevalence of TBI/PTSD ranged from 33% to 66% using a cut score of 50 (3 studies),[22,53,55] and 35% to 45% using a cut score of 44 (2 studies).[52,81] Each of the four studies using the Impact of Events Scale (IES) involved participants with a positive history of TBI. Using a cutoff of 35, Greenspan and colleagues reported a prevalence of 11% six months after injury and a prevalence of 16% twelve months after injury.[58] Two studies used a cutoff of 26 and reported prevalence levels of 18% and 34%.[64,75] Lastly, Middelboe and colleagues reported that no participants with TBI diagnoses "fulfilled the DSM-III-R criteria for post-traumatic stress disorder," but 11% had "moderate" or higher scores on the IES.[76]

Methods of identifying TBI cases also varied widely across studies. Frequently, survey study participants were asked questions varying by study to assess a positive history of TBI.[5,21,22,55,63,64,73] Alternatively, participants were recruited from hospitals following treatment for trauma or, specifically, head injury. These patients' TBI history was obtained from medical records alone or a combination of medical records review supplemented by questionnaire.[52,53,56-62,65-70,72,74-76,78,79-81] As a result, systematically examining prevalence of TBI/PTSD by method of TBI assessment was not possible.

Key Question #2.

#2a What is known about the relative accuracy of diagnostic tests used for assessing mild TBI when comorbid with PTSD?
#2b What is known about the relative accuracy of diagnostic tests used for assessing PTSD when comorbid with mild TBI?

Summary of Findings

There were no published studies addressing the relative accuracy of diagnostic tests used for assessing mTBI history or current PTSD when one condition co-occurs with the other.

Secondary Findings

One study compared the relative accuracy of four PTSD assessment tools in a cohort of individuals with a history of severe TBI. A sub-study involving the same population of individuals qualitatively explored reasons for false positive PTSD diagnoses when using a self-report assessment tool versus a structured clinical interview.

Details of Studies – Secondary Findings

Comparison of PTSD assessment tools in individuals with a history of severe TBI
One single-center small study compared four diagnostic measures of PTSD in individuals who had been diagnosed with severe TBI (defined as history of post-traumatic amnesia for more than one day).[62] Results varied widely depending on the measures used. Authors administered two self-report measures of PTSD, the IES and the Post-traumatic Diagnostic Scale (PDS), and a structured clinical interview measure for PTSD, the CAPS, to a convenience sample of 34 civilians whose severe TBI event had occurred at least three months prior to the study (Table 3). Four sets of criteria were used to define cases of PTSD: 1) IES scores > 25; 2) fulfillment of PDS criteria B-F; 3) fulfillment of CAPS criteria B-F; and 4) fulfillment of CAPS criteria B-F *plus* a clinician's judgment that the endorsed symptoms were valid and indeed related to trauma. The latter two criteria were referred to as "CAPS-without clinical judgment" and "CAPS-with clinical judgment," respectively. Participants were primarily male (88%), were aged 20-60 years (mean=34; SD=11), and had 10-20 years of formal education (mean=12; SD=2). The sources of injury were motor vehicle crashes (47%), falls (32%), assaults (18%), and sports activities (3%).

Fulfillment of CAPS-with clinical judgment was considered the gold-standard PTSD diagnostic tool in this study. Only one individual (3%) met criteria for PTSD based on this assessment tool. Six individuals (18%) met criteria based on CAPS-without clinical judgment, 15 (44%) met criteria based on the IES, and 20 (59%) met criteria based on the PDS. Both self-report questionnaires (IES and PDS) identified significantly more ($p<0.05$) false positive PTSD cases than CAPS-without clinical judgment. There were no false negative cases identified by the IES or PDS; all cases identified by CAPS-without clinical judgment were also identified by these self-report questionnaires. Therefore, based on the definitions used by these authors, this study supports the use of the IES and PDS self-report questionnaires as screening tools for PTSD

among individuals with severe TBI. However, structured clinical interviews were deemed the most appropriate diagnostic tool for diagnosis of PTSD after severe TBI. There was indication that individuals may have mistaken their TBI-related symptoms for PTSD symptoms on the self-report questionnaires, with these discrepancies becoming clear only during the process of structured clinical interview. Clinical judgment thus provided the opportunity for differential diagnosis of PTSD versus symptoms of severe TBI based on the context of the symptoms as well as potentially confounding factors.

Potential reasons for false positive PTSD diagnoses in individuals with a history of severe TBI
One qualitative study was conducted by the same authors as above and explored reasons for false positive PTSD diagnoses when using a self-report assessment tool (PDS) as compared to a structured clinical interview (CAPS) as the "gold-standard" assessment method.[35] The study population consisted of the same 34 civilians with a severe TBI history; however, the sole individual diagnosed with PTSD using the CAPS-with clinical judgment was excluded so as to examine PTSD symptoms that were reported by individuals without PTSD.

Self-reported and clinician-rated PTSD symptoms (PDS versus CAPS) were compared by DSM-IV PTSD symptoms clusters: re-experiencing, avoidance, and hyperarousal. Based on the PDS, 91% of participants reported two or more hyperarousal symptoms, 78% reported three or more avoidance symptoms, and 67% reported at least one re-experiencing symptom. Only one PTSD symptom (insomnia) was reported in more than 20% of participants when using the CAPS. Using a standardized interview prompt to explore the identified discrepancies, investigators found that cognitive impairments, misunderstanding of self-report items, and true symptoms overlap seemed to lead to endorsement of PTSD symptoms on the PDS. For example, individuals with loss of memory for their traumatic event confused "curiosity" about their event for "re-experiencing" the event. While symptoms may have been reported as "intrusive," they were not found to be accompanied by fear or emotional distress. Additionally, while participants frequently endorsed "having upsetting thoughts," these thoughts were often associated with the effects of the severe TBI and not with the trauma itself. Similarly, avoidance-related questions (e.g., loss of interest, detachment, or reduction in affect) were frequently endorsed in relation to functional difficulties associated with the severe TBI rather than the traumatic event. Endorsement of hyperarousal symptoms often had to do with individuals having to cope with cognitive and physical impairments and fear of re-injury. In all, this study highlights the overlap and potential confusion around assessment of symptoms of PTSD and symptoms related to a TBI.

Table 3. Secondary findings for Key Question 2: Assessment of PTSD in individuals with severe TBI

Study / Country	Study design and population	n	Characteristics of participants	Traumatic brain injury definition/measure	Post-traumatic stress disorder assessment	% of subjects fulfilling criteria for PTSD
Sumpter 2005;[62] Sumpter 2006[35] United Kingdom	Cross-sectional Subjects recruited from community outpatient and rehabilitation services, and volunteer organizations	n=34; all TBI	*Data for all study subjects* Trauma etiology: MVC 47%; fall 32%; assault 18%; sports injury 3% TBI severity: severe 100% Time of assessment or since trauma: 6 years (0.6-34) Mean age (range): 40 (20-60) Women: 12% Race: NR Education: NR Pain: NR Mental health disorders other than PTSD: NR	Not reported, subjects with severe TBI history recruited from community outpatient and rehabilitation services and voluntary organizations.	Compared 4 assessment tools: 1) Post-traumatic Diagnostic Scale (PDS), based on DSM-IV criteria, criteria B-F fulfilled 2) Impact of Event Scale questionnaire (IES), total score > 25 = "case" 3) Clinician-Administered PTSD Scale (CAPS), without clinical judgment, criteria B-F fulfilled 4) CAPS, with clinical judgment, criteria B-F fulfilled	1) PDS: 59% (n=20) 2) IES: 44% (n=15) 3) CAPS w/o clinical judgment: 18% (n=6) 4) CAPS with clinical judgment: 3% (n=1)

Key Question #3.

#3a Are there psychosocial or pharmacological therapies used for treatment of mTBI and PTSD simultaneously?
#3b Are therapies for treatment of mTBI effective when mTBI is comorbid with PTSD? Is there evidence of harms?
#3c Are therapies for treatment of PTSD effective when PTSD is comorbid with mTBI? Is there evidence of harms?

Summary of Findings:

3A: We found no randomized or non-randomized controlled clinical trials, systematic reviews, cohort studies, case control studies, or cross-sectional studies that discussed psychosocial or pharmacological therapies designed to simultaneously treat symtpoms of mTBI and PTSD.

3B: We found no randomized or non-randomized controlled clinical trials, systematic reviews, cohort studies, case control studies, or cross-sectional studies that examined the effectivess of treatments for mTBI symptoms when patients had PTSD.

3C: We found no randomized or non-randomized controlled clinical trials, systematic reviews, cohort studies, case control studies, or cross-sectional studies that examined the effectivess of treatments for PTSD when patients had a history of mTBI.

Secondary Findings:

One small, single-center, good-quality randomized controlled trial examined the efficacy of a cognitive-behavioral treatment for individuals with acute stress disorder (ASD) and a history of mTBI. The study found that patients who received cognitive-behavioral therapy developed PTSD at a lower rate than those who received supportive therapy.

Two case reports discussed treatment approaches that utilized empirically supported therapies to treat individuals with mTBI history and current PTSD.

Details of Studies – Secondary Findings

Treatment of mTBI and Acute Stress Disorder
One small, good quality study examined the comparative efficacy of cognitive-behavior therapy (CBT) and supportive therapy in reducing symptoms and preventing the development of PTSD in 24 civilians with history of mTBI and current acute stress disorder (ASD; Table 4).[82] ASD is a post-traumatic stress reaction that occurs within the first month post-trauma. The symptoms are similar to PTSD, with the exception that individuals with ASD must also experience symptoms of dissociation. Previous research has shown that approximately 80% of people with ASD go on to develop PTSD.[83]

This randomized controlled trial enrolled men and women who had experienced either a motor vehicle crash or nonsexual assault within the preceding two weeks. In order to be eligible,

patients must have met criteria for ASD, as determined by the Acute Stress Disorder Interview, and mTBI, which was defined as post-traumatic amnesia of less than 24 hours and a Glasgow Coma Scale score of 13-15. Those randomized to CBT received five weekly 90-minute sessions that included psychoeducation, progressive muscle relaxation, imaginal exposure to the traumatic event, cognitive restructuring, and in vivo exposure to avoided stimuli. Patients in the supportive counseling condition also received five weekly 90-minute sessions, comprised of psychoeducation and problem-solving skills. There was no mention of modificiations made to the therapy protocols due to potential cognitive impairments in the study participants.

Immediately post-treatment, PTSD was less prevalent in the CBT group (8%; n=1) than the supportive therapy group (58%; n=7). At the six-month follow-up, 17% (n=2) of the CBT group and 58% (n=7) of the supportive therapy group met criteria for PTSD. Further, at post-treatment and six-month follow-up, patients in the CBT condition experienced large, significant decreases in PTSD symptomology (as measured by both the IES and CAPS). Both groups experienced a moderate decrease in depressive symptoms at post-treatment and a small decrease at six-month follow-up, but there was not a statistically significant difference between the groups. The authors concluded that CBT is effective in reducing symptoms and preventing onset of PTSD in patients with ASD and mTBI history.

Case studies reporting on the treatment of patients with mTBI/PTSD

Two case reports (one involving a U.S. military patient) presented information regarding the treatment of mTBI symptoms and PTSD in individual patients (Table 4).[84,85] In both case reports, the therapist used cognitive-behavioral techniques to treat the symptoms of PTSD (cognitive processing therapy; exposure and cognitive restructuring) with few modifications. To manage mTBI-related symptoms, the therapists encouraged the patients to use compensatory strategies (e.g., using personal digital assistants, scheduling cognitive breaks). Both reports highlighted the range of problems experienced by the individuals they were treating (e.g., anger, depression, substance abuse) and advocated for an idiographic, integrative approach. These case studies reported a decrease in symptoms of anxiety and depression; however, significant residual symptoms remained.

Table 4. Secondary findings for Key Question 3: Treatment of mTBI/PTSD

Study / Country / Study design	# Subjects; % Dropout / Lost to follow-up	Subjects	Method of assessment	Treatment	Duration of therapy	Treatment outcomes	Study quality
Bryant 2003[82] Australia Randomized Controlled Trial (RCT)	n=24	Mean age (range): 31 (18 - 60) Women: 67% Race: NR Trauma etiology: motor vehicle crash (MVC) or non-sexual assault Pain: NR Other mental health conditions: NR	TBI: Glasgow Coma Scale PTSD: Impact of Event Scale (IES) and Clinician Administered PTSD Scale (CAPS)	1. Cognitive Behavior Therapy (CBT) Group (n=12) 2. Supportive Counseling (SC) Group (n=12)	6 mos	<u>Mean CAPS scores (SD)</u> Baseline CBT: 65.42 (10.60) SC: 62.42 (14.58) Frequency subscale a. Post-treatment CBT: 13.50 (10.24) SC: 23.83 (15.30); p=0.002 b. 6 mos follow-up CBT: 16.83 (13.04) SC: 25.25 (16.21); p=0.03 Intensity subscale a. Post-treatment CBT: 12.00 (9.71) SC: 21.33 (12.49); p=0.003 b. 6 mos follow-up CBT: 14.62 (9.12) SC: 24.50 (13.13); p=0.02 <u>Subjects meeting PTSD criteria</u>: a. Post-treatment CBT: 8% (n=1) SC: 58% (n=7); p<0.05 b. 6 mos follow-up CBT: 17% (n=2) SC: 58% (n=7); p<0.05	Good

Batten 2008[84] U.S. Case Report	1	24 year old, Caucasian male Trauma etiology: Combat Pain: joint pain and headaches Other mental health conditions: depression, alcohol abuse, marijuana abuse	TBI: Clinic diagnosis, criteria unknown PTSD: Clinician Administered PTSD Scale (CAPS) & PTSD Checklist (PCL)	Cognitive processing therapy; two sessions outlining behavioral activation for depression & sleep hygiene; one session on decreasing substance abuse; addressed memory compensation strategies with polytrauma team	19 individual therapy sessions	Lost PTSD diagnosis, although still had significant symptoms; decreased symptoms of depression; decreased alcohol use; marijuana abstinence	Poor
McGrath 1997[85] England Case Report	1	33 year old male Race: NR Trauma etiology: MVC Pain: Ear pain and headaches Other mental health conditions: NR	TBI: Head injury with PTA of 40 minutes PTSD: Clinical interview used to determine DSM-IV criteria	Progressive muscle relaxation; anger management; cognitive restructuring; graded in vivo exposure; response prevention for checking behaviors; compensatory cognitive strategies; supportive therapy	NR	Slight decrease in anxiety symptoms; decrease in anger; decrease in symptoms of depression; no change in subjective cognitive symptoms, but improved work functioning	Poor

LITERATURE REVIEW KQ 1-3 - LIMITATIONS

The existing literature has several limitations. The quality of identified studies was generally fair and external validity was generally poor. Few prevalence studies were actually population-based. Most were small and conducted in a single medical or research center. Authors frequently only recruited individuals who had been hospitalized or received medical attention specifically for their trauma. No large studies representative of the entire OEF/OIF veteran population have been conducted using currently implemented screening and diagnostic tools. Therefore, the applicability of the current literature to existing populations of interest, screened and diagnosed with currently utilized tools, is not known. By extension, the true prevalence of TBI/PTSD, particularly mTBI/PTSD, is not known. Reported findings from most studies likely overestimate the prevalence of TBI/PTSD, especially mTBI/PTSD, in the populations of interest. For example, civilian individuals recruited from emergency departments likely represent more severe, more symptomatic cases of TBI (and PTSD) than individuals who experience a TBI for which they do not seek medical attention. Assessment instruments, ascertainment methods, timing, and diagnostic criteria used to identify TBI and PTSD cases varied widely. Different methods and thresholds to define disease and injury can have profound impact on the prevalence, severity, natural history and response to treatment of a condition. This may be particularly relevant where individual responses may be affected by the potential for compensation. Study populations were heterogeneous and results were rarely reported according to key clinical characteristics of interest (e.g., age, gender, race, socioeconomic status, trauma etiology or time, presence of pain or mental health disorders other than PTSD) that may have an impact on prevalence estimates. We attempted to minimize publication bias by using broad search terms and multiple databases, and by seeking input from our Technical Advisory Panel members and external peer reviewers (including consensus panel members). We included the large RAND study,[5] even though it may not technically meet definitions for peer-reviewed publications.

ACTIVE RESEARCH

Summary of Findings

Although there are a number of ongoing, active research studies that include patients with TBI/PTSD, few will specifically address the key questions identified for this report.

Details of Findings

The ongoing studies, sorted by key question, are summarized in Appendix E, Tables 1-3. We identified seven studies that will provide information about the prevalence of TBI/PTSD (Table 1). Six of the studies include OEF and/or OIF soldiers or veterans. Sample sizes vary widely; the largest study intends to assess TBI history and PTSD in up to 60,000 veterans. The methods of assessment of TBI history and PTSD vary and include chart review, self report, symptom checklists, and structured diagnostic interviews.

We identified eight studies that will provide information related to the assessment of mTBI/PTSD (Table 2). Three of the studies will also address key question #1 and are included in Appendix E, Table 1. All but one of the studies include military personnel, with reported sample sizes ranging from 120 to 850. The methods of assessment are largely similar to those reported in Table 1, although magnetic resonance imaging, sleep studies, neuroendocrine measures, and a smell test are also being used.

Six studies were identified that examine treatments for symptoms of mTBI/PTSD. Five of the studies include OEF/OIF veterans or their family members; the remaining study will likely include veterans. Reported sample sizes range from 6 to 300. Treatments to be evaluated include psychotherapy, psychiatric and sleep medications, relaxation therapy, sleep education, support teams, and hyperbaric oxygen therapy. One of the studies is a randomized, controlled trial.

ACTIVE RESEARCH - LIMITATIONS

Our reporting of active research is based solely on responses obtained from individuals who received our request for information and chose to respond. No follow-up contact was made with non-responders. Thus, there may be other ongoing studies pertinent to our key questions that were not identified by this process. Most ongoing studies we identified are not enrolling broad-based populations of individuals to estimate population prevalence of TBI/PTSD (especially mTBI/PTSD). We did not identify any studies that attempt to compare the diagnostic accuracy of different assessment tools for identification of TBI history or current PTSD when the conditions co-occur (especially for individuals likely to have mTBI/PTSD). We identified only one ongoing randomized and controlled treatment trial. Future research needs to incorporate these items to ensure that the key questions covered in this review can be addressed.

The studies listed in Appendix E all include at least some patients with TBI/PTSD. Given the ongoing nature of the studies, it was not always possible to identify the exact proportion of patients who would have TBI/PTSD or the severity of the TBI experienced by the patients.

SUMMARY AND DISCUSSION

Our findings indicate that reported prevalence of TBI/PTSD varies widely. Differences in populations, study methodology, trauma severity and etiology, and methods and definitions of ascertainment weaken the strength of the evidence and do not permit accurate prevalence estimates, particularly for patient subgroups of greatest interest to the Department of Veterans Affairs. The three largest studies involving U.S. military personnel and veterans of OEF/OIF, while based on different study populations and survey methods, had relatively consistent results. Results of these three studies indicated that TBI/PTSD (the majority in the RAND study likely to have mTBI/PTSD) occurred in approximately 5% to 7% of individuals. Among individuals who reported a history of probable TBI, probable PTSD was identified in 33% to 39%. Prevalence varied widely in other studies, likely due to different methods to define and identify cases of TBI and PTSD. We emphasize that these factors can have a profound impact on estimates for prevalence, severity, natural history, and response to treatment for these conditions. In particular, methods that utilize highly sensitive but less specific screening instruments that incorporate self-reported outcomes that can be influenced by financial compensation are likely to increase prevalence estimates and over-diagnose individuals with milder conditions. These points are evidenced by the recent commentary and letters of response published in the *New England Journal of Medicine*.[23,28] Similarly, studies that enroll subjects hospitalized or receiving medical care specifically for their trauma are likely to overestimate prevalence. Because these individuals may differ substantially in many ways (both known and unknown) from individuals with less severe TBI/PTSD and/or cases detected through other screening methods/thresholds, caution should be taken when extrapolating findings from one population to another.

We were unable to identify any studies that evaluated the accuracy of diagnostic tests for individuals with suspected mTBI/PTSD. Furthermore, we were unable to identify any randomized controlled trials and only two case reports related to efficacy of treatment specifically for mTBI/PTSD. Therefore, there is insufficient evidence required to make high quality diagnostic and treatment recommendations pertinent to our key questions. While we identified a large number of ongoing studies related to TBI and PTSD, none are likely to provide high-quality, direct evidence pertaining to key questions 2 and 3 (methods of assessment and treatment). We have provided some recommendations below for the general design, conduct, and outcome measurements for future research studies.

CONCLUSIONS

The reported prevalence of TBI/PTSD varies widely, likely depending on patient characteristics, trauma etiology, disease definition, and ascertainment method. There is no information on the diagnostic accuracy of commonly used tests to assess history of mTBI or current PTSD when both conditions are present. There is no information on the effectiveness and harms of therapies in adults with mTBI/PTSD. There is considerable on-going research in this area. However, long-term prospective observational studies are needed that use standardized, validated measures of TBI (particularly mTBI) history and PTSD to determine TBI/PTSD prevalence, severity, and outcomes. Among military personnel, pre-deployment as well as post-deployment assessment should be obtained using objective measures that limit ascertainment, recall, or reporting

bias. Outcomes according to clinically-relevant patient characteristics, trauma etiology and subtypes, and time from trauma are required. Diagnostic accuracy studies are needed that utilize established quality methods as reported in the STARD initiative[47] and recommended in the QUADAS report.[86] Adequately powered, high-quality randomized, controlled treatment trials in populations of interest are required to evaluate the clinical effectiveness and harms of potential therapeutic options, especially among individuals with mTBI/PTSD.

FUTURE RESEARCH RECOMMENDATIONS

Long-term prospective observational studies are needed that use standardized and validated measures of TBI history and PTSD to determine prevalence, severity, and outcomes of TBI/PTSD. There is a clear need for researchers to come to consensus on the definitions and measures that will be used consistently across studies in order to facilitate comparison of results. Among military personnel, pre-deployment as well as post-deployment assessment should be obtained using objective measures that limit ascertainment, recall, or reporting bias. Outcomes according to clinically relevant patient characteristics, trauma etiology and severity, and time from trauma are required. Diagnostic accuracy studies are needed that utilize established quality methods such as QUADAS. Randomized controlled treatment trials in populations of interest are required to evaluate the effectiveness and harms of potential therapeutic options, especially among individuals with mTBI/PTSD. Research specific to care coordination and treatment planning between specialty clinics and providers should also be considered.

Future research should be devoted to addressing these question using more representative samples and longitudinal methods. Methodologically, we recommend that future research in this area adhere to guidelines for reporting observational studies as report in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[87] As most research relies on samples with probable TBI history recruited from hospital settings, future investigations should include both nationally representative samples, as well as specific samples of interest, such as OEF/OIF veterans or populations seeking services primarily for trauma exposure (e.g., those seeking mental health services, victims' advocacy, or legal services as victims of crime). Future research should develop innovative methods to obtain information necessary for assessing the occurrence of TBI near the time of injury without relying on subject recall or hospital admission to identify patient populations, especially given the suspected low rates at which those with potential mTBI seek emergency medical treatment.

Research optimizing the diagnostic accuracy of assessment for both TBI history and current PTSD in representative populations using gold-standard assessments is of paramount importance. Accuracy is contingent upon research clarifying diagnostic debates regarding how to best assess these conditions when they co-occur. Additionally, little is known regarding the trajectory of symptoms over time for those with either TBI history or current PTSD, and whether outcomes differ among individuals classified as having mTBI/PTSD versus those with just PTSD (especially after controlling for potentially confounding variables). Longitudinal research is needed to assess the degree of overlap in these conditions and long-term outcomes using gold-standard instruments with increasing time from the traumatic event. Future research (and clinical care) would benefit from studies that adhere to the Standards for Reporting of Diagnostic Accuracy (STARD) statement.[47]

Finally, further research is needed that directly compares prevalence of TBI/PTSD among samples matched on important domains such as the type of traumatic events to which individuals were exposed (e.g., combat vs. MVC, physical assault, intimate partner violence), the number and severity of TBI events, demographic characteristics (e.g., gender, race, age), and methods of assessment. Results should be stratified by these clinical characteristics of interest. Furthermore, among military personnel, assessing symptomology prior to deployment and then immediately post-deployment could provide useful information regarding causation.

In regard to the treatment of PTSD among individuals with a history of mTBI, we recommend first evaluating the effectiveness of empirically supported treatments (ESTs) for PTSD (e.g., prolonged exposure therapy and cognitive processing therapy) among individuals with a history of mTBI. Ideally, individuals would be stratified by mTBI status (mTBI/PTSD vs. PTSD without mTBI), then randomized to either the EST or a minimal contact control condition. This design would enable researchers to examine the efficacy of the treatment among adults with mTBI/PTSD and to evaluate differential outcomes between participants with mTBI/PTSD and participants with PTSD but no mTBI history. If the two groups have equivalent outcomes on a variety of measures (PTSD symptomology, functioning, and quality of life), we recommend future research focus on improving outcomes for all individuals with PTSD, rather than focusing specifically on treatments for those with a history of mTBI. Within such a trial, we also suggest extracting treatment process data that would allow researchers to examine whether adults with mTBI/PTSD have more difficulty with tasks related to memory and attention (e.g., homework completion, engagement in imaginal exposure) than individuals with PTSD but no mTBI history. In the case of differential outcomes, such process data would allow researchers to begin to examine factors that may have contributed to lower levels of recovery among individuals with mTBI/PTSD. If memory or attentional problems do contribute to differential outcomes, we suggest the development and evaluation of a set of compensatory strategies that can be used in conjunction with existing ESTs to improve outcomes (e.g., the use of a personal digital assistant to remind individuals to complete homework and track anxiety levels). Of note, given the concentration difficulties associated with PTSD, such strategies may be benefecial for all veterans undergoing an EST for PTSD. Finally, if adding compensatory strategies to existing ESTs for PTSD does not improve outcomes among individuals with mTBI/PTSD, researchers should look to more substantially alter existing ESTs or begin to develop novel interventions.

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