
Relationship of Deployment-related Mild Traumatic Brain Injury to Posttraumatic Stress Disorder, Depressive Disorders, Substance Use Disorders, Suicidal Ideation, and Anxiety Disorders: A Systematic Review

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the **Minneapolis VA Medical Center, Minneapolis, MN**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. 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 or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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This topic was developed in response to a nomination by Stuart Hoffman, PhD, Scientific Program Manager for Brain Injury and Senior Scientific Advisor for Brain Injury; Ralph DePalma, MD, FACS, Special Operations Officer; and David X. Cifu, MD, National Director of Physical Medicine and Rehabilitation Program Office and Chair, VHA TBI Advisory Committee, for use by the VHA TBI Advisory Committee to inform clinical practice guideline development and by the Office of Research and Development to inform future research priorities. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below (* indicates person was also a peer reviewer):

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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EXECUTIVE SUMMARY

INTRODUCTION

More than 2 million United States (US) service members have deployed to Iraq and Afghanistan in support of Operations Enduring Freedom (OEF), Iraqi Freedom (OIF), and New Dawn (OND) since September 11, 2001. Approximately 10% of active duty service members deployed to Iraq and Afghanistan between 2003 and 2014 received a new TBI diagnosis within 3 years after returning from these deployments. The US Department of Defense (DoD) reported a total of 379,519 first-time traumatic brain injuries (TBIs) world-wide from 2000 to 2017 with 312,495 (82%) classified as mild (mTBI). Within the Veterans Health Administration (VHA), between the start of required screening for TBI in 2007 through September 2016, 1,066,474 Veterans were screened, 201,997 screened positive, and 147,744 completed the VA Comprehensive TBI Evaluation. There were 83,318 confirmed TBI diagnoses, mostly mTBI.

OEF/OIF/OND service members and Veterans are also at increased risk for psychiatric conditions including posttraumatic stress disorder (PTSD), depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders. It is unknown, however, whether these psychiatric conditions are more common in OEF/OIF/OND service members and Veterans with a deployment-related TBI than among those without TBI. Evidence for whether the rates of these psychiatric comorbidities are comparable among deployed service members and Veterans who incurred a TBI vs those who did not is critical to inform policy, programming, and treatment decisions involving those with TBI. Moreover, clinicians need to know the effectiveness and safety of evidence-based mental health treatments in service members and Veterans who also have a history of TBI. This report focuses on the prevalence of psychiatric conditions and the effectiveness of mental health interventions in service members and Veterans with a history of deployment-related mTBI.

We addressed the following key questions:

Key Question 1a. Is the **prevalence** of psychiatric conditions (posttraumatic stress disorder [PTSD], depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders) different in service members and Veterans with and without deployment-related **mild traumatic brain injury** (mTBI) (one or more)?

Key Question 1b. How do **severity and persistence** of psychiatric conditions (PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders) differ in service members and Veterans with and without deployment-related mTBI?

Key Question 2. What are the effectiveness and comparative effectiveness and harms of interventions for treatment of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders in service members and Veterans with history of deployment-related mTBI?

Primary and secondary outcomes were specified for each key question. For Key Question 1 our primary outcome was the prevalence of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders in service members and Veterans with and

without deployment-related mTBI(s); secondary outcomes included symptom severity and persistence. For Key Question 2, our primary outcome was clinically significant changes in symptoms following treatment for a psychiatric condition of interest. Our secondary outcomes were changes in symptom scores and quality of life following treatment for a psychiatric condition of interest.

METHODS

Topic Development

We consulted with our Operational Partners and Technical Expert Panel (TEP) members to develop the scope, key questions, inclusion criteria, and outcomes of interest. Our protocol was registered in PROSPERO (CRD42018083990).

Data Sources and Searches

We searched MEDLINE, PsycINFO, the Published International Literature on Traumatic Stress (PILOTS) database, VA Health Services Research and Development (HSR&D) publications, and the Defense and Veterans Brain Injury Center (DVBIC) Web site for English language publications indexed from 2000 to October 2017. We also reviewed suggested articles from Operational Partners and TEP members and searched reference lists from relevant systematic reviews and included studies.

Study Selection

Two investigators or research assistants independently completed abstract triage and full text review.

For Key Question 1a/1b, we included studies that reported prevalence, severity, or symptom persistence of the identified psychiatric conditions in nationally representative or geographically diverse samples of US service members and/or Veterans (OEF/OIF/OND era) with and without a history of mTBI(s) incurred during deployment. If the study included both deployment- and non-deployment related TBI or different severities of TBI, at least 75% of the population must have a history of deployment-related mTBI(s). If study participants had more than one TBI, at least one must have been deployment-related. If the study did not specify severity of TBI(s), typically in a study that determined history of TBI from *International Classification of Diseases, Ninth Revision* (ICD-9) codes, we included the study because prior research indicates that a high percentage of TBI in OEF/OIF/OND is mTBI. Results are reported separately for studies with confirmed mTBI(s) and those with TBI unspecified.

For Key Question 2, we included studies of interventions/treatments for the 5 psychiatric conditions of interest (PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders) in US service members and/or Veterans (OEF/OIF/OND era) with mTBI histories.

For both Key Questions, we excluded studies: 1) enrolling non-US service members or Veterans, 2) with fewer than 75% of participants from the OEF/OIF/OND service era, 3) with fewer than 75% of participants reporting occurrence of TBI in a deployed environment or specifying that greater than 25% of the sample had a moderate or severe TBI, 4) not reporting on psychiatric

conditions of interest, 5) not reporting outcomes of interest (see above), and 6) not using observational or randomized controlled trial designs (*eg*, case reports, narrative reviews, editorials). Additionally, for Key Questions 1a/1b, we excluded studies 1) enrolling a sample from a single facility (*ie*, not nationally representative) and 2) reporting prevalence or severity/symptom persistence in a mTBI group without a no-TBI comparison group.

Data Abstraction and Quality Assessment

Data were abstracted by one investigator or research associate and verified by a second. We assessed risk of bias of individual studies using criteria adapted from the Joanna Briggs Institute Critical Appraisal Checklists for 1) Observational Epidemiological Studies Reporting Prevalence and Incidence Data and 2) Quasi-Experimental Studies (experimental studies without random allocation). Results were stratified by psychiatric condition or intervention.

Data Synthesis and Analysis

For Key Question 1, results were qualitatively synthesized. For Key Question 2, data were analyzed using Review Manager Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). When pre- and post-treatment data were provided, within study effect sizes and corresponding 95% confidence intervals (CIs) were computed using Hedges' g (adjusted for sample size). When data were provided, between-group effect sizes and corresponding 95% CIs were computed based on the mean change from baseline for each group.

We rated overall strength of evidence for 1) the prevalence of the psychiatric conditions based on data from national samples and 2) the effectiveness of interventions for the psychiatric conditions. The strength of the evidence was evaluated based on 4 domains: 1) risk of bias (whether the studies for a given outcome or comparison have good internal validity); 2) consistency (the degree of similarity in the effect sizes, *ie*, same direction of effect, of the included studies); 3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and 4) precision (degree of certainty surrounding an effect estimate of a given outcome).

RESULTS

Results of Literature Search

After removing 245 duplicate citations, we screened 1,215 abstracts. Seven hundred forty records were excluded, leaving 475 citations to be reviewed at the full text level. We excluded 434 articles for one or more of the reasons listed above; 41 studies were included in the review.

Key Question 1

We identified 11 studies of national samples and 22 studies of geographically diverse samples reporting prevalence and/or severity of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, or anxiety disorders in OEF/OIF/OND service members or Veterans with a history of TBI compared to no history of TBI. In 5 of the 11 national sample studies, participants had a history of mTBI; the remaining studies did not specify TBI severity. Among the 11 national sample studies, 4 studies enrolled service members. Two of the 4 studies included US Army or US Army Special Operations Command personnel deployed between 2008

and 2011. Another study included service members from all branches deployed from 2008 to 2010. The fourth study included Navy sailors and Marines deployed from 2008 to 2009. It is unclear whether there is duplication of the samples across studies. Of the 7 national sample studies enrolling Veterans, 4 included all Veterans using VHA care during time periods of 1 to 5 years between 2007 and 2014. Additionally, 2 studies included Veterans who had completed the VA Comprehensive TBI Evaluation (CTBIE) between 2007 and 2012 and the seventh study included Veterans who received alcohol screening in 2012. Thus, all of the studies of Veterans included samples from the population of VA users between 2007 and 2014.

Of the 22 geographically diverse sample studies, 20 focused on mTBI and 2 did not specify TBI severity. Studies varied widely in sample size, used different measures of the psychiatric conditions, and assessed psychiatric status at varying time points post injury.

Studies based on national samples and geographically diverse samples generally reported a higher prevalence (KQ1a) of PTSD and depressive disorders in service members and Veterans with a history of mTBI or TBI unspecified (Executive Summary Tables 1 and 2). In the national samples, the prevalence of PTSD was 63% to 77% in Veterans using VHA care with a history of mTBI or TBI unspecified and 10% to 64% in those with no TBI history. The prevalence of depressive disorders was 31% to 50% in service members who completed a post-deployment health assessment and Veterans using VHA care with a history of mTBI or TBI unspecified compared to 11% to 35% in those with no TBI. National samples generally found a higher prevalence of substance use disorders in the service member and Veterans groups with a history of mTBI or TBI unspecified vs the no-TBI groups. For alcohol abuse the prevalence was 4% to 19% for the TBI groups and 2% to 11% in those with no TBI history. Results for substance use disorders were mixed for the geographically diverse samples with several studies finding similar prevalence in service members with a history of mTBI compared to those with no TBI history. One national sample study of Veterans reported a higher prevalence of suicide attempts in Veterans with a history of mTBI (0.5%) vs no-TBI (0.1%). Two geographically diverse sample studies of service members reported the prevalence of suicidal ideation was higher in the mTBI groups compared to the no-TBI groups. National samples of Veterans using VHA care found a higher prevalence of anxiety disorders other than PTSD (based on diagnostic codes) in the mTBI or TBI unspecified (17% to 31%) vs the no-TBI groups (8% to 16%). One national sample of Veterans who completed the VA CTBIE found no difference in the prevalence of suspected symptoms of anxiety disorder other than PTSD in the mTBI (24%) and no-TBI (26%) groups. In geographically diverse samples, the prevalence of anxiety disorders (diagnostic codes other than PTSD or above a specified cut-off on the self-report Beck Anxiety Inventory [BAI]) was higher in Veterans with a history of mTBI or TBI unspecified. One study of service members found a similar prevalence of anxiety disorders including PTSD in the mTBI and no-TBI groups.

Strength of evidence based on data from the national samples was moderate for the prevalence of PTSD, low for the prevalence of depressive disorders, substance use disorders, and anxiety disorders and insufficient for the prevalence of suicidal ideation and severity of any of the psychiatric conditions (Executive Summary Table 3)

Two national sample studies reported severity or persistence of symptoms of the psychiatric conditions of interest. One study reported higher PCL (version not specified) scores in active duty service members with a history of mTBI although all PCL scores were below the suggested

cut-off score for PTSD. Another study reported slightly higher percentages of both moderate (11% vs 9%) and severe (8% vs 6%) alcohol misuse in Veterans with a history of mTBI (insufficient evidence).

In geographically diverse studies, PTSD severity scores were generally higher in the groups with a history of mTBI/TBI unspecified. Differences in symptom severity were less consistent for depressive and substance use disorders with studies reporting mixed results depending on injury type (blast or non-blast) or the comparison (mTBI vs no mTBI/no PTSD or mTBI/PTSD vs PTSD only). One study reported scores from a suicidal behavior measure that assessed ideation, threat of suicide attempt, and likelihood of suicidal behavior in the future, finding higher values in the service members with a history of mTBI. None of the geographically diverse studies reported anxiety severity in individuals with anxiety disorders.

Executive Summary Table 1. Prevalence and Severity/Persistence of Psychiatric Conditions in Veterans and Service Members with and without Deployment-related TBI – National Samples

	PREVALENCE					SEVERITY/PERSISTENCE				
	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
SERVICE MEMBERS (4 studies)		↑ 1 study	↑ 2 studies			↑ 1 study				
VETERANS (7 studies)	↑ 7 studies	↑ 5 studies ↔ 1 study	↑ 3 studies ↔ 1 study	↑ 1 study	↑ 3 studies ↔ 1 study			↑ 1 study		
TOTAL	↑ 7 studies	↑ 6 studies ↔ 1 study	↑ 5 studies ↔ 1 study	↑ 1 study	↑ 3 studies ↔ 1 study	↑ 1 study		↑ 1 study		

↑=Higher prevalence or severity in deployment-related TBI group compared to no deployment-related TBI group

↔=Similar prevalence or severity in deployment-related TBI group compared to no deployment-related TBI group



Executive Summary Table 2. Prevalence and Severity/Persistence of Psychiatric Conditions in Veterans and Service Members with and without Deployment-related TBI – Geographically Diverse Samples

	PREVALENCE					SEVERITY/PERSISTENCE				
	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
SERVICE MEMBERS (15 studies)	↑ 9 studies ↔ 2 studies Mixed 1 study	↑ 3 studies ↔ 1 study Mixed 1 study	↑ 1 study ↔ 2 studies	↑ 2 studies	↔ 1 study	↑ 4 studies Mixed 2 studies	↑ 2 studies ↔ 1 study Mixed 2 studies	↔ 1 study Mixed 1 study	↑ 1 study	
VETERANS (7 studies)	↑ 5 studies	↑ 2 studies	↑ 3 studies		↑ 2 studies	↑ 2 studies	↑ 2 studies	↑ 1 study		
TOTAL	↑ 14 studies ↔ 2 studies Mixed 1 study	↑ 5 studies ↔ 1 study Mixed 1 study	↑ 4 studies ↔ 2 studies	↑ 2 studies	↑ 2 studies ↔ 1 study	↑ 6 studies Mixed 2 studies	↑ 4 studies ↔ 1 study Mixed 2 studies	↑ 1 study ↔ 1 study Mixed 1 study	↑ 1 study	

↑=Higher prevalence or severity in deployment-related TBI group compared to no deployment-related TBI group

↔=Similar prevalence or severity in deployment-related TBI group compared to no deployment-related TBI group

Mixed=mix of higher or similar prevalence or severity depending on type of injury (eg, blast or non-blast), degree of loss/alteration of consciousness, or comparator group



Executive Summary Table 3. Strength of Evidence – Key Question 1

Key Question 1a: Prevalence of psychiatric conditions from national samples (k=11)			
Condition	Number of studies	Strength of evidence	Comments
PTSD	7	Moderate	<ul style="list-style-type: none"> · Risk of bias for these observational studies was generally moderate · Presence of psychiatric conditions were determined using varying criteria across studies. Severity of TBI was often unspecified (<i>ie</i>, based on ICD-9 codes) · Estimates of the prevalence of mental conditions were consistently higher in Veterans or active duty personnel with history of TBI. Wider variation in estimates observed for depressive, substance use, and anxiety disorders · Wider variation in estimates of prevalence observed in those with no history of TBI · Precision of estimates difficult to determine
Depressive disorders	7	Low	
Substance use disorders	6	Low	
Suicidal ideation	0	Insufficient	
Anxiety disorders	4	Low	
Key Question 1b: Severity of psychiatric conditions from national samples (k=11)			
PTSD	1	Insufficient overall	<ul style="list-style-type: none"> · Severity of symptoms rarely reported
Depressive disorders	0		
Substance use disorders	1		
Suicidal ideation	0		
Anxiety disorders	0		

ICD-9=*International Classification of Diseases, Ninth Revision*; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury

Key Question 2

We found no randomized controlled trials (RCTs) that tested the efficacy or effectiveness of interventions for the treatment of psychiatric conditions in service members or Veterans with a history of deployment-related mTBI. We identified 6 studies of psychotherapies for PTSD, depressive, or anxiety disorders in OEF/OIF/OND service members and Veterans with a history of TBI and one study of hyperbaric oxygen therapy (HBO₂) for post-concussion syndrome (PCS) and PTSD in service members and Veterans with a history of mild to moderate blast-related TBI. No studies reported on treatments for substance use disorders or suicidal ideation in service members or Veterans with a history of mTBI.

TBI severity varied with one study of Veterans with a history of mTBI, 2 studies of Veterans with a history of predominantly mTBI, 3 studies enrolling Veterans with a history of mild to moderate TBI, and one reporting that TBI severity was unknown but presumed to be mild. Five of the studies were small, non-randomized, pre- to post-treatment studies; 2 were secondary analyses of RCTs conducted to test the comparative effectiveness of select psychotherapies in OEF/OIF/OND Veterans, some of whom had TBI.

Limited evidence from 3 studies (1 pre-post study and 2 secondary analyses of RCTs) suggested that the treatment effects did not vary by TBI status. Cognitive processing therapy (CPT) and prolonged exposure therapy (PE) were associated with similar levels of improvements in PTSD (PTSD Checklist-Specific; PCL-S) and symptoms of depression (Beck Depression Inventory; BDI-II) for Veterans with PTSD who did and did not have a history of TBI of unknown severity. Combined data from groups receiving either PE or Present Centered Therapy (PCT) showed similar improvement in PTSD symptoms (Clinician Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; CAPS-IV) in Veterans with PTSD who also had a history of “mostly” mTBI and those with no history of TBI. Both PCT and Acceptance and Commitment Therapy (ACT) resulted in significant but modest reductions in depressive and anxiety symptoms (Brief Symptom Inventory; BSI-18) in Veterans with and without a history of mild to moderate TBI who met criteria for at least one anxiety (including PTSD) or depressive disorder.

Quality of life was reported only in the study of PCT and ACT. There were modest but statistically significant improvements over time in Short Form 12 Health Survey mental health component scores in both treatment groups; physical health component scores did not change significantly. Treatment effects did not vary in Veterans with and without mild to moderate TBI.

Three additional pre-post intervention studies reported outcomes following either CPT or PE for service members or Veterans with PTSD and a history of mild to severe TBI. Compared to baseline, authors reported significantly reduced PTSD (CAPS-IV; PCL [version not specified], PCL-S, or PTSD Checklist-Military [PCL-M]), and depressive (BDI-II) symptoms following treatment.

No studies provided data on harms associated with the psychological interventions.

Observed changes in PTSD symptoms scores from baseline to end of intervention exceeded minimal clinically important differences (MCIDs) reported for the PCL-M (5-10 points) and CAPS-IV (10 points). Similarly, observed changes in depressive disorder symptom scores exceeded the MCID reported for the BDI-II (17.5% reduction from baseline). However, because studies lacked usual care or wait-list controls and were not specifically designed to examine differential effectiveness by TBI status the evidence is insufficient to adequately assess possible differential effectiveness of the interventions in this population (Executive Summary Table 4).

One small, pre-post, uncontrolled, proof-of-concept study of HBO₂ for PCS and PTSD among service members and Veterans with mild to moderate TBI reported a significant reduction in PCL-M scores following treatment (insufficient evidence, Executive Summary Table 4). There were reports of mild reversible middle ear barotrauma in 5 subjects (one of whom withdrew from the study) and transient deterioration of symptoms (including mood, headaches, and depression) in 4 subjects.

We found no studies of the effect of pharmacological interventions for the psychiatric conditions of interest in service members or Veterans with and without a history of mTBI.

Executive Summary Table 4. Strength of Evidence – Key Question 2

Key Question 2: Effectiveness and comparative effectiveness and harms of interventions for psychiatric conditions in service members and Veterans with a history of TBI			
Intervention	Number of studies	Strength of evidence	Comments
Behavioral Therapies			
Cognitive Processing Therapy (CPT)	2	Insufficient overall	<ul style="list-style-type: none"> 4 small nonrandomized studies with a pre- and post-study design and 2 small post-hoc analysis of RCTs were evaluated; risk of bias was moderate to high Improvements in PTSD and depressive symptom scale scores were observed with all therapies and were consistent across studies where multiple studies existed but lack of usual care or wait-list control group limits interpretation of the effect No differences in outcomes regardless of TBI status (history or no history; data from 3 studies) however studies were not specifically designed to examine differential effectiveness by TBI status and were likely underpowered to do so
Prolonged Exposure Therapy (PE)	3		
Acceptance and Commitment Therapy	1		
Present Centered Therapy	1		
PE combined with Present Centered Therapy (PCT)	1		
Non-behavioral Therapies			
Hyperbaric oxygen therapy	1	Insufficient	<ul style="list-style-type: none"> One small pre- and post-study, moderate risk of bias Improvement in PTSD symptom scale
Pharmacological	0	Insufficient	<ul style="list-style-type: none"> No studies identified

PTSD=postraumatic stress disorder; RCT=randomized controlled trial; TBI=traumatic brain injury

DISCUSSION**Key Findings and Strength of Evidence***Prevalence and Severity of Psychiatric Conditions (Key Question 1a/1b)**National samples of Veterans and service members with a history of mTBI vs no history of TBI:*

- PTSD was more prevalent in Veterans with a history of mTBI vs no-TBI (moderate strength evidence, Executive Summary Table 3). In all but one study the difference in prevalence between the mTBI and no-TBI groups was at least 20%. No eligible studies reported PTSD prevalence for active duty service members.
- Depressive disorders were more prevalent in Veterans and service members with a history of mTBI vs no-TBI (low strength evidence). The differences in prevalence ranged from 5% to 37%. One study of Veterans reported similar prevalence rates of depressive disorders in TBI and no-TBI groups.
- Substance use disorders (including alcohol, drug, and tobacco abuse) were more prevalent in service members and Veterans with a history of mTBI or TBI unspecified vs no-TBI; one study of Veterans reported similar prevalence rates across groups for both alcohol and drug abuse (low strength evidence).

- Suicidal ideation was not reported (insufficient evidence). Only a single study reported on the prevalence of attempted suicides finding higher prevalence in Veterans with a history of mTBI vs no-TBI.
- Anxiety disorders were generally more prevalent in Veterans with a history of mTBI vs no-TBI; one study of Veterans reported similar prevalence of anxiety symptoms across groups (low strength evidence). No studies reported prevalence of anxiety disorders for service members.
- The prevalence of PTSD, depressive disorders, substance use disorders, suicidal ideation, and anxiety disorders was primarily determined from diagnostics codes.
- Psychiatric condition severity or persistence were rarely reported in the national samples (insufficient evidence).

Geographically diverse samples of Veterans and service members with a history of mTBI vs no history of TBI:

- PTSD (based on a diagnostic interview, a symptom score exceeding a specified cut point, or diagnostic codes) was more prevalent in Veterans with a history of TBI (mTBI or TBI unspecified) vs no-TBI and service members with a history of mTBI vs no-TBI. Differences in prevalence between those with a history of mTBI or TBI unspecified vs no TBI ranged from 17% to 48%. There were a few exceptions with 2 studies reporting similar prevalence rates in service members with a history of mTBI and no-TBI and one study reporting similar prevalence rates for those with blast-related mTBI and no-TBI but higher prevalence for those with non-blast mTBI compared to no-TBI. PTSD symptom severity scores were also higher with few exceptions.
- Depressive disorders (defined as a diagnosis of major depressive disorder, a symptom score exceeding a specified cut point, or a positive screen) were generally more prevalent in Veterans with a history of TBI (mTBI or TBI unspecified) vs no-TBI and service members with a history of mTBI vs no-TBI. In studies reporting a higher prevalence in the groups with a history of TBI vs no TBI, differences ranged from 8% to 28%. One study reported a higher prevalence of major depressive disorder in service members with a history of mTBI with loss of consciousness compared to no TBI but similar prevalence for mTBI with altered state compared to no TBI. Another study reported a similar prevalence of depression (a symptom score exceeding a cut point) in service members with a history of mTBI vs no TBI. Depressive symptom severity results were mixed.
- Substance use disorders (primarily alcohol abuse defined as a diagnosis or as a positive screen) were generally more prevalent in Veterans with a history of TBI (mTBI or TBI unspecified) vs no-TBI and service members with a history of mTBI vs no-TBI. Differences in prevalence ranged from 6% to 21%. Two studies reported the groups were similar. Results for alcohol abuse severity were mixed.
- Suicidal ideation was more prevalent among service members with a history of mTBI vs no-TBI and suicidal ideation scores were higher. No studies reported suicidal ideation in Veterans.

- Anxiety disorders (defined by a diagnostic code or a symptom score exceeding a cut point) were more prevalent in Veterans with a history of TBI (mTBI or TBI unspecified) vs no-TBI. One study of service members found anxiety disorder prevalence based on diagnostic codes (including the code for PTSD) was similar for the mTBI and no-TBI groups. No studies reported severity of anxiety symptoms.

Interventions for Treatment of Psychiatric Conditions (Key Question 2)

- No randomized controlled trials evaluated the effectiveness of pharmacologic or behavioral interventions for treatment of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, or anxiety disorders in service members or veterans with a history of deployment-related mTBI.
- Limited data from one pre-post study and 2 secondary analyses of RCTs, designed to examine psychotherapy effectiveness in OEF/OIF/OND Veterans, did not find a differential treatment effect in individuals with a history of TBI compared to those without a history of TBI. CPT and PE were associated with similar improvements in PTSD (PCL-S) and symptoms of depression (BDI-II) for Veterans with and without a history of TBI of unknown severity. Combined data from groups receiving either PE or Present Centered Therapy (PCT) showed similar improvement in PTSD symptoms (CAPS-IV) in Veterans with a history of “mostly” mTBI and Veterans with no history of TBI. Both PCT and ACT resulted in significant but modest reductions in depressive and anxiety symptoms (BSI-18) in Veterans with and without a history of mild to moderate TBI. However, these studies were not specifically designed to examine differences by TBI status.
- Compared to baseline, CPT, PE, ACT, and PCT were associated with significant reductions in PTSD symptoms measured with the CAPS-IV or versions of the PCL, and, with the exception of one study of CPT, a reduction in symptoms of depression (BDI-II) or distress (*ie*, depression or anxiety symptoms; BSI-18). Effect sizes ranged from 0.46 to 3.49 with all but 2 effect sizes greater than 1.00. Observed changes in PTSD and depressive symptom scores from baseline to end of intervention exceeded minimal clinically important differences for the PCL-M, CAPS-IV and BDI-II. However, because these studies lacked usual care or wait-list control groups and were not specifically designed to examine differential effectiveness by TBI status we concluded that evidence is insufficient regarding treatment effectiveness among Veterans and service members with mTBI (Executive Summary Table 4).
- A small, pre-post, uncontrolled, proof of concept study of hyperbaric oxygen therapy for PCS among service members and Veterans with mild to moderate TBI and PTSD symptoms reported a significant reduction in PCL-M scores following treatment.

Discussion and Applicability

In data from national samples of Veterans who used VHA services, we found a higher prevalence of PTSD, depressive disorders, substance use disorders, and anxiety disorders in Veterans with a history of mTBI compared to those with no TBI. We found few studies reporting prevalence of the psychiatric conditions in active duty service members. National sample studies were cross-sectional with little information on the timing of the mental health diagnoses with respect to the TBI event(s). A variety of measures were used to assess the psychiatric conditions with different cut-points for defining a mental health diagnosis making comparisons across studies difficult. We included studies where TBI severity was not reported or where up to 25% of the participants had a history of moderate to severe TBI which may have skewed our findings with respect to mTBI. Our findings, however, do support the need for comprehensive evaluation of psychiatric conditions in service members and Veterans with a history of TBI so they receive appropriate care to improve recovery and long-term outcomes.

While behavioral therapies including CPT, PE, PCT, and ACT may be effective for service members and Veterans with PTSD and a history of deployment-related TBI, particularly mTBI, studies lacked usual care or wait-list control groups, making it difficult to assess the effect of the intervention. Furthermore, studies were not specifically designed to examine differential effectiveness by TBI status and were likely underpowered to do so. No studies reported on harms associated with the interventions.

Research Gaps/Future Research

Our review identified several limitations in the research and gaps in the existing evidence. Studies of psychiatric condition prevalence and severity and their association with mTBI are potentially limited by case-ascertainment and data collection methods. Additionally, a wide range of outcome measures was reported and time of assessment post-injury varied making summary difficult. Much of the prevalence data are from VHA users. It has been reported that, through June 2015, approximately 62 percent (1,218,857) of all separated OEF/OIF/OND Veterans have used VA health care since October 1, 2001. No randomized controlled trials evaluated the effectiveness of behavioral interventions for treatment of PTSD, depressive disorders, substance use disorders, suicidal ideation, or anxiety disorders in service members or Veterans with a history of deployment-related mTBI. No studies examined the effectiveness of pharmacological interventions for the psychiatric conditions of interest. Only one study reported harms - a small proof of concept study of hyperbaric oxygen therapy.

The recommended study design to address gaps in evaluating the prevalence, severity, and persistence of psychiatric conditions in service members and Veterans with and without a history of mTBI would be a cohort study with in-person data collection by appropriately trained personnel, using validated measures, and including follow-up at regular time intervals. Ideally, baseline data from the time of entering military service (including relevant history prior to service) and details of TBI events and other exposures should be well-documented (etiology, duration of loss of consciousness if appropriate, etc.). However, information collection would be resource intensive and require a large sample size. Alternatively, existing longitudinal study registries (*eg*, Project VALOR [Veterans' After-discharge Longitudinal Registry], Millennium Cohort Study, Marine Resiliency Study, or Neurocognition Deployment Health Study) may already include this information or existing databases could be modified to ensure that

information needed to address questions of prevalence, severity, and persistence is uniformly collected and as complete as possible.

Randomized trials are needed to evaluate the effectiveness of interventions for psychiatric conditions, both behavioral and pharmacological, in service members and Veterans with a history of mTBI. Ideally, a trial would include both short- and long-term outcomes post-treatment including functioning and quality of life measured in addition to symptom measures. Existing data might be re-analyzed to highlight findings in Veterans and service members with mTBI vs no-TBI though given the small sample size of these existing studies it is unlikely that they are adequately powered. Finally, harms of interventions including physical, mental, financial, and opportunity costs are not known.

Conclusions

Reports from national samples provide moderate strength evidence of increased prevalence of PTSD and low strength evidence of increased prevalence of depressive disorders, substance use disorders, and anxiety disorders in active duty service members and Veterans with a history of mTBI compared to those with no TBI. In geographically diverse samples, results were generally similar. There was little reporting of the prevalence of suicidal ideation.

Behavioral treatments for PTSD achieved minimal clinically important differences for changes in PTSD and depressive symptoms in Veterans with a history of TBI with no indication of harm. Results from studies that included groups with and without a history of TBI suggest TBI status does not affect treatment outcomes. Lacking usual care or wait-list control groups in the predominantly pre- to post-treatment studies, the strength of the evidence for effectiveness of interventions for psychiatric conditions in service members and Veterans with a history of mTBI is insufficient.

ABBREVIATIONS TABLE

ACT	Acceptance and Commitment Therapy
AIS	Abbreviated Injury Scale
AOC	Alteration of consciousness
AS	Altered state
AUDIT-(C)	Alcohol Use Disorders Identification Test-(Consumption)
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BHM	Behavioral Health Measure
BSI	Brief Symptom Inventory
CAGE	Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers
CAPS (CAPS-IV)	Clinician Administered PTSD Scale (CAPS for DSM-IV)
CCT	Controlled clinical trial
CESD	Center for Epidemiologic Studies Depression
CPT	Cognitive Processing Therapy
CTBIE	Comprehensive Traumatic Brain Injury Evaluation
DoD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
DVBIC	Defense and Veterans Brain Injury Center
ES	Effect size
HAM-A	Hamilton Anxiety Rating Scale
HBO ₂	Hyperbaric Oxygen Therapy
HSR&D	Health Services Research & Development
ICD	International Classification of Diseases
ISS	Injury Severity Score
LOC	Loss of consciousness
MADRS	Montgomery-Asberg Depression Rating Scale
MAST	Michigan Alcohol Screening Test
MDD	Major depressive disorder
OEF/OIF/OND	Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn
PC-PTSD	Primary Care- Posttraumatic Stress Disorder screen
PCL-(C)(M)(S)	Posttraumatic Stress Disorder Checklist-(Civilian) (Military) (Specific)
PCS	Post-concussive syndrome
PCT	Present Centered Therapy

PDHA/PDHRA	Post Deployment Health Assessment/Reassessment
PE	Prolonged Exposure Therapy
PHQ	Patient Health Questionnaire
PILOTS	Published International Literature on Traumatic Stress
PNS	Polytrauma Network Sites
PST	Problem Solving Treatment
PTBRI	Polytrauma and Blast Related Injury
PTSD	Posttraumatic stress disorder
QUERI	Quality Enhancement Research Initiative
RCT	Randomized controlled trial
SBQ-(R)	Suicide Behaviors Questionnaire-(Revised)
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder
SPI	Suicide Potential Index
STDI	Structured Traumatic Brain Injury Diagnostic Interview
(m)TBI	(mild) Traumatic brain injury
TEP	Technical Expert Panel
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
WARCAT	Warrior Administered Retrospective Casualty Assessment Tool