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.

ACKNOWLEDGMENTS

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.

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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

Condition	Number of studies	Strength of evidence	Comments
Key Question 1a: Prevalence of psychiatric conditions from national samples (k=11)			
PTSD	7	Moderate	· 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 (*ie,* 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	· 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 (HBO_2) 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 HBO_2 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	· 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	· One small pre- and post-study, moderate risk of bias · Improvement in PTSD symptom scale
Pharmacological	0	Insufficient	· No studies identified

PTSD=posttraumatic 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, 4th 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

EVIDENCE REPORT

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.[1] 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.[2] 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).[3] 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.[4]

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, anxiety disorders, and suicidal ideation or attempts. 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?

We defined the following Population, Intervention, Comparator, Outcomes, and Timing (PICOT) of interest:

Population:
OEF/OIF/OND active duty service members and Veterans with one or more deployment-related mTBI(s)

Intervention:
Deployment-related mTBI(s) (KQ1a/1b, KQ2)
Pharmacological or nonpharmacological interventions for the management of psychiatric conditions (KQ2)

Comparator:
Veterans and service members without deployment-related mTBI(s) (KQ1a/1b)
Placebo or alternative pharmacological or nonpharmacological intervention including wait-list controls (KQ2)

Outcomes:
KQ1: Prevalence, severity, and symptom persistence of the psychiatric conditions in service members and Veterans with and without deployment-related mTBI(s)
KQ2: Clinically important changes in symptoms (improvement, loss of diagnosis, and harms) following treatment for psychiatric conditions of interest in service members and Veterans with and without deployment-related mild TBI(s); changes in function and quality of life following treatment for psychiatric conditions of interest in service members and Veterans with and without deployment-related mild TBI(s)

Timing:
Any time post-deployment.

METHODS

TOPIC DEVELOPMENT

We developed the scope, key questions, inclusion/exclusion criteria, and outcomes of interest with input from the Operational Partners and Technical Expert Panel. The protocol was registered in PROSPERO (CRD42018083990). The report will be used by the Veterans Health Administrative TBI Advisory Committee to inform clinical practice guideline development and by the Office of Research and Development to inform future research priorities.

SEARCH STRATEGY

We searched MEDLINE, PsycINFO, the PILOTS database, publications from VA HSR&D, and research from the Defense and Veterans Brain Injury Center (DVBIC) to identify English language observational studies, RCTs, and CCTS published and indexed from 2000 to October 2017. Search terms included Medical Subject Headings (MeSH) and keywords for TBI, psychiatric conditions of interest, service members and Veterans, and service era (Appendix A). Reference lists from relevant systematic reviews and included studies were searched to identify additional eligible studies. Articles identified by the Operational Partners and Technical Expert Panel were also reviewed for inclusion.

STUDY SELECTION

Two investigators or research associates independently reviewed abstracts to identify articles eligible for full text review. Two investigators or research associates then independently reviewed full text articles to determine studies that met inclusion criteria. Conflicts were resolved through discussion or by a third investigator when necessary. Abstract and full text review were done using DistillerSR (Evidence Partners; https://www.evidencepartners.com/).

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.[5] 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.

Reasons for exclusion were documented for articles undergoing full text review. 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

We developed table templates for data abstraction. Data were abstracted by one investigator or research associate and verified by a second.

The following elements were abstracted from each study:

1. Study/population characteristics including study design, age, gender, race, service era, time since injury or discharge, TBI diagnostic method or etiology, and history of TBI.
2. Psychiatric condition(s) including type, severity, condition specific information, and diagnostic tool.
3. Intervention/comparator characteristics (Key Question 2) including length of treatment and/or number of sessions.
4. Outcomes including prevalence, severity, symptom persistence of the psychiatric conditions (Key Question 1), and effectiveness of interventions for the treatment of the psychiatric conditions of interest including clinically important changes in symptoms, harms, and changes in function and quality of life. We noted whether data were from self-report or clinician administered assessments.

QUALITY ASSESSMENT

Risk of bias for prevalence studies was determined based on sampling methods; reporting of subject and setting characteristics; use of valid, standard methods for case definition and outcomes assessment, and response rate. The criteria were adapted from the Critical Appraisal Checklist for Studies Reporting Prevalence Data developed by the Joanna Briggs Institute (http://joannabriggs.org/research/critical-appraisal-tools.html).[6]

For non-randomized intervention studies, risk of bias was determined based on appropriateness of sampling, completeness of follow-up, use of standard assessment methods, manualized treatment with monitoring of fidelity, and independent outcome assessment. The criteria were adapted from the Joanna Briggs Institute Critical Appraisal Tool for Quasi-Experimental Studies (experimental studies without random allocation) (http://joannabriggs.org/research/critical-appraisal-tools.html).[7]

DATA SYNTHESIS

For Key Question 1, results were qualitatively synthesized. Subsets (*eg,* active duty vs Veteran, time since TBI(s), gender, age, or severity of psychiatric condition(s)) were considered when feasible. 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). The effect sizes can be interpreted using Cohen's definition of small (0.2), medium (0.5), and large (0.8) effect sizes.[8] When data were provided, between-group effect sizes and corresponding 95% CIs were computed based on the mean change from baseline for each group.

RATING THE BODY OF EVIDENCE

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 using methods developed by AHRQ and the Effective Health Care Program.[9] 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).

PEER REVIEW

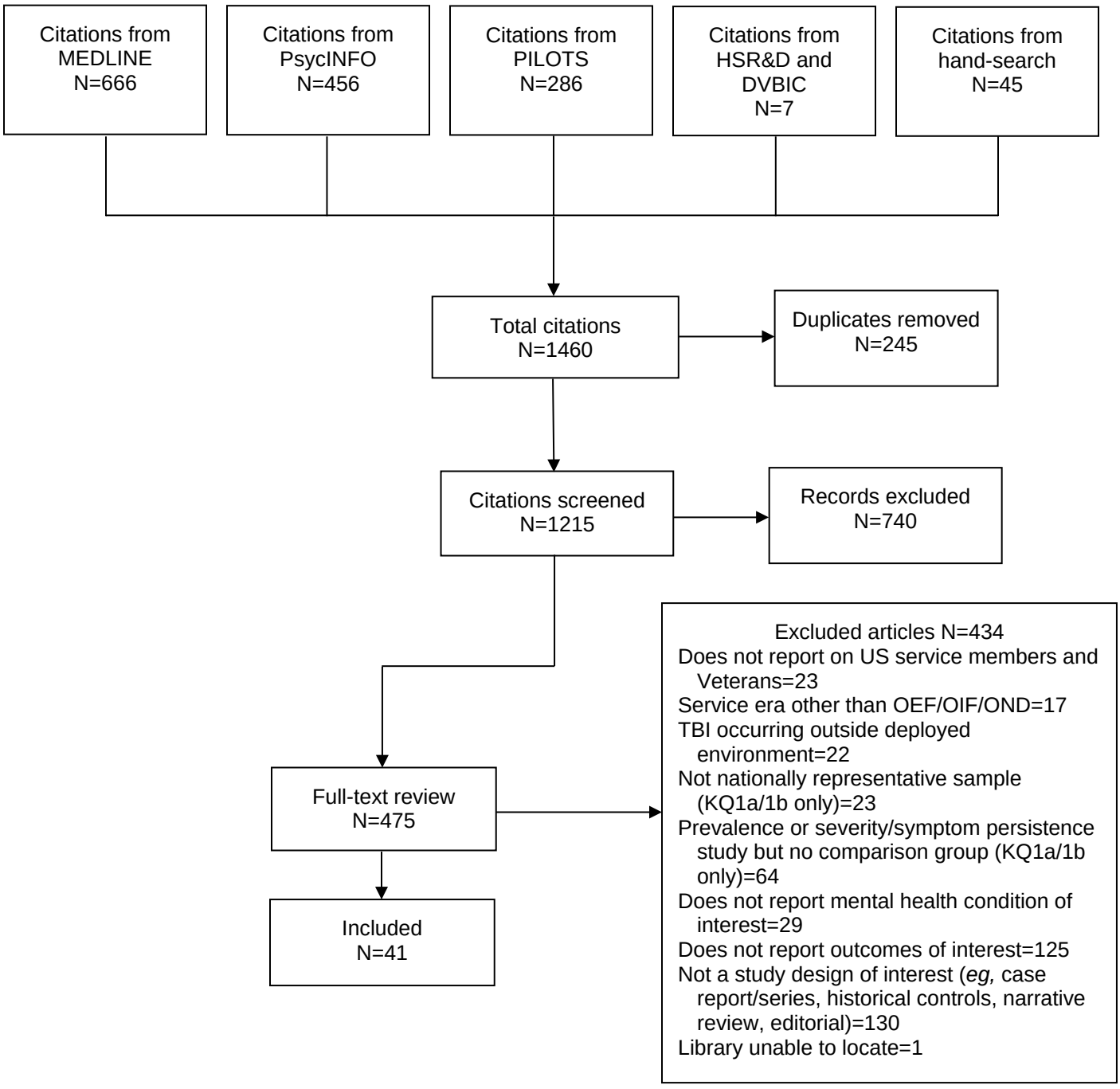
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C and the report was modified as needed.

RESULTS

LITERATURE FLOW

After removing 245 duplicate citations, we screened 1,215 abstracts (Figure 1). We excluded 740 records leaving 475 citations for full text review. An additional 434 references were excluded resulting in 41 included articles (34 articles representing 33 studies for Key Question 1 and 7 articles for Key Question 2).

Figure 1. Literature Flow Chart



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?

Overview of Included Studies

We identified 33 unique studies in 34 articles that reported prevalence and/or symptom severity and persistence of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, or anxiety disorders in OEF/OIF/OND service members or Veterans with and without deployment-related TBI, predominantly mTBI. Table 1 summarizes the studies. There were 11 studies that reported data from a national sample[10-20] and 22 studies (in 23 articles) where data were collected from a geographically diverse sample including multiple sites (*eg*, multiple Veterans medical centers) or individuals that represented a broader population than would be found at a single medical center (*eg*, a military base in Iraq or a National Guard Brigade Combat Team).[21-43] Four of the national sample studies[10,11,13,20] and 7 of the geographically diverse sample studies[26,28,29,35-38] specified that the purpose of the study was to report prevalence of the psychiatric conditions.

Among the 11 national sample studies, 4 studies enrolled service members. Two of the 4 studies included US Army[10] or US Army Special Operations Command personnel[16] deployed between 2008 and 2011. Another study included service members from all branches deployed from 2008 to 2010.[15] The fourth study included Navy sailors and Marines deployed from 2008 to 2009.[17] 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.[11,14,19,20] Additionally, 2 studies included Veterans who had completed the VA Comprehensive TBI Evaluation (CTBIE) between 2007 and 2012[12,18] and the seventh study included Veterans who received alcohol screening in 2012.[13] Thus, all of the studies of Veterans included samples from the population of VA users between 2007 and 2014.

One of the national sample studies included only service members with a history of mTBI,[16] one included any TBI severity with 83% mTBI,[15] and 2 did not specify TBI severity.[10,17] Of the 7 studies enrolling OEF/OIF/OND Veterans, 2 reported on Veterans with a history of mTBI,[18,19] one included any TBI severity with 88% mTBI,[12] and 4 did not specify TBI severity. Accurate information on TBI severity can be difficult to obtain from administrative records commonly used to obtain nationally representative samples.

Sample sizes ranged from 9,258 to 684,133. Only one study reported time since TBI, a mean of 4.8 years.[11] Four studies reported TBI etiology including 100% blast injury,[17] 74% to 80% blast or blast plus other cause,[12,18] and 60% blunt force trauma.[16] Three studies obtained data from

medical records,[12,14,15] 3 obtained data from surveys/questionnaires,[10,16,17] and 5 obtained data from administrative databases.[11,13,18-20] Complete study characteristics and outcomes data are presented in Appendix C, Table 1.

Of the 22 geographically diverse studies, 15 enrolled service members,[22-25,28,29,31-36,38,40,42,43] 6 enrolled Veterans,[21,26,27,30,37,39] and one included both Veterans and service members.[41] Four of the studies enrolling service members included only Army members.[22,29,38,42] Three studies included more than 75% Army members,[23,24,32,33] 2 studies included more than 75% Marine Corps members,[28,35] and the remaining studies were either mixed or did not specify service branch. Sample sizes ranged from 65 to 11,828 with 15 enrolling fewer than 1,000. The studies of service members all enrolled only individuals with a history of mTBI with the exception of one study where 87% had a history of mTBI.[43] Four studies of Veterans and the study of service members and Veterans enrolled only individuals with a history of mTBI[21,27,37,39,41]; 2 studies did not specify TBI severity but was presumed to be largely mTBI.[26,30]

Nine studies reported time since TBI with mean or median values of less than 14 days in 5 studies,[23-25,31-33] less than 1 year in 3 studies,[36,41,43] and greater than 1 year in one study.[21] Three studies reported time from last deployment (4 to 6 months,[42] 23 months,[37] and 32 months[40]) and one reported time since discharge (430 days[26]). TBI etiology included exclusively blast exposure in 5 studies[25,28,33,36,41] and 65% to 95% of participants with blast exposure in 6 studies.[26,29,32,34,35,38] Seven studies evaluated service members at a medical facility, 3 used administrative/database data, and 12 obtained data from self-report or interview. Additional information is presented in Appendix C, Table 2.

Of the 11 studies of national samples, one was rated low risk of bias, 9 as moderate risk of bias, and one as moderate-to-high risk of bias (Appendix C, Table 3). Of the 22 studies of geographically diverse samples, one was rated low risk of bias, 16 as moderate risk of bias, 3 as moderate-to-high risk of bias, and 2 as high risk of bias.

PTSD prevalence was the most frequently reported outcome – reported in 24 of 33 studies (Table 1). Nine studies reported PTSD symptom scores. Prevalence of depressive disorders was reported in 14 studies; 7 reported depressive symptom scores. The prevalence of substance use disorders (including alcohol, drug, and tobacco abuse) was reported by 12 studies with 4 reporting symptom scores. Fewer studies reported on suicidal ideation (2 prevalence, 1 symptom scores with 1 additional study reporting on suicide attempts) or anxiety disorders (7 prevalence, 1 symptom scores).

Table 1. Overview of Prevalence and Severity/Persistence Studies (KQ1a/1b)

Author, year	Sample (Primary Data Source) or Site	Veteran or SM	Sample Size	mTBI or Unspecified TBI	PTSD		Depressive Disorders		Substance Use Disorders		Suicidal Ideation		Anxiety Disorders	
					P	S	P	S	P	S	P	S	P	S
NATIONAL SAMPLES (k=11)														
Kontos 2013[16]	National (Web-based evaluation)	SM (Army Special Operations Command)	22,203	mTBI		ü								
Johnson 2015[15]	National (Medical records)	SM (41% Army, 22% Air Force, 21% Navy, 14% Marine Corps)	162,898	83% mTBI, 6% moderate, 4% severe, 1% penetrating, 6% unclassified					ü					
Adams 2017[10]	National (Post-deployment questionnaire)	SM (Army)	267,100	TBI					ü					
Macera 2012[17]	National (Post-deployment questionnaire)	SM (75% Marine Corps, 25% Navy)	9,902	TBI			ü							
Pogoda 2016[18]	National (CTBIE and Patient care databases)	Veteran	9,337	mTBI[a]	ü		ü		ü				ü	
Seal 2016[19]	National (Patient care database)	Veteran	66,089	mTBI	ü		ü							
Fonda 2017[12]	National (Medical records)	Veteran	273,591	88% mTBI, 6% moderate, 6% severe	ü		ü		ü		ü		ü	

Author, year	Sample (Primary Data Source) or Site	Veteran or SM	Sample Size	mTBI or Unspecified TBI	PTSD		Depressive Disorders		Substance Use Disorders		Suicidal Ideation		Anxiety Disorders	
					P	S	P	S	P	S	P	S	P	S
Cifu 2013[11]	National (Patient care database)	Veteran	613,391	TBI	ü									
Grossbard 2017[13]	National (Corporate Data Warehouse)	Veteran	358,147	TBI	ü		ü		ü	ü			ü	
Jaramillo 2015[14]	National (VA inpatient and outpatient files)	Veteran	303,716	TBI	ü		ü							
Taylor 2015[20]	National (Corporate Data Warehouse)	Veteran	684,133	TBI	ü		ü		ü				ü	
Subtotal (k=11)					**7**	**1**	**7**	**0**	**6**	**1**	**1**	**0**	**4**	**0**
GEOGRAPHICALLY DIVERSE SAMPLES (k=22)														
Brenner 2010[22]	Brigade Combat Team (Questionnaire)	SM (Army)	1,247	mTBI	ü									
Bryan 2013[23,24]	Combat support hospital (Iraq) outpatient TBI clinic (Interview)	SM (79% Army, 13% Air Force, 5% Marine Corps)	158	mTBI		ü		ü			ü	ü		
Bryant 2015[25]	Combat theater hospital (Routine assessment)	SM (details not reported)	685	mTBI	ü									
Heltemes 2011[28]	Forward-deployed medical treatment facilities (Database)	SM (77% Marine Corps, 17% Army, 5% Navy)	3,123	mTBI					ü					

Author, year	Sample (Primary Data Source) or Site	Veteran or SM	Sample Size	mTBI or Unspecified TBI	PTSD		Depressive Disorders		Substance Use Disorders		Suicidal Ideation		Anxiety Disorders	
					P	S	P	S	P	S	P	S	P	S
Hoge 2008[29]	Post-deployment survey	SM (Army)	2,525	mTBI	ü	ü	ü							
MacDonald 2014[33]	Landstuhl Regional Medical Center (Germany) (Clinical assessment)	SM (88% Army, 9% Marine Corps, 3% Air Force)	65	mTBI	ü	ü	ü	ü						
MacDonald 2014[32]	Landstuhl Regional Medical Center (Germany) (Clinical assessment)	SM (85% Army, 8% Air Force, 7% Marine Corps, <1% Navy)	178	mTBI	ü	ü		ü		ü				
MacDonald 2017[31]	Landstuhl Regional Medical Center (Germany) (Clinical assessment)	SM (62% Army, 22% Navy, 13% Marine Corps, 3% Air Force)	72	mTBI		ü		ü						
MacGregor 2013[34]	EMED (Database and questionnaire)	SM (57% Marine Corps, 33% Army, 9% Other)	992	mTBI	ü		ü							
MacGregor 2010[35]	EMED (Database)	SM (76% Marine Corps, 20% Army, 9% Other)	762	mTBI[a]	ü				ü				ü	

Author, year	Sample (Primary Data Source) or Site	Veteran or SM	Sample Size	mTBI or Unspecified TBI	PTSD		Depressive Disorders		Substance Use Disorders		Suicidal Ideation		Anxiety Disorders	
					P	S	P	S	P	S	P	S	P	S
Mora 2009[36]	US Army Institute of Surgical Research Burn Center (Database)	SM	110	mTBI	ü									
Polusny 2011[38]	Army National Guard Brigade Combat Team (Questionnaire)	SM (Army)	937	mTBI	ü	ü		ü		ü				
Vanderploeg 2015[40]	Florida National Guard (Survey)	SM (Branch not reported)	1,443	mTBI	ü		ü		ü		ü			
Wilk 2012[42]	Brigade Combat Teams (Questionnaire)	SM (Army)	1,502	mTBI	ü		ü							
Yurgil 2014[43]	Southern California infantry battalions (Interview)	SM (Marine Corps and Navy	1,648	87% mTBI, 1% unknown, 12% severity not reported	ü									
Baldassarre 2015[21]	VA Polytrauma Network Sites (Interview)	Veteran	396	mTBI	ü		ü		ü				ü	
Gaines 2016[27]	VA Clinics in California (Questionnaire)	Veteran	114	mTBI				ü						
Pietrzak 2009[37]	Connecticut Department of Veterans Affairs (Survey)	Veteran	277	mTBI	ü									

Author, year	Sample (Primary Data Source) or Site	Veteran or SM	Sample Size	mTBI or Unspecified TBI	PTSD		Depressive Disorders		Substance Use Disorders		Suicidal Ideation		Anxiety Disorders	
					P	S	P	S	P	S	P	S	P	S
Tsai 2012[39]	VA Hawaii Program Registry for OEF/OIF/OND (Survey)	Veteran	233	Concussion	ü				ü					
Carlson 2010[26]	VA Medical Centers and clinics in VISN 23 (Administrative data)	Veteran	11,828	TBI	ü		ü		ü				ü	
King 2017[30]	VA Medical Centers and clinics in upstate New York (Interview)	Veteran	291	TBI	ü	ü				ü				
Walker 2017[41]	VA Medical Center and 3 Military Bases (Interview and questionnaire)	Veteran & SM (1 Army base, 2 Marine Corps bases)	216	mTBI		ü		ü						
Subtotal (k=22)					**17**	**8**	**7**	**7**	**6**	**3**	**2**	**1**	**3**	**0**
TOTAL (k=33)					**24**	**9**	**14**	**7**	**12**	**4**	**3**	**1**	**7**	**0**

[a]Reported data separately for mTBI and moderate/severe TBI; only mTBI data included in this review

CTBIE=Comprehensive TBI Evaluation; EMED=Expeditionary Medical Encounter Database); mTBI=mild traumatic brain injury; P=Prevalence of Psychiatric Conditions; PTSD=posttraumatic stress disorder; S=Severity or Persistence based on Symptom Scores; SM=Service Members (active duty); TBI=traumatic brain injury; VISN=Veterans Integrated Service Network

PTSD

National Samples

Prevalence

Seven studies of Veterans reported PTSD prevalence (Table 2, Appendix C, Table 1).[11-14,18-20] There were no reports of PTSD prevalence in the studies of active duty service members. In 6 studies, the prevalence was based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes;[11-14,19,20] one obtained data from the checklist clinicians complete as part of the VA's Comprehensive Traumatic Brain Injury Evaluation (CTBIE).[18] All of the studies reported a higher prevalence of PTSD in individuals with a history of mTBI or TBI unspecified (Table 2). The percentage of individuals with a PTSD diagnosis in the history of TBI groups ranged from 63% to 77%; the percentage in the no-TBI groups ranged from 10% to 64% (moderate strength evidence, Table 3). In all but one study[19] the difference in prevalence between the TBI and no-TBI groups was at least 20%.

Severity/Persistence

One study of active duty service members also reported Posttraumatic Stress Disorder Checklist (PCL) scores (version not reported), an assessment of PTSD symptom severity, for the mTBI and no-TBI groups.[16] In the mTBI group, the mean scores were 20.3 for those with a blunt injury, 22.6 for those with a blast-related injury, and 24.3 for those with a combination of blast and blunt injury. The mean PCL score in the no-TBI group was 18.4. The authors noted that none of the scores met suggested cut scores for PTSD diagnosis (Appendix C, Table 1).

Geographically Diverse Samples

Prevalence

Seventeen geographically diverse studies reported prevalence of PTSD (Table 4, Appendix C, Table 2). Nine studies used PCL scores (5 PCL-M, 1 PCL-C, 1 PCL-17, 2 version not reported; cut points varied), 4 used Clinician Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (CAPS-IV) scores, 2 used ICD-9 codes, one used the Primary Care-Posttraumatic Stress Disorder (PC-PTSD) screen, and one used Post Deployment Health Assessment (PDHA) data to identify PTSD cases. Among the 12 studies of service members reporting PTSD prevalence, 9 found higher prevalence in the group with a history of mTBI.[22,25,29,33,34,38,40,42,43] Two studies reported similar prevalence in the history of mTBI and no-TBI groups, one based on PCL-M cut-off scores[36] and the other on ICD-9 codes.[35] One study reported mixed results. There was a similar prevalence of service members meeting criteria for PTSD (CAPS-IV) in the blast-related mTBI and blast-exposed control (no-TBI) groups but a higher prevalence in the mTBI groups (either blast-related or non-blast-related) compared to the non-blast exposed control group.[32] PTSD prevalence was reported in 5 of the 7 studies of Veterans – all reported higher prevalence in the groups with a history of mTBI[21,37,39] or TBI unspecified.[26,30]

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

Author, year Study Characteristics Study Period	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										
Kontos, 2013[16] N=22,203/mTBI Nov 2009-Dec 2011						↑				
Johnson, 2015[15] N=162,898/83% mTBI 2008-2010			↑ Alcohol ↑ Drug ↑ Both							
Adams, 2017[10] N=267,100/TBI FY 2008-2011			↑ Binge Drinking							
Macera, 2012[17] N=9,902/TBI 2008-2009		↑[a]								
VETERANS										
Pogoda, 2016[18] N=9,337/mTBI Oct 2007-June 2009	↑	↑	↔ Alcohol ↔ Drug		↔					
Seal, 2016[19] N=66,089/mTBI April 2007-May 2012	↑	↔								
Fonda, 2017[12] N=273,591/88% mTBI April 2007-Sept 2012	↑	↑	↑ Alcohol ↑ Other	↑ Attempted	↑					
Cifu, 2013[11] N=613,391/TBI FY 2009-2011	↑									

Author, year Study Characteristics Study Period	Prevalence					Severity/Persistence				
	PTSD	Depressive disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders	PTSD	Depressive disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
Grossbard, 2017[13] N=358,147/TBI 2012	↑	↑	↑ Alcohol ↑ Drug ↑ Tobacco		↑			↑ Alcohol		
Jaramillo, 2015[14] N=303,716/TBI FY 2010-2011	↑	↑								
Taylor, 2015[20] N=684,133/TBI FY 2014	↑	↑	↑ Substance ↑ Nicotine		↑					
TOTALS	**↑ 7**	**↑ 6 ↔ 1**	**↑ 5 ↔ 1**	**↑ 1**	**↑ 3 ↔ 1**	**↑ 1**		**↑ 1**		

↑=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

[a]Higher prevalence for TBI vs No TBI; difference was not significant for TBI Only (no PTSD) vs No TBI/No PTSD

FY=fiscal year; TBI=traumatic brain injury; mTBI=mild traumatic brain injury

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	· Risk of bias for these observational studies was generally moderate · Different measures and criteria for psychiatric conditions were reported. Severity of TBI often unspecified (based on ICD-9 code) · 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	· 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

Table 4. Prevalence and Severity/Persistence of Psychiatric Conditions in Veterans and Service Members with and without Deployment-related TBI – Geographically Diverse Samples

Author, year Study Characteristics	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										
Brenner 2010[22] N=1,247/mTBI	↑									
Bryan 2013 [23,24] N=158/mTBI				↑		↑	↑		↑	
Bryant 2015[25] N=685/mTBI	↑									
Heltemes 2011[28] N=3,123/mTBI			↔							
Hoge 2008[29] N=2,525/mTBI	↑ LOC ↑ AS	↑ LOC ↔ AS				↑ LOC ↑ AS				
MacDonald 2014[33] N=65/mTBI	↑	↔				↑	↔			
MacDonald 2014[32] N=178/mTBI	↔ Blast mTBI vs Blast/no TBI ↑ Non Blast mTBI vs Non Blast/no TBI					↔ Blast mTBI vs Blast/no TBI ↑ Non Blast mTBI vs Non Blast/no TBI	↔ Blast mTBI vs Blast/no TBI ↑ Non Blast mTBI vs Non Blast/no TBI	↔ Blast mTBI vs Blast/no TBI ↔ Non Blast mTBI vs Non Blast/no TBI		
MacDonald 2017[31] N=72/mTBI						↑	↑			

Author, year Study Characteristics	Prevalence					Severity/Persistence				
	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
MacGregor 2013[34] N=963/mTBI	↑	↑								
MacGregor 2010[35] N=762/mTBI	↔ mTBI vs Other Head Injury ↔ mTBI vs Non-Head Injury		↔ mTBI vs Other Head Injury ↔ mTBI vs Non-Head Injury		↔ mTBI vs Other Head Injury ↔ mTBI vs Non-Head Injury					
Mora 2009[36] N=110/mTBI	↔									
Polusny 2011[38] N=937/mTBI	↑					↑ mTBI vs no TBI/no PTSD ↔ mTBI/PTSD vs PTSD	↑ mTBI vs no TBI/no PTSD ↔ mTBI/PTSD vs PTSD	↑ mTBI vs no TBI/no PTSD ↔ mTBI/PTSD vs PTSD		
Vanderploeg 2015[40] N=1,443/mTBI	↑	↑	↑	↑						
Wilk 2012[42] N=1,502/mTBI	↑ LOC ↑ AOC	↑ LOC ↑ AOC								
Yurgil 2014[43] N=1,648/87% mTBI	↑ CAPS-IV ≥65 ↑ CAPS-IV 40-64									

Author, year Study Characteristics	Prevalence					Severity/Persistence				
	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
VETERANS										
Baldassarre 2015[21] N=396/mTBI	↑	↑	↑		↑					
Gaines 2016[27] N=114/mTBI							↑			
Pietrzak 2009[37] N=277/mTBI	↑									
Tsai 2012[39] N=233/Concussion	↑		↑							
Carlson 2010[26] N=11,828/TBI	↑	↑	↑		↑					
King 2017[30] N=291/TBI	↑					↑		↓		
SERVICE MEMBERS AND VETERANS										
Walker 2017[41] N=216/mTBI						↑ Baseline ↑ 12 months	↑ Baseline ↔ 12 months			
TOTALS	**↑14 ↔2 Mixed 1**	**↑5 ↔1 Mixed 1**	**↑4 ↔2**	**↑2**	**↑2 ↔1**	**↑6 Mixed 2**	**↑4 ↔1 Mixed 2**	**↓1 ↔1 Mixed 1**	**↑1**	**NR**

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

↓=Lower 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

AOC=alteration of consciousness; AS=altered state; CAPS-IV=Clinician Administered PTSD Scale for DSM-IV; LOC=loss of consciousness; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury; mTBI=mild traumatic brain injury

Severity/Persistence

Eight studies reported PTSD severity, 5 based on PCL[29,30,41] or PCL-Military Version (PCL-M)[23,24,38] total scores and 3 based on CAPS-IV scores.[31-33] Six studies, 4 enrolling active duty service members and 2 enrolling Veterans, found higher scores in the groups with a history of TBI of any severity or mTBI compared to no-TBI (Table 4, Appendix C, Table 2). One of these studies reported that higher mean PCL total scores (version not reported) in the history of mTBI group persisted at 12 months.[41] Two studies reported mixed results depending on the comorbidity or TBI etiology. Among service members with no probable PTSD assessed 1 year following deployment, Polusny et al. observed higher PCL-M scores for the group with a history of mTBI compared to the group with no history of TBI. Among service members with probable PTSD, the presence of a mTBI was not associated with greater severity of PTSD symptoms.[38] MacDonald observed higher CAPS-IV scores in service members with non-blast injury mTBI compared to the no-TBI group but similar scores for the blast injury mTBI group compared to the no-TBI group.[31]

Depressive Disorders

National Samples

Prevalence

The prevalence of depressive disorders was reported in 6 studies of Veterans[12-14,18-20] and one study of active duty service members (Table 2, Appendix C, Table 1).[17] As with the PTSD data, most prevalence information was obtained from ICD-9 codes. One study used 2 items from the Patient Health Questionnaire[17] and one used clinical report from the checklist embedded in the CTBIE.[18] Six studies reported a higher prevalence of depressive disorders in the history of mTBI or TBI unspecified groups (31% to 50%) than in the no-TBI groups (11% to 35%).[12-14,17,18,20] The differences in prevalence ranged from 5% to 37%. One of these studies noted that the prevalence of depressive disorders was similar in the TBI and no-TBI groups if the TBI group was limited to those with no PTSD but higher in the TBI with PTSD group compared to the no TBI and no PTSD group.[17] The remaining study found a similar prevalence of depressive disorder in Veterans with a history of mTBI (47%) or no-TBI (45%) (low strength evidence, Table 3).[19]

Severity/Persistence

None of the national sample studies reported severity or persistence of depressive disorders.

Geographically Diverse Samples

Prevalence

Seven geographically diverse sample studies reported prevalence of depressive disorders. Three studies of service members and 2 studies of Veterans reported higher prevalence of depressive disorders in the groups with a history of TBI unspecified[26] or mTBI[21,34,40,42] (Table 4, Appendix C, Table 2). The findings were based on the Patient Health Questionnaire – 9 item (PHQ-9),[40,42] the Post Deployment Health Reassessment (PDHRA),[34] Beck Depression Index-II (BDI-II),[21] and ICD-9 codes.[26] One study, based on Patient Health Questionnaire – 15 item (PHQ-15) scores found mixed results among service members with higher prevalence in those with a history of mTBI with a loss of consciousness compared to those with other injury (*ie*, injury with no loss of

consciousness or altered mental status) and a similar prevalence in those with a history of mTBI with altered mental status compared to those with other injury.[29] MacDonald found the prevalence of depressive disorders, based on MADRS scores, was similar in service members with and without a history of mTBI.[31]

Severity/Persistence

Four studies reported higher depressive symptom scores in the groups with a history of mTBI vs no-TBI (Table 4, Appendix C, Table 2). Two of these studies enrolled service members,[23,24,31] one enrolled Veterans,[27] and one enrolled both service members and Veterans.[41] They used different measures of depressive symptoms – the Behavioral Health Measures-20 item,(BHM-20)[23,24] the Montgomery-Asberg Depression Rating Scale (MADRS),[31] the BDI-II.[27] and the Center for Epidemiologic Studies Depression (CESD) scale.[41] One of these studies re-assessed outcomes at 12 months and found no difference between groups.[41]

Two other studies reported mixed results depending on comorbidity and TBI etiology. Consistent with what the same authors observed regarding PTSD severity, Polusny observed higher BDI-II scores for the mTBI group compared to the group with no history of TBI and no PTSD but similar scores when the group with comorbid mTBI and PTSD was compared to the PTSD only group.[38] MacDonald observed higher MADRS scores in service members with non-blast injury mTBI compared to the no-TBI group but similar scores for the blast injury mTBI group compared to the no-TBI group.[31] The last study observed no differences in MADRS scores among service members with and without a history of mTBI.[33]

Substance Use Disorders

National Samples

Prevalence

Two studies of active duty service members[10,15] and 4 studies of Veterans[12,13,18,20] reported on prevalence of substance use disorders in those with and without TBI unspecified[10,15 13,20] or mTBI[12,18](Table 2, Appendix C, Table 1). One study of service members presented data on self-reported binge drinking obtained from the PDHA. The rate of binge drinking was found to be higher in the group with TBI (28%) vs no-TBI group (19%).[10] The other study of service members reported prevalence values for alcohol use disorder, other drug use disorder, and combined alcohol and other drug use disorders obtained with ICD-9 codes.[15] The overall percentages for each of the 3 disorders were low (4% or less in the mTBI groups and 2% or less in the no TBI groups) with higher values consistently found for the mTBI group compared to the no TBI group.

The studies of Veterans reported data based ICD-9 codes[12,13,20] or the clinical report from the checklist embedded in the CTBIE.[18] Two[12,13] of 3 studies reporting alcohol abuse found higher prevalence in the mTBI or TBI unspecified groups (8% to 13%) compared to the no-TBI groups (4% to 11%); the third study, with data from the CTBIE, found similar prevalence of alcohol abuse in the mTBI and no-TBI groups.[18] In another study, substance use disorders (excluding nicotine dependence) were higher in the TBI group compared to the no-TBI group (38% vs 21%).[20] Substance-use disorder other than alcohol or tobacco[12] or drug abuse[13] were higher in the mTBI or TBI unspecified groups in 2 of the 3 studies reporting.[12,13] As with alcohol

dependence, the study with data from the CTBIE checklist found similar prevalence of drug abuse in the mTBI and no-TBI groups.[18] Tobacco abuse was higher in the TBI groups (25% in 2 studies) than the no-TBI group (14% to 19%) (low strength evidence, Table 3).[13,20]

Severity/Persistence

One study reported severity of alcohol misuse based on Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scores (Table 2, Appendix C, Table 1).[13] There was a higher percentage of moderate alcohol abuse (AUDIT-C of 5 to 7) and severe alcohol abuse (AUDIT-C of 8 to 12) in the TBI group. The percentages were 11% in the TBI vs 9% in the no TBI group for moderate alcohol abuse and 8% in the TBI vs 6% in the no TBI group for severe alcohol abuse.

Geographically Diverse Samples

Prevalence

Six studies reported prevalence of substance use disorders (Table 4, Appendix C, Table 2). Four studies found a higher prevalence of alcohol abuse in the groups with a history of TBI unspecified[26] or mTBI[21,39,40] compared to no TBI. Three of these studies enrolled Veterans[21,26,39] and one enrolled service members.[40] Outcomes were based on the AUDIT,[21,40] Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers (CAGE),[39] or ICD-9 codes.[26] Two studies, both based on ICD-9 codes, reported a similar prevalence of either alcohol abuse[28] or any substance disorder[35] in service members with and without a history of mTBI.

Severity/Persistence

Scores from measures of alcohol misuse were reported by 3 studies (Table 4, Appendix C, Table 2). King reported lower AUDIT-C scores in Veterans with a history of TBI compared to no-TBI although mean scores for both groups indicated potentially hazardous alcohol intake.[30] Polusny reported higher AUDIT scores for service members in the mTBI group compared to the group with no history of TBI and no PTSD but similar scores when the group with comorbid mTBI and PTSD was compared to the PTSD only group.[38] MacDonald reported that Michigan Alcohol Screening Test (MAST) scores were similar for service members who experienced a blast-related TBI, a non-blast related TBI, blast exposed controls, and non-blast exposed controls.[32]

Suicidal Ideation or Attempts

National Samples

Prevalence

None of the included studies reported on prevalence of suicidal ideation (insufficient evidence, Table 3). One study provided data on attempted suicides among Veterans defined using ICD-9 codes for suicide and self-inflicted injury recorded during an emergency department visit or hospitalization (Table 2, Appendix C, Table 1).[12] There was a greater prevalence in the Veterans with a history of TBI (0.5% vs 0.1%).

Severity/Persistence

No study reported scores from a measure that assesses suicidal ideation.

Geographically Diverse Samples

Prevalence

Two studies of active duty service members reported higher prevalence of suicidal ideation in the groups with a history of mTBI (Table 4, Appendix C, Table 2). Ideation was assessed using the Suicide Behaviors Questionnaire – Revised (SBQ-R)[23,24] or a single item from the PHQ-9 that asks frequency of experiencing "thoughts that you would be better off dead, or of hurting yourself".[40]

Severity/Persistence

One study reported higher scores on the SBQ-R in service members with a history of mTBI compared to no-TBI (Table 4, Appendix C, Table 2).[23,24]

Anxiety Disorders

National Samples

Prevalence

Four studies of Veterans reported prevalence of anxiety disorders other than PTSD (Table 2, Appendix C, Table 1).[12,13,18,20] Three studies, all using ICD-9 codes, reported higher prevalence of anxiety disorders in Veterans with a history of TBI unspecified[13,20] or mTBI[12] compared to no TBI. The prevalence in the TBI groups ranged from 17% to 31%; prevalence in the no-TBI groups ranged from 8% to 16%. The fourth study identified anxiety disorder using the clinical report from the checklist embedded in the CTBIE.[18] Prevalence of anxiety disorder was similar: 24% in the TBI group and 26% in the no-TBI group (low strength evidence, Table 3).

Severity/Persistence

No study reported scores from a measure that assesses anxiety disorders.

Geographically Diverse Samples

Prevalence

Two studies of Veterans found higher prevalence of anxiety disorders in those with a history of TBI unspecified[26] or mTBI[21] compared to no-TBI (Table 4, Appendix C, Table 2). The findings were based on the Beck Anxiety Index (BAI)[21] with scores of 8 and higher indicating mild to severe anxiety disorder and ICD-9 codes for anxiety disorders other than PTSD.[26]. A study of ICD-9 codes in active duty service members found similar prevalence of anxiety disorders including PTSD when the history of mTBI group was compared to a no-TBI head injury group and a non-head injury group.[35]

Severity/Persistence

No study reported scores from a measure that assesses anxiety disorders.

Summary of Findings

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. Four studies enrolled service members. It is unclear whether there is duplication of the samples across studies. All 7 of the national sample studies enrolling 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 mental health 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 compared to 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. 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. 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 in the mTBI or TBI unspecified vs the no-TBI groups. 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 and no-TBI groups. In geographically diverse samples, the prevalence of anxiety disorders 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 (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 and severe alcohol misuse in Veterans with a history of mTBI (insufficient evidence, Table 3).

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.

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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?

Overview of Studies - Randomized Controlled Trials

We found no randomized studies that evaluated the effectiveness of pharmacologic or behavioral therapies for the 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.

Overview of Studies - Non-randomized Studies

Seven non-randomized studies met eligibility criteria.[44-50] Three studies compared treatment of a psychiatric condition of interest in service members or Veterans with a history of TBI to treatment of those without a history of TBI.[44,47,48] Four studies exclusively explored treatments in service members or Veterans with a history of TBI.[45,46,49,50]

Six studies examined the effectiveness of behavioral therapies for PTSD, depressive, or anxiety disorders.[44,45,47-50] Most were pre-treatment to post-treatment studies; two were secondary analyses of RCTs.[44,48] Sample sizes ranged from 10 to 129. The studies included mostly Veterans, 78% to 100% male, with mean ages between 33 and 35 years and the majority Caucasian/white. Etiology of TBI and history of multiple TBIs were rarely reported. Additional population and study characteristics are presented in Appendix C, Table 4; outcomes are presented in Appendix C, Table 5. Risk of bias for these studies was mostly moderate-to-high (Appendix C, Table 6). Most of the studies did not assess or report treatment fidelity and independent outcome assessment was either not conducted or was unclear.

Hyperbaric oxygen therapy (HBO_2) was evaluated in one small, proof-of-concept, pre-post study enrolling 16 male service members and Veterans (mean age 30 years) with PCS and PTSD and a history of mild to moderate blast-related TBI (Appendix C, Tables 4 and 5).[46] Risk of bias was moderate (Appendix C, Table 6).

We report mean differences and effect sizes for pre- to post-treatment scores in groups with a history of TBI (Table 5) and effect sizes for the differences in mean change from baseline for studies reporting data for groups with a history of TBI and groups with no history of TBI (Table 6). The effect sizes should be interpreted with caution. In studies without a usual care or wait-list control group, it is difficult to assess the effect of the intervention. Strength of evidence for the treatment interventions is presented in Table 7.

Behavioral Therapies

Studies of Veterans with and without a History of TBI

One study included Cognitive Processing Therapy (CPT) and Prolonged Exposure Therapy (PE) groups.[47] The study was retrospective, using clinical data collected during routine pre- and post-treatment assessments. TBI status was obtained from medical records; severity could not be determined. Both CPT (n=10) and PE (n=9) significantly reduced PTSD symptoms in Veterans with a history of TBI as assessed with the PCL-S (Table 5). Improvements in symptoms of depression, assessed with the BDI-II, were significant only in the PE group. The effect sizes were large with wide confidence intervals (lower confidence limit crossing an ES of 0.5) (insufficient evidence, Table 7). Improvements in PTSD and depressive symptoms were similar in those with a history of TBI (n=19), compared to those with PTSD only (n=22), for the CPT group, the PE group, and when data from both groups were combined indicating that a history of TBI did not affect treatment outcome (Table 6).

Another study included Acceptance and Commitment Therapy (ACT) and Present Centered Therapy (PCT) groups.[44] The study was a secondary analysis (n=129) of a multisite RCT in male and female (22%) Veterans who met current criteria for at least one anxiety or depressive disorder (including PTSD) based on DSM-IV criteria.[44] The study included Veterans with a history of mild to moderate TBI (64%, n=83) and those with no TBI (36%, n=46). TBI was assessed using the Injury and Traumatic Stress clinical consortium TBI screen. Symptoms of depression and anxiety were assessed with the Brief Symptom Inventory-18 (BSI-18). A T-score ≥ 63 (raw scores converted to age- and gender-normed T-scores) was considered clinical elevation. The BSI-18 T-scores at baseline for participants with a history of TBI in the PCT and ACT groups were 73 and 75, respectively and were comparable to those without a history of TBI (73 for both groups). At the post-treatment assessment, there were statistically significant but modest reductions (<10 point improvements) in the BSI-18 observed for both therapies in Veterans with and without a history of TBI, indicating treatment response did not differ between the TBI and non-TBI groups, regardless of the intervention (Tables 5 and 6). TBI did not moderate or predict post-treatment outcomes (insufficient evidence, Table 7). This study also assessed quality of life. 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.

The third study was a post-hoc analysis of an RCT enrolling Veterans receiving either PE or PCT at a VA PTSD specialty clinic.[48] In 8 Veterans with PTSD and a history of mostly mild TBI receiving either PE or PCT, CAPS-IV scores were reduced from pre-treatment (Table 5) but the study did not report how many of the Veterans were in the PE or PCT groups, limiting interpretation of the effectiveness of the interventions (insufficient evidence, Table 7). There was no effect of TBI status when the Veterans with a history of mostly mild TBI (n=8) were compared to those with PTSD only (n=14).[48] Mean change in scores from pre- to post-testing was similar between groups and an effect of TBI was not found (Table 6).

Table 5. Results from Treatment Studies in Service Members or Veterans with a History of TBI

Author, year TBI severity Setting	Therapy Mean # sessions N	Measures	Pre-treatment Score, mean (SD)	Post-treatment Score, mean (SD)	Change from Pre-treatment, mean	Effect Size (ES) [95%CI] (Pre vs Post Treatment Scores)
Cognitive Processing Therapy (CPT) or Prolonged Exposure Therapy (PE)						
Ragsdale 2016[47] TBI severity unknown Outpatient	CPT 12 N=10	PCL-S	59.30 (12.09)	42.90 (13.84)	16.40	ES 1.21 [0.24 to 2.18]
		BDI-II	26.10 (11.10)	19.80 (15.02)	6.30	ES 0.46 [-0.43 to 1.35]
	PE 10 N=9	PCL-S	62.67 (11.35)	32.89 (15.98)	29.78	ES 2.05 [0.85 to 3.24]
		BDI-II	28.33 (15.22)	12.11 (14.56)	16.22	ES 1.04 [0.04 to 2.04]
Acceptance and Commitment Therapy (ACT) or Present Centered Therapy (PCT)						
Bomyea 2017[44] Mild to moderate TBI Outpatient	ACT NR[a] N=41	BSI-18	73.29 (8.48)	NR	<10 points	ES not estimable, graphed data only
	PCT NR[a] N=42	BSI-18	74.74 (7.73)	NR	<10 points	ES not estimable, graphed data only
PE Combined with PCT						
Sripada 2013[48] "Most" mTBI Outpatient	PE and PCT 10-12 N=8	CAPS-IV	82.4 (11.7)	45.5 (32.5)	36.90	ES 1.43 [0.29 to 2.56]
Cognitive Processing Therapy (CPT)						
Chard 2011[45] mTBI Residential (7 weeks)	CPT 14 N=28[b]	CAPS-IV	75.14 (5.85)	48.96 (22.29)	26.18	ES 1.58 [0.98 to 2.19]
		PCL-S	61.82 (10.32)	46.54 (16.11)	15.28	ES 1.11 [0.55 to 1.68]
		BDI-II	32.64 (10.71)	23.71 (10.98)	8.93	ES 0.81 [0.27 to 1.36]
Prolonged Exposure Therapy (PE)						
Wolf 2015[49] Mild-to-severe TBI 78% Outpatient 22% Inpatient	PE 9.5 N=69	PCL (version NR)	64.75 (10.10)	43.51 (16.81)	21.24	ES 1.52 [1.14 to 1.90]
		BDI-II	29.61 (9.49)	18.07 (12.62)	11.54	ES 1.03 [0.67 to 1.38]
Wolf 2012[50] 75% mTBI Outpatient	PE 13 N=10	PCL-M	69.2 (8.1)	38.0 (9.0)	31.20	ES 3.49 [2.00 to 4.98]
		BDI-II	34.4 (9.7)	17.7 (8.6)	16.70	ES 1.74 [0.68 to 2.81]

[a]Mean number of sessions completed in TBI group = 8.9 (not reported by intervention)
[b]Participants with a history of mTBI. An additional 14 had a history of moderate to severe TBI.
BDI-II=Beck Depression Inventory-II; BSI-18=Brief Symptom Inventory-18 Global Severity Index; CAPS-IV=Clinician-Administered PTSD Scale for DSM-IV; NR=not reported; PCL=PTSD Checklist; PCL-M=PTSD Checklist – Military Version; PCL-S=PTSD Checklist-Specific; PTSD=posttraumatic stress disorder; SD=standard deviation; TBI=traumatic brain injury

Table 6. Results from Treatment Studies in Veterans with a History of TBI vs No History of TBI

Study author, year N TBI severity	Measure	*History of TBI* Change from Pre-treatment mean (SD); n	*No History of TBI* Change from Pre-treatment mean (SD); n	Effect Size (ES) [95%CI] Based on mean change from baseline for each group
CPT, Veterans with TBI+PTSD vs PTSD only				
Ragsdale 2016[47] N=20 TBI severity unknown	PCL-S	16.40 (8.76); n=10	11.50 (14.14); n=10	ES 0.40 [-0.49 to 1.29]
	BDI-II	6.30 (7.92); n=10	6.80 (10.04); n=10	ES -0.05 [-0.93 to 0.82]
PE, Veterans with TBI+PTSD vs PTSD only				
Ragsdale 2016[47] N=21 TBI severity unknown	PCL-S	29.78 (13.65); n=9	34.58 (10.34); n=12	ES -0.39 [-1.26 to 0.49]
	BDI-II	16.22 (8.65); n=9	17.25 (10.38); n=12	ES -0.10 [-0.97 to 0.76]
CPT combined with PE, Veterans with TBI+PTSD vs PTSD only				
Ragsdale 2016[47] N=41 TBI severity unknown	PCL-S	22.74 (12.97) n=19	24.09 (16.74) n=22	ES -0.09 [-0.70 to 0.53]
	BDI-II	11.00 (9.52) n=19	12.50 (11.32) n=22	ES -0.14 [-0.75 to 0.47]
PCT, Veterans with TBI vs no TBI history				
Bomyea 2017[44] N=67/mild to moderate TBI	BSI-18	<10 points	<10 points	ES not estimable, graphed data only. No difference between groups
ACT, Veterans with TBI vs no TBI history				
Bomyea 2017[44] N=62/mild to moderate TBI	BSI-18	<10 points	<10 points	ES not estimable, graphed data only. No difference between groups
PE combined with PCT, Veterans with TBI+PTSD vs PTSD only				
Sripada 2013[48] N=22/"most" mTBI	CAPS-IV	36.90 (22.80)	37.00 (16.80)	ES -0.01 [-0.87 to 0.86]

ACT=Acceptance and Commitment Therapy; BDI-II=Beck Depression Inventory-II; BSI-18=Brief Symptom Inventory-18 Global Severity Index; CPT=Cognitive Processing Therapy; PCL-S=PTSD Checklist-Specific; PCT=Present Centered Therapy; PE=Prolonged Exposure Therapy; PTSD=posttraumatic stress disorder; SD=standard deviation; TBI=traumatic brain injury

Table 7. 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	· 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	· One small pre- and post-study, moderate risk of bias · Improvement in PTSD symptom scale
Pharmacological	0	Insufficient	· No studies identified

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

Studies of Service Members or Veterans with a History of TBI

One study evaluated a VA TBI-PSTD residential program that incorporated Cognitive Processing Therapy (CPT-Cognitive) in 28 mostly combat Veterans (89%) with a history of mTBI.[45] The Veterans met criteria for PTSD according to the CAPS-IV. Over one half (57%) had a PTSD service-connected disability. Over 7 weeks, with a mean of 14 sessions, CAPS-IV and PCL-S scores improved significantly from the pre-treatment assessment with better improvement observed with CAPS-IV (Table 5). Symptoms of depression, based on the BDI-II, were also improved compared to pre-treatment (insufficient evidence, Table 7).

A larger study (n=69) evaluated Veterans (74%) and active-duty personnel with PTSD and a history of TBI receiving outpatient (78%) and inpatient Prolonged Exposure (PE) therapy as part of routine clinical care at 2 VA medical centers.[49] TBI severity was mixed, with 75% mild and 25% moderate to severe. Blast accounted for 51% of the TBIs and the mean number of reported TBIs was 2.8. Diagnosis of PTSD was confirmed by a psychiatrist or psychologist following a positive screen. Over an average of 9.5 sessions, PE therapy was found to improve both PTSD and depressive symptoms with ESs of 1.52 [95%CI 1.14 to 1.90] and 1.03 [95%CI 0.67 to 1.38] for the PCL (version not reported) and the BDI-II, respectively (Table 5). Among the 44 Veterans who completed therapy, these improvements were even greater. Clinically significant changes based on cut-off scores and reliable changes in points were established for both scales. Clinically significant change in symptom severity for the PCL, defined as a pretreatment score of at least 50 points that changed to a score of 49 points or lower and a reliable change of at least 10 points, was achieved by 61% (n=42) of the all the participants and 86% of those who completed

therapy. Clinically significant change for the BDI-II, defined as a pretreatment score of at least 15 points that changed to a score of 14 points or lower and a reliable change of at least 5 points, was achieved by 45% of the 69 participants and 55% of the completers (insufficient evidence, Table 7).

An earlier study by Wolf examined 10 male Veterans diagnosed with PTSD with a history of mild/moderate TBI who received outpatient PE therapy.[50] Over an average of 13 sessions, PE therapy was also found to improve both PTSD and depressive symptoms (Table 5). Clinically significant change was also examined, based on cutoff values halfway between the clinical and nonclinical normative samples on both the PCL-M and BDI-II. Changes in symptom severity were clinically significant if the score changed from above the cutoff pretreatment to below the cutoff posttreatment. Posttreatment scores below 49.5 and 14.9 were identified as clinically significant for the PCL-M and BDI-II, respectively. Based on these thresholds, 9 participants (90%) had clinically significant change and no longer met criteria for PTSD. For the BDI-II, 4 participants (40%) had scores below 14.9 post-treatment, indicating clinically significant reduction in depressive symptoms (insufficient evidence, Table 7).

Hyperbaric Oxygen Therapy

One pre-post proof of concept study (n=16) evaluated the impact of HBO_2 therapy on PCS and PTSD in male participants with a history of mild to moderate TBI characterized by loss of consciousness due to blast injury (Appendix C, Tables 4 and 5).[46] Eight of the men were active duty and the other 8 were Veterans. Mean number of TBIs due to blast was 2.7. All participants met DSM-IV criteria for PTSD; 15 participants met the PCL-M threshold (≥50) for PTSD. The participants were treated with 1.5 HBO_2 atmospheres absolute until 40 sessions were completed over a 29-day period. At the post-treatment assessment, pre-treatment scores for PCL-M were reduced from 67 to 47, with an ES of 1.5 [95%CI 0.6 to 2.3] (insufficient evidence, Table 6). 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.

Summary of Findings

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 behavioral therapies 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 (HBO_2) 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 and no studies reported on the effect of pharmacological interventions for the psychiatric conditions of interest in service members or Veterans with and without a history of mTBI.

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 behavioral therapies 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. CPT and 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 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 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. Mental health component scores improved significantly in both treatment groups; physical health component scores did not. 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 psychological intervention exceeded minimal clinically important differences (MCIDs) reported for the PCL-M (5-10 points)[51-53] and CAPS-IV (10 points).[53,54] Similarly, observed changes in depressive symptom scores exceeded the MCID reported for the BDI-II (17.5% reduction from baseline).[55] 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 (Table 7).

One small, pre-post, uncontrolled, proof-of-concept study of HBO_2 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, Table 7). 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.

SUMMARY AND 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 OF FINDINGS TO THE VA POPULATION

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 behavioral therapy interventions. We included one uncontrolled, preliminary report of HBO_2 for service members with a history of TBI and PTSD. Other reviews have looked at HBO_2 in service members with a history of TBI and persistent postconcussion symptoms.[56] The etiology of postconcussion symptoms remains uncertain and we did not include these studies in our review because the treatment was not directed at one of the 5 psychiatric disorders that were the focus of our review.

LIMITATIONS

Our review identified several limitations in the research. Studies of psychiatric condition prevalence and severity and their association with mTBI are potentially limited by case-ascertainment and data collection methods. Much of the data from the nationally representative samples and a portion of the data from the geographically diverse samples were from electronic administrative databases. As a result, TBI severity was not always available. Additionally, a wide range of outcome measures were 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.[57]

No randomized controlled trials evaluated the effectiveness behavioral therapies 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. Most studies used pre-post designs and enrolled small sample sizes. Not all of the studies included a group with a history of mTBI and a no-TBI control group. 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.

For both Key Questions, the timing of the mental health evaluation or treatment relative to the TBI was rarely documented. Few studies reported the number of TBIs or the TBI etiology. There is evidence of increased risk of major depressive disorders, anxiety disorders, and PTSD associated with experiencing more than one mTBI.[40]

RESEARCH GAPS/FUTURE RESEARCH

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)[58-61] 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.

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APPENDIX A. SEARCH STRATEGIES

Table 1. Ovid (MEDLINE) Search Strategy

	Search Terms
1	exp Veterans/
2	veteran$.mp.
3	exp Veterans Health/
4	(active duty or military or service member$ or soldier$ or national guard or reserv$).mp.
5	1 or 2 or 3 or 4
6	exp Iraq War, 2003-2011/
7	exp Afghan Campaign 2001-/
8	(Operation Enduring Freedom or Operation Iraqi Freedom or Operation New Dawn).mp.
9	6 or 7 or 8
10	5 or 9
11	(TBI or mTBI or traumatic brain injur$).mp.
12	exp Brain Injuries, Traumatic/
13	((mild adj2 traumatic) or (m adj2 TBI) or (mild adj2 TBI)).mp.
14	11 or 12 or 13
15	10 and 14
16	exp Stress Disorders, Post-Traumatic/
17	(((post-traumatic or posttraumatic) adj2 stress) or PTSD).mp.
18	exp Depressive Disorder/ or exp Depressive Disorder, Treatment-Resistant/ or exp Depressive Disorder, Major/
19	depression.mp.
20	exp Substance-Related Disorders/
21	suicide.mp. or exp Suicide/ or exp Suicide, Attempted/
22	exp Suicidal Ideation/
23	exp Anxiety Disorders/

24	((problem adj2 (alcohol or drink$ or drug$ or substance)) or (substance adj2 abuse) or (substance adj2 disorder) or ((alcohol or drug or tobacco) adj2 (abuse or addiction or disorder))).mp
25	(general adj2 anxiety).mp.
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27	15 and 26
28	limit 27 to (English language and humans and yr="2000 -Current")

Table 2. PsycINFO Search Strategy

1	exp Military Personnel/ or exp MILITARY VETERANS/ or Veteran$.mp.
2	(soldier$ or "service member$" or "national guard" or "active duty" or reserves).mp.
3	exp Military Deployment/
4	exp Combat Experience/
5	(Operation Enduring Freedom or Operation Iraqi Freedom or Operation New Dawn).mp.
6	exp Traumatic Brain Injury/
7	("traumatic brain injur$" or TBI or mTBI).mp.
8	1 or 2 or 3 or 4 or 5
9	6 or 7
10	8 and 9
11	posttraumatic stress disorder.mp. or exp Posttraumatic Stress Disorder/
12	exp Major Depression/ or depressive disorder.mp.
13	depression.mp.
14	exp Treatment Resistant Depression/
15	exp "Substance Use Disorder"/ or exp Drug Abuse/
16	problem drinking.mp. or exp Alcohol Abuse/
17	("substance abuse" or "substance disorder" or "tobacco abuse").mp.
18	suicidal ideation.mp. or exp Suicidal Ideation/
19	exp ATTEMPTED SUICIDE/ or exp SUICIDE/ or Suicide.mp.
20	exp Anxiety Disorders/ or exp Generalized Anxiety Disorder/ or anxiety.mp.

21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	10 and 21
23	limit 22 to (human and English language and yr="2000 -Current")

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Question Text	Reviewer Comment	Author Responses
1) Are the objectives, scope, and methods for this review clearly described?	Yes	Thank you.
	Yes	
	Yes	
	Yes	
	Yes	
	No: Concerned about: Key question 1: suicide attempt and death not being included; key question 2: efficacy not explored	Please see responses under Question 4) below.
2) Is there any indication of bias in our synthesis of the evidence?	No	Thank you.
	No	
	No	
	No	
	No	
	No	
3) Are there any published or unpublished studies that we may have overlooked?	No	
	Yes - The report lists only 1 study that examined HBOT for combat-associated TBI and PTSD. The study cited is uncontrolled and not worthy of inclusion while there are results from the 3 military HBOT trials that examine an effect in PTSD. These are RCT's and worthy of discussion.	The military HBOT trials included service members with a history of TBI and persistent postconcussion symptoms, not PTSD. Our KQ2 was focused on whether treatments for 5 specific psychiatric conditions are effective in individuals who have both the condition and a history of TBI or does the presence of a TBI history limit or moderate treatment effectiveness. Therefore, the military HBOT studies would not have been eligible because participants did not have one of the 5 pre-defined psychiatric conditions of interest for our review. We clarified in the Introduction that the focus of our review is on the specific psychiatric conditions.
	No	
	Yes - The authors say there have been no RCTs of treatment for mental health conditions in TBI. However, there are three that reported PTSD Checklist outcomes following HBOT: Miller, Cifu,	Please see the comment above regarding eligibility of these trials. We reviewed the Portland ESP Evidence Brief on HBOT and cite the report in the

Question Text	Reviewer Comment	Author Responses
	and Wolf. Overall, I think the section on treatment could benefit from discussion with the Portland ESP center that did the recent review on HBOT. That review also cites a 4th RCT that was published only as a conference proceeding.	Discussion section. We also modified the statements about no RCTs of treatment to specify the psychiatric conditions of interest for our review.
	No	
	No	
4) Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	Adequate to outstanding	Thank you.
	1) The introduction cites that there is an increase in TBI in wars as a result of improvements in IEDs - is this actually true or simply a continuation of the myth of OEF/OIF? There were significant percentages of TBI in WWII and Vietnam that were unreported, but likely higher than OEF/OIF given the numbers of troop involved, the amount of large ammunition utilized and the high rate of mines/IEDs (in Vietnam). Since >50% of all the TBI's in OEF/OIF were related to motor vehicle trauma, this would seem to be important to emphasize, not include as an afterthought. 2) I don't believe the use of the term "psychiatric" disorders and diagnoses is the preferred adjective and would prefer either mental health or psychologic diagnoses/disorders, 3) While it may be a premise of this review, I'm believe that the overwhelming majority of TBI clinicians actually feel that the standard treatments for mental health conditions are safe and effective even in the face of a TBI (given their practice patterns). Again, I am concerned with this report spreading the same misleading myths that the DoD (and certain researchers) have perpetuated. Clinicians that I work with feel comfortable with these treatments, and this review was an attempt to support that practice.	1) We appreciate the reviewer's comments. We modified the introduction in both the Executive Summary and full report. 2) In accordance with the Diagnostic and Statistical Manual of Mental Disorders we choose to use the term psychiatric disorders. 3) The purpose of our review was to identify and report on the evidence. We do not make recommendations for treatment. At present, there is limited evidence on which clinicians can base treatment decisions.
	Please remove all text and table occurrences, as well as the reference for the Harch Hyperbaric oxygen study.	We have added text to emphasize that this is a small, uncontrolled, pre-post study. However, it does meet our eligibility criteria and therefore it would be selective reporting were we to remove it.
	The review is well done in many ways, so these comments are meant to help strengthen a good report. 1. In the reviews of prevalence, to what extent is there a problem with the same VA admin data being used in different studies. The data included in two studies focused differently enough to be	Thank you. 1. There is clearly overlap. "Study Periods" are reported in column one of Table 2 and in the description of the Sampling Method in Appendix C,

Question Text	Reviewer Comment	Author Responses
	independent papers could still be non-independent, but appear as two different studies. This would be a much greater problem in meta-analysis in which the Ns were being used for weighting, but it is also a potential problem here in the sense that there may appear to be more supportive evidence than is actually the case if the same people are contributing to findings across studies. 2. As mentioned specifically in response to the question about excluded studies, I believe there are 3 or 4 excluded RCTs of HBOT. The failure to include the RCTs seems to have resulted in a misstatement about the evidence for HBOT, e.g., p. 10. I cannot see how the inclusion/exclusion criteria would have led to these studies being excluded. If the criteria in fact are responsible, this is a more significant problem. 3. Should RCTs that examined TBI status as an effect modifier be summarized differently than studies that simply compare TBI/no TBI in a pre-post design? 4. P. 12, although 10 points on the CAPS-IV has been validated in multiple studies (e.g., Schnurr & Lunney, 2016), 8 points on the PCL is not an agreed-upon MCID for the PCL. Monson et al (2008), for example, found 10 points to be a good number, and Shiner et al. (2011) found 5 points to be a good number. 5. Is the method of PTSD assessment (clinical admin diagnosis, structured clinical interview, self-report) important in its relation to outcome? 6. On p. 12, the suggestion to create further study fails to account for ongoing longitudinal studies that could be used to answer important questions TBI and its comorbidities. These studies include the Neurocognition Deployment Health Study (Vasterling), VALOR (Marx & Keane), Mil Cohort Study, and the Marine Resiliency Study. 7. P. 15, re the possible reasons for the comorbidity of PTSD and TBI, one additional one is that the same event that could cause a TBI could cause PTSD. I think this is the view that is more predominant in the field.	Table 1. The population-based studies provide information on the population of VA users within the identified time period (*ie*, the VA as a population rather than a sample). We comment on the overlap in the Executive Summary and full report. 2. Please see note above regarding the exclusion of these studies. We also clarified the Study Selection sections in the Executive Summary and full report. 3. The text and tables for Key Question 2 have been rearranged to emphasize the studies with TBI as an effect modifier. 4. Thank you for this information. We modified the statement about the PCL to include a range of values and added the suggested citations to the full report. 5. Yes. We now describe the method of assessment for all of the mental health outcomes with greater detail on the Appendix tables. 6. Thank you for the suggestion. We added this information In the Discussion/Future Research sections of the Executive Summary and full report. 7. We modified the Introduction to remove information about reasons for the comorbidity of PTSD and TBI given that this is not the focus of our review.

Question Text	Reviewer Comment	Author Responses
	Overall, I found this to be an excellent review of the current literature relating mTBI to mental health conditions, including, PTSD, depression, substance abuse, anxiety disorders and suicidal ideation (attempt). I found the criteria for inclusion of the studies to be sound and feel that the literature assembled accurately represents the literature.	Thank you.
	As a general comment, I question the use of the phrase “combat-deployed mTBI”. There is no other kind of combat TBI if not incurred during deployment. If this phrase is to refer to either combat-related mTBI OR deployment-related mTBI, I would simply use the latter phrase (deployment-related, as it is almost never specified if the injury was incurred in a combat situation).	We replaced “combat-deployed” with deployment-related. Our study inclusion criteria required that at least 75% of the TBIs were experienced while deployed (not necessarily in a combat role).
	Also, where specific clinical assessment scores are reported, especially for PTSD (CAPS or PCL), it would be helpful to note whether the assessment was for the DSM IV or 5 diagnostic criteria. The scores are not comparable (e.g., scores on CAPS IV ≠ CAPS 5), so it is important to note from which they are derived so the score you report can be put into the proper context.	We verified that all references to the CAPS or PCL include the version (if reported).
	The following are both editorial and content suggestions throughout the manuscript:	
	1. Page 1: The paragraph beginning “The focus of our review”. I would suggest that the fact that the review is focused on mTBI be moved up to the first paragraph and the methodology for presuming mTBI in studies where the severity of the TBI is unspecified be explained only in the methods section. The rationale for this decision as described in this paragraph is unclear.	1) We revised the Introduction in the Executive Summary and the full report. We agree with including the details of study selection in the Methods section.
	2. Page 2, first paragraph. I assumed that the outcomes were for current diagnoses, meaning that the Veterans and SM included in the studies had active psychological conditions.	2) Yes,
	3. Page 2 Study Selection. I tried to follow the inclusion and exclusion criteria reported here with the flow diagram on page 20 (this is also the case for the main study description). The n’s reported for the various exclusions noted in the figure do not match up with the actual exclusionary criteria. There are more exclusionary criteria on Page 20 than are noted on Page 2. Also,	3) Thank you for pointing this out. We revised the descriptions of the Inclusion and Exclusion criteria in the Executive Summary and main report. They now are aligned with Figure 1.

Question Text	Reviewer Comment	Author Responses
	on Page 3, it would be helpful if paragraph beginning on Line 30 describing the exclusions referred to the figure on page 20.	
	4. The Executive Summary Tables (page 6 & 9) should use the same legends (page 9 more informative).	4) We made the suggested change.
	5. Page 7 Executive Summary Table 2. Under the comments section, 2nd bullet, “Type of TBI”. Should this be severity of TBI? Type can be confused with etiology.	5) Thank you – we meant severity.
	6. Page 8 Line 12. I do not think that “one reporting similar severity in the groups with a history of mTBI and no TBI” is reported in Table 3.	6) This was an error on Table 3 – now corrected.
	7. Page 11 Line 50 insert either “combat” or “deployment-related” between that and mTBI.	7) We added ”deployment-related”.
	8. Page 12 Line 10. “changed” should be “changes”.	8) This has been corrected
	9. The important issue of reintegration is first mentioned on Page 11 in the discussion. It feels like it comes out of the blue there because it has not been motivated prior to this. I would suggest moving the issue of reintegration to Page 12 in the Research Gaps/Future Research section. It is critically important that no studies to date have looked at this issue and the need for treatment studies to include this as an outcome measure should be stressed.	9) Thank you for the suggestion. We deleted the mention of reintegration in the Discussion section and added to the Research Gaps/Future Research section that outcomes should include both functioning and quality of life measures in addition to symptom measures. Reintegration reflects both functioning and quality of life (and more), but in a very specific population during a set period of time. Also, only one study looked at mental health quality of life, so we need more information in this area.
	10. Page 16, Line 45. It doesn’t make sense to have Timing be “Any time post-TBI” because the studies include non-TBI. I am not sure where that time point should be anchored (post-deployment?).	10) We agree and changed “Timing” to post-deployment
	11. Page 17, Line 35. “abstract” should be “abstracts” and “were” should be inserted between that and eligible (on next line).	11) We corrected this sentence.
	12. Page 18, again the exclusion criteria do not follow information on Page 20.	12) As noted above, we revised the text to align with Figure 1
	13. Thought the tables reporting the Prevalence and Severity data were great.	13) Thank you
	14. Page 36. Sentence on Line 54 is incomplete. “The rate of binge drinking….”	14) We corrected this sentence.
	15. Page 39 there is reference again to assessment of health status at “varying times post injury”. Relating #10 above.	15) We changed this to post-deployment.
	16. Page 40. I believe there should be a reference to Figure 2 in the paragraph describing findings for CPT.	16) Thank you – we modified the KQ2 text and this figure is no longer included.

Question Text	Reviewer Comment	Author Responses
	17. Page 51-52. Here I feel that you take a step back in the innovation department by simply referring back to current VA/DoD guidelines for the management of PTSD and the other comorbidities, given the limited evidence on the effectiveness of treatments for mental health conditions. These guidelines don't take advantage of what has been learned through this review. Given that this is the discussion section, I would much rather see some thoughtful, albeit speculative, recommendations regarding the treatment of the common comorbidities. I also don't believe that TBI should be listed here as a mental health condition because it is the base condition forming the comorbidities as far as this report is concerned.	17) Thank you for the suggestion. We removed the section on the VA/DoD guidelines. We comment that the studies showed no indication of harms for evidence-based treatments for treatment of PTSD in service members and Veterans with and without a history of TBI.
	1) Summaries in executive summary do not sufficiently couch findings in the context of risk of bias findings. At times findings seem to stray from key questions - particularly pertaining to Key Question 2 2) Was there a reason why suicide attempts or death were not included in key questions? (this seems like a major weakness) - nonetheless some data is reported on SA (pg. 5) - this is confusing 3) Some concern re: inclusion of up to 25% moderate to severe - as results could certainly be skewed - same with those in which % were not reported 4) Further articulation of the purpose of the studies included - Key Question #1 (particularly if it was not to measure prevalence) would be useful 5) In terms of Key Question 1 - would be helpful to report throughout if symptoms reported were above clinical cutoffs - see page 5 final bullet (line 46) - this is great 6) In terms of Key Question 2 - would be helpful to report throughout if symptoms were "clinically significant" a. Why was simple efficacy not explored?	1) We modified summary paragraphs in the Executive Summary and moved the strength of evidence tables closer to the summary text. 2) Suicidal ideation was identified by the operational partners as the psychiatric condition of interest for the review. One study reported suicide attempts so we did extract and include that outcome. A review of studies excluded from our review did not find additional reports of "attempts." 3) Studies typically enroll a mixed population and in evidence reviews we often use 75% as the threshold. Had we required strict reporting of 100% mTBI, we would have few, if any, eligible studies. 4) We noted this in the Overview of Studies for Key Question 1. 5) In Appendix C, Tables 1 and 2 we provide information on clinical cut-offs from the KQ1 studies although we note that there is disagreement on clinical cut-offs. 6) In Appendix C, Table 5 we provide information on clinical cut-offs for the KQ2 studies. a. We considered the included studies to be "effectiveness" studies – evaluating the interventions in "real world" settings. We did not

Question Text	Reviewer Comment	Author Responses
	b. Would suggest that the lack of RCTs needs to be further emphasized 7) Believe that the word effectiveness is used when efficacy would likely be more correct (see page 10) a. same page - term TBI status is confusing 8) Unclear why the team included outcome associated with negative psychiatric outcomes (page 11) - Pugh 2018 9) With low to no evidence - unclear how team can suggest that therapies are effective and safe - page 11 (this seem like a major weakness) 10) Tables are useful; however, would suggest adding citations in those where they are not provided 11) Research gaps - what other models besides cohort might be appropriate?	exclude any studies of interventions based on whether they were efficacy or effectiveness studies. b) We note the need for RCTs in the Discussion and Future Research sections. 7) We believe that effectiveness is correct – the studies are testing efficacy in “real world’ settings a) We modified and rearranged these statements. We replaced TBI status with “history of TBI” 8) We removed the text referred to in this comment. 9) We modified the Discussion and Applicability section but note that we did find clinically significant differences in outcomes and no reported harms. 10) Thank you. Citations are added in the final report version. 11) We noted that existing registries may contain relevant information.

APPENDIX C. EVIDENCE TABLES

Table 1. Prevalence and/or Severity of Psychiatric Conditions – National Samples (KQ1)

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Adams, 2017[10] National, data from the Substance Use and Psychological Injury Combat Study National Institute of Drug Abuse (NIDA) Sampling method: Subsample of Army active duty members who completed both initial and follow	Sample size: 267,100 (TBI: 19,240, No TBI: 247,860) Mean age: NR, 46% age 17-24 y, 24% age 25-29 y, 23% age 30-39 y, 6% age 40+ y Male (%): 90 Race/ethnicity (%): White, non-Hispanic 53; Black, non-Hispanic 18; Asian/Pacific Islander 15; American Indian/Alaskan Native 1, Hispanic 11 Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: self-report	**PTSD**	NR	NR	NR	NR
		Depressive Disorders	NR	NR	NR	NR
		Substance Use Disorders, frequent binge drinking	PDHRA (6+ drinks per occasion) 28% (5312/19,240) *TBI only (by gender*) 26% M/8% F *TBI+mental health problems* 34% M/16% F	PDHRA (6+ drinks per occasion) 19% (47,478/247,860) *Mental health problems only (by gender)* 29% M/12% F *No TBI or mental health problems* 20% M/7% F	NR	NR
		Suicidal Ideation	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
up questionnaires (DoD post-deployment heath surveillance program FY2008-2011)	Multiple TBI: NR TBI etiology: NR Eligibility: OEF/OIF service members who completed questionnaires within 30–300 days of the end date of deployment (>90% within 3–9 months)	**Anxiety Disorders**	NR	NR	NR	NR
Cifu, 2013[11] National VA HSR&D Sampling method: VA FY2009-2011 National Patient Care Database	Sample size: 613,391 (TBI: 58,885 "majority likely mild", No TBI: 554,506) Mean age: 32 Male (%): 88 Race (%): White 58, non-White 20, unknown 22 Ethnicity (%): Hispanic 10, non-Hispanic 71, unknown 19 Time since TBI: NR	**PTSD**	ICD-9 76% (44,777/58,885)	ICD-9 24% (135,559/554,506)	NR	NR
		Depressive Disorders	NR	NR	NR	NR
		Substance Use Disorders	NR	NR	NR	NR
		Suicidal Ideation	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
	Time since discharge: NR Method of TBI diagnosis: unclear, captured TBI diagnoses at any point in medical care received at a VA facility Multiple TBI: NR TBI etiology: NR Eligibility: OIF/OED/OND Veterans, diagnosed with TBI, PTSD, and/or common head, neck, or back pain (by ICD-9-CM codes) and receiving inpatient or outpatient VHA care	**Anxiety Disorders**	NR	NR	NR	NR
Fonda, 2017[12] National Study performed without financial support Sampling method: National VA electronic	Sample size: 273,591 (TBI: 42,392 mild 88%, No TBI: 231,199) Mean age: 29 Male (%): 84 Race/ethnicity (%): White 65, Black 14, Unknown/missing 16 Time since TBI: NR Time since discharge: NR	**PTSD**	ICD-9 63% (26,781/42,392)	ICD-9 10% (22,365/231,199)	NR	NR
		Depressive Disorders	ICD-9 Mood Disorder 31% (13,068/42,392)	ICD-9 Mood Disorder 12% (27,362/231,199)	NR	NR
		Substance Use Disorders	ICD-9 *Alcohol* 13% (5,631/42,392) *Other* 7% (2,739/42,392)	ICD-9 *Alcohol* 4% (8,894/231,199) *Other* 2% (4,462/231,199)	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
medical records databases April 2007-September 2012	Method of TBI diagnosis: VA CTBIE Multiple TBI: NR TBI etiology: blast 74%, other injuries 47%, motor vehicle accidents 40%, falls 39% Eligibility: US Veterans deployed in support of OEF/OIF/OND after 9/11/2001; received VA health care 4/2007 to 9/2012, aged 18–40 years at time of first VA care *Excluded* diagnoses of bipolar disorder; schizophrenia or related psychiatric disorder (except psychosis due to trauma-related hallucinations); inconclusive TBI data	**Suicidal Ideation**	ICD-9 Attempted Suicide[d] 0.5% (227/42,392)	ICD-9 Attempted Suicide[d] 0.1% (318/231,199)	NR	NR
		Anxiety Disorders	ICD-9 17% (7,326/42,392)	ICD-9 8% (17,728/231,199)	NR	NR
Grossbard, 2017[13] National VA PTBRI QUERI, VA Center of	Sample size: 358,147 (TBI: 30,197 % mild NR, No TBI: 327,950) Mean age: NR, 35% <30 years, 33% 30-39 years, 32% ≥40 years Male (%): 87	**PTSD**	ICD-9 73% overall (22,107/30,197) 74% M/64% F	ICD-9 33% overall (106,752/327,950) 34% M/26% F	NR	NR
		Depressive Disorders	ICD-9 43% overall (13,047/30,197) 43% M/52% F	ICD-9 26% overall (85,382/327,950) 25% M/33% F	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Excellence in Substance Abuse Treatment and Education, VA Clinical Sciences R&D Career Development Award, and National Institute on Alcohol Abuse and Alcoholism Sampling method: VA Corporate Data Warehouse, 2012	Race (%): Black 16, White 68, missing 11 Ethnicity (%): Hispanic 11, non-Hispanic 82, missing 7 Time since TBI: NR Time since discharge: NR Method of TBI diagnosis: unclear (ICD-9 code in medical record); TBIs diagnosed outside VA and not documented in medical record were not captured Multiple TBI: NR TBI etiology: NR Eligibility: Veterans age ≥18; received alcohol screening (AUDIT-C) in 2012, documented OEF/OIF service (VA Decision Support System), used outpatient or inpatient VA services (≥1 visit) in year before AUDIT-C	**Substance Use Disorders**	ICD-9 *Alcohol (AUDIT-C ≥5)* 19% overall (5,879/30,197) 20% M/11% F *Drug* 12% overall (3,570/30,197) 12% M/6% F *Tobacco* 25% overall (7,660/30,197) 26% M/16% F	ICD-9 *Alcohol (AUDIT-C ≥5)* 11% overall (34,473/327,950) 11% M/5% F *Drug* 5% overall (17,389/327,950) 6% M/3% F *Tobacco* 19% overall (60,899/327,950) 19% M/13% F	Moderate alcohol misuse (AUDIT-C 5-7) 11% overall (3,387/30,197) 12% M/5% F Severe alcohol misuse (AUDIT-C 8-12) 8% overall (2,516/30,197) 9% M/2% F	Moderate alcohol misuse (AUDIT-C 5-7) 9% overall (30,684/327,950) 10% M/4% F Severe alcohol misuse (AUDIT-C 8-12) 6% overall (18,291/327,950) 6% M/2% F
		Suicidal Ideation	NR	NR	NR	NR
		Anxiety Disorders	ICD-9 26% overall (7,994/30,197) 26% M/32% F	ICD-9 16% overall (53,549/327,950) 16% M/19% F	NR	NR
Jaramillo, 2015[14] National	Sample size: 303,716 (TBI: 42,520, No TBI: 261,196)	**PTSD**	ICD-9 77% (32,800/42,520)	ICD-9 33% (85,951/26,1196)	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
VA HSR&D Sampling method: 1) Identified individuals deployed in Afghanistan or Iraq using the OEF/OIF roster file 2) Selected Veterans who received care at VA in FY2010 and FY2011 3) Linked inpatient and outpatient data	Mean age: 35 Male (%): NR Race/ethnicity (%): NR Time since TBI (days): NR Time since discharge: NR Method of TBI diagnosis: ICD-9 codes Multiple TBI: NR TBI etiology (%): NR Eligibility: received inpatient or outpatient care at least once each year	**Depressive Disorders**	ICD-9 50% (21,259/42,520)	ICD-9 28% (73,195/26,1196)	NR	NR
		Substance Use Disorders	NR	NR	NR	NR
		Suicidal Ideation	NR	NR	NR	NR
		Anxiety Disorders	NR	NR	NR	NR
Johnson, 2015[15] National Funding NR	Sample size: 162,898 (TBI: 11,122 mild 83%, No TBI: 151,776) Mean age: NR, 47% age 17-24 y, 21% age 25-29 y, 22% age 30-39 y, 9% age 40+ y	**PTSD**	NR	NR	NR	NR
		Depressive Disorders	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Sampling method: 1) Retrospective cohort; active service members with electronic health records in Defense Medical Surveillance System (2008-2010); includes military and civilian inpatient and outpatient encounters; additional data from Theater Medical Data Store 2) Exposed = all incident TBI; unexposed = 10% random sample of any other medical encounter diagnosis	Male (%): 85 Race/ethnicity (%): White 63, Black 16, Hispanic 11, American Indian/Alaskan Native 0.4, Asian/Pacific Islander 4 Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: ICD-9 codes meeting DoD case definition, diagnosed while deployed or within 30 days of return Multiple TBI: NR TBI etiology: NR Eligibility: service members with ≥365 days of continuous active service from start of study, no prior TBI, AUD, or ODUD diagnoses	**Substance Use Disorders**	ICD-9-CM AUD 4% (452/11,122) ODUD 2% (176/11,122) AUD and ODUD 0.7% (82/11,122)	ICD-9-CM AUD 2% (2,726/151,776) ODUD 0.6% (858/151,776) AUD and ODUD 0.3% (435/151,776)	NR	NR
		Suicidal Ideation	NR	NR	NR	NR
		Anxiety Disorders	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Kontos 2013[16] National US Special Operations Command Biomedical Initiatives Steering Committee Sampling methods: web-based baseline evaluation of all available US Army Special Operations Command (USASOC) personnel (11/2009-12/2011); 82% eligible after exclusions	Sample size: 22,203 (mTBI: 2,813, No mTBI 19,390) Mean age: 30 Male (%): 96 Race/ethnicity (%): NR Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: mTBI defined as head injury with a Glasgow Coma Scale score of 13-15 and no associated pathology on neuroimaging Multiple TBI: NR TBI etiology: 60% blunt trauma, 31% blast-related, 9% blast-blunt combination Eligibility: no history of moderate to severe TBI, brain surgery, major psychiatric disorder, or neurological disorder; neurocognitive assessment deemed invalid	**PTSD**	NR	NR	PCL (range 17-85)* Blunt: 20.3 (7.1) Blast: 22.6 (8.8) Blast-blunt: 24.3 (10.7) *Version not reported	PCL (range 17-85) 18.4 (5.3)
		Depressive Disorders	NR	NR	NR	NR
		Substance Use Disorders	NR	NR	NR	NR
		Suicidal Ideation	NR	NR	NR	NR
		Anxiety Disorders	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Macera 2012[17] National US Navy Bureau of Medicine and Surgery Sampling method: Navy and Marine Corps who completed the PDHA and PDHRA (2008-2009)	Sample size: 9,902 (TBI: 473, TBI&PTSD 644, No TBI and No PTSD: 8,785) Mean age: 27 Male (%): 100 Race/ethnicity (%): NR Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: self-report of injury in blast or explosion with alteration/loss of consciousness or posttraumatic amnesia Multiple TBI: NR TBI etiology: blast-related Eligibility: Navy sailors and Marines deployed to Iraq, Afghanistan, or Kuwait in 2008-2009; completed PDHA within 30 days of deployment and PDHRA 30 to 365 days later; responded "yes" to at least 1 of 3 combat experience items; excluded women and non-blast TBI	**PTSD**	NR	NR	NR	NR
		Depressive Disorders	PHQ-2 items *TBI Only* 11% (52/473) *TBI & PTSD* 48% (309/644)	PHQ-2 items *No TBI & No PTSD* 11% (978/8785)	NR	NR
		Substance Use Disorders	NR	NR	NR	NR
		Suicidal Ideation	NR	NR	NR	NR
		Anxiety Disorders	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Pogoda, 2016[18] National Sampling method: 1) Retrospective analysis of data from OEF/OIF Veterans who completed VA CTBIE (10/2007 to 6/2009) 2) Demographic, deployment and health data obtained from VA Patient Care	Sample size: 9,337 (mTBI: 6,352, No mTBI: 2,985)* Mean age: NR, 22% age 18-24 y, 34% age 25-29 y, 25% age 30-39, 20% age 40+ y Male (%): 94 Race/ethnicity (%): NR Time since TBI (days): NR Time since discharge: NR Method of TBI diagnosis: Clinician rating based on CTBIE Multiple TBI: NR	**PTSD**	CTBIE checklist 74% (4,711/6,352)	CTBIE checklist 54% (1,602/2,985)	NR	NR
		Depressive Disorders	CTBIE checklist 40% (2,562/6,352)	CTBIE checklist 35% (1,053/2,985)	NR	NR
		Substance Use Disorders	CTBIE checklist *Alcohol* 8% (483/6,352) *Drugs* 2% (133/6,352)	CTBIE checklist *Alcohol* 7% (209/2,985) *Drugs* 2% (51/2,985)	NR	NR
		Suicidal Ideation	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
Services and DoD Manpower Data Management Center **NOTE: Prevalence data obtained from author**	TBI etiology (%): Non-blast only 20; Blast only 39; Non-blast + blast 41 Eligibility: completed CTBIE; sufficient data to determine TBI status and severity; TBI status agreement between CTBIE and VA/DoD criteria; no pre-or-post deployment TBI(s); known employment status *Demographics for full study population, including 1,481 individuals with moderate/severe TBI	**Anxiety Disorders**	CTBIE checklist 24% (1,544/6,352)	CTBIE checklist 26% (760/2,985)	NR	NR
Seal 2016[19] National VA HSR&D Sampling method: VA CTBIE database (enrolled in VA	Sample size: 66,089 (mTBI: 38,556, No mTBI: 27,533) Median age: 28 Male (%): 94 Race/ethnicity (%): White 54, Non-White 46 Time since TBI: NR	**PTSD**	ICD-9[e] 74% (28,532/38,556)	ICD-9 64% (17,706/27,533)	NR	NR
		Depressive Disorders	ICD-9[f] 47% (17,943/38,556)	ICD-9 45% (12,348/27,533)	NR	NR
		Substance Use Disorders	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
healthcare, at least one first-level TBI screen since 4/14/2007); other sources include VA OIF/OEF/OND Roster, VA National Patient Care Database, VA Decision Support System	Time since discharge: NR Method of TBI diagnosis: CTBIE Multiple TBI: NR TBI etiology: NR Eligibility: OIF/OEF Veterans; completed Level 1 TBI screen (positive) and CTBIE with determinate diagnosis	**Suicidal Ideation**	NR	NR	NR	NR
		Anxiety Disorders	NR	NR	NR	NR
Taylor 2015[20] National VA HSR&D Sampling method: All Iraq and Afghanistan War Veterans who used VHA inpatient or outpatient care in FY2014 and had records in the Planning Services and Support Group	Sample size: 684,133 (TBI: 47,845, No TBI: 636,288) Mean age: 36 Male (%): 87 Race/ethnicity (%): White 67, Black 17, Native American/ Alaska Native 1, Asian 2, Native Hawaiian/Pacific Islander 1, Multiracial 2 Ethnicity (%): Non-Hispanic 83, Hispanic 11 Time since TBI: NR	**PTSD**	ICD-9 73% (34,927/47,845)	ICD-9 28% (178,161/636,288)	NR	NR
		Depressive Disorders	ICD-9 48% (22,966/47,845)	ICD-9 24% (152,709/636,288)	NR	NR
		Substance Use Disorders	ICD-9 38% (18,181/47,845) Nicotine dependence 25% (11,961/47,845)	ICD-9 21% (133,620/636,288) Nicotine dependence 14% (89,080/636,288)	NR	NR
		Suicidal Ideation	NR	NR	NR	NR

Study, year (ref) Location Funding Sampling Method	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)		Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)	
			mTBI	No mTBI	mTBI	No mTBI
FY2014 enrollment files; other data sources included patient geocode files, VETSNET, Corporate Data Warehouse	Time since discharge: NR Method of TBI diagnosis: ICD-9 codes Multiple TBI: NR TBI etiology: NR Eligibility: Iraq and Afghanistan War Veterans; used VHA care with records in Planning Services and Support Group FY2014 enrollment files	**Anxiety Disorders**	ICD-9 31% (14,832/47,845)	ICD-9 16% (101,806/636,288)	NR	NR

AUDIT-C=Alcohol Use Disorders Identification Test-Consumption Questions; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; CAGE=Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers; CAPS=Clinician Administered PTSD Scale for DSM-IV; CESD=Center for Epidemiologic Studies Depression; CTBIE-Comprehensive TBI Evaluation (VA); FY=fiscal year; GAD-7=Generalized Anxiety Disorders Questionnaire; HAM-A=Hamilton Rating Scale for Anxiety; HSR&D=Health Services Research and Development; ICD-9=*International Classification of Diseases, Ninth Revision*; IQR= interquartile range; NA=not applicable; NR=not reported; OEF=Operation Enduring Freedom; OIF=Operation Iraqi Freedom; OND=Operation New Dawn; PCL-C=PTSD Checklist-Civilian Version; PCL-M= PTSD Checklist-Military Version; PDHA=Post-Deployment Health Assessment; PDHRA=Post-Deployment Health Reassessment; PHQ=Patient Health Questionnaire; PNS=Polytrauma Network Sites; PTBRI=Polytrauma and Blast-Related Injury; PTSD=Post Traumatic Stress Disorder; QUERI=Quality Enhancement Research Initiative; R&D=Research and Development; STDI=Structured TBI Diagnostic Interview; TBI=traumatic brain injury; mTBI=mild traumatic brain injury; VA=Veterans Affairs

[a]Calculated (not reported in manuscript)
[b]At 1 year post-deployment
[c]Lenient criteria (CAPS-IV): score of "yes" for at least 1 re-experiencing symptom, at least 3 avoidance and numbing symptoms, and at least 2 hyperarousal symptoms
[d]Resulting in emergency department visit or hospitalization
[e]With or without comorbid depression
[f]With or without comorbid PTSD

Table 2. Prevalence and/or Severity of Psychiatric Conditions – Geographically Diverse Samples (KQ1)

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
Baldassarre, 2015[21] 3 VA Polytrauma Network Sites: Kentucky Arizona Illinois VA HSR&D Sampling method: 1) OEF/OIF registries at 3 PNSs (Veterans could opt-out) (Aug 2010-Sept 2011) 2) OEF/OIF Veterans presenting for care at any clinic at the PNSs	Sample size: 398 (mTBI: 210, No mTBI: 188) Mean age: 32 Male (%): 89 Race/ethnicity (%): Caucasian/white 75 Time since TBI: 4.8 years Time since discharge: NR Method of TBI diagnosis: STDI Multiple TBI: NR TBI etiology: NR Eligibility: Veterans, age ≥18 years, deployed in OEF or OIF conflicts, no treatment for concussion in 30 days preceding study enrollment	**PTSD**	CAPS-IV (lenient)[c] 56% (117/210)	CAPS-IV (lenient)[c] 28% (52/188)	<.0001	NR	NR	
		Depressive Disorders	BDI-II (≥17) 49% (103/210)	BDI-II (≥17) 21% (40/188)	<.0001	NR	NR	
		Substance Use Disorders	AUDIT (≥4 [M] or ≥3 [F]) 50% (105/210) probable alcohol use disorder	AUDIT (≥4 [M] or ≥3 [F]) 44% (83/188) probable alcohol use disorder	.0013	NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	BAI (≥8) 63% (132/210)	BAI (≥8) 35% (65/188)	<.0001	NR	NR	
Brenner, 2010[22] Fort Carson, Colorado, USA Sampling Method: 1) Retrospective analysis; US	Sample size: 1247 (mTBI: 878, No mTBI: 369) Age group (%): 51% age 18-24 y, 24% age 25-29 y, 21% age 30-39 y, 4% age 40-53 y	**PTSD**	PDHA survey-4 (+ on ≥ 2 questions) 37% (323/878)	PDHA survey-4 (+ on ≥ 2 questions) 22% (82/369)	<.0001[d]	NR	NR	
		Depressive Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
Army Brigade Combat Team returning from 1 year deployment in Iraq (date NR) 2) Soldiers participated PDHA, completed WARCAT and were interviewed by clinicians 3) Military and demographic characteristics from Army Medical Surveillance Activity	Male (%): 99 Race/ethnicity (%): NR Time since TBI (days): NR Time since discharge: NA Method of TBI diagnosis: WARCAT and clinician interviews Multiple TBI: NR TBI etiology (%): NR Eligibility: Self-reported injury during deployment (full-duty status at time of assessment); complete demographic and PTSD data	**Substance Use Disorders**	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
Bryan, 2013, Bryan, 2013[23,24] Iraq (US Army base) No funding Sampling Method: 1) Referred to outpatient TBI clinical at combat	Sample size: 158 (mTBI: 135, No mTBI: 23) Mean age: 28 Male (%): 93 Race/ethnicity (%): White 72, Black 15, Hispanic 10, Asian/ Pacific 3 Time since TBI (days): 2 (median)	**PTSD**	NR	NR		PCL-M (cut point ≥ 50) 32.7 (14.5)	PCL-M (cut point ≥ 50) 20.5 (5.1)	<.001
		Depressive Disorders	NR	NR		BHM-20 Depression (clinical range: >1.38) 1.0 (0.9)	BHM-20 Depression (clinical range: >1.38) 0.2 (0.3)	<.001
		Substance Use Disorders	NR	NR		NR	NR	NR

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
support hospital in 2009 2) Standardized intake evaluation including clinical interview	Time since discharge: NA Method of TBI diagnosis: Clinical interview using DOD and Department of VA criteria Multiple TBI: NR TBI etiology (%): NR Eligibility: Referred to TBI clinic; excluded if moderate or severe TBI	**Suicidal Ideation**	SBQ-R (≥7) *Ideation* 13% (18/135) *Ideation with plan* 1.4% (2/135)	SBQ-R (≥7) *Any suicidal behavior* 0% (0/23)	<.05[d]	SBQ-R (cut point ≥7) 3.5 (1.6)	SBQ-R (cut point ≥7) 0.0 (0.0)	<.001
		Anxiety Disorders	NR	NR		NR	NR	
Bryant, 2015[25] Iraq military combat theater hospital NR Sampling method: Military personnel serving in Iraq; received routine assessment for blast exposure at military combat theater hospital (2006-2007)	Sample size: 685 (mTBI: 567, No mTBI: 118) Mean age: 26 Male (%): NR Race/ethnicity (%): NR Time since TBI: 7.4 (21.3) days Time since discharge: NA Method of TBI diagnosis: Documented occurrence of injury to the head, loss of consciousness < 30 min, posttraumatic amnesia < 24 hr, normal CT findings with no focal	**PTSD**	PCL-M met criteria (unspecified) for PTSD without minimum 1-month duration 25% (142/567)	PCL-M met criteria (unspecified) for PTSD without minimum 1-month duration 11% (13/118)	0.001	NR	NR	
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
	neurological deficit or intracranial complications Multiple TBI: 13% reported prior blast-related TBI TBI etiology: 100% blast Eligibility: Exposed to explosive blast	**Anxiety Disorders**	NR	NR		NR	NR	
Carlson, 2010[26] Upper Midwest VA HSR&D, PT/BRI-QUERI Sampling method: 1) OEF/OIF Veterans screened for TBI in Upper Midwest VA integrated Service Network (VISN 23); Screened April 2007-Oct 2008	Sample size: 11,828 (TBI: 836, No TBI: 10,992) Mean age: 33 Male (%): 90 Race/ethnicity (%): Caucasian: 82 Time since TBI: NR Time since discharge (median): 430 days Method of TBI diagnosis: positive screen (VA TBI Screening Instrument) and assigned TBI-related ICD-9 codes in rehabilitation, neurology, mental health, or primary care clinics Multiple TBI: NR TBI etiology (%): Blast/explosion 90 Vehicular crashes 43 Falls 44	**PTSD**	ICD-9 codes 64% (534/836)	ICD-9 codes 18% (2,001/10,992)	<.05	NR	NR	
		Depressive Disorders	ICD-9 codes 46% (387/836)	ICD-9 codes 22% (2,367/10,992)	<.05	NR	NR	
		Substance Use Disorders	ICD-9 codes 26% (219/836)	ICD-9 codes 10% (1,056/10,992)	<.05	NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	ICD-9 codes 36% (298/836)	ICD-9 codes 13% (1,430/10,992)	<.05	NR	NR	NR

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
	Eligibility: Veterans screened for TBI in VISN 23							
Gaines, 2016[27] VA health centers, California VA of Greater Los Angeles Health Care System Sampling method: 1) Participants recruited through fliers and word of mouth at VA locations in California 2) Potential participants screened over the phone or in person to determine eligibility	Sample size: 114 (mTBI: 57, No mTBI: 57) Mean age: 30 Male (%): 100 Race/ethnicity (%): Caucasian 25, African American 9, Hispanic 43, Asian 12, Other 11 Time since TBI (days): NR Time since discharge: NR Method of TBI diagnosis: Criteria from American College of Rehabilitation and the American Congress of Rehabilitation Medicine Multiple TBI: NR TBI etiology (%): NR Eligibility: Served in Iraq or Afghanistan 2007-2012, history of learning disabilities or attention deficit hyperactivity disorder, no diagnoses of substance abuse or	**PTSD**	NR	NR		NR	NR	
		Depressive Disorders	NR	NR		BDI-II 22.4 (12.2)	BDI-II 12.9 (11.0)	.002
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
	dependence, and no major neurological or medical conditions							
Heltemes, 2011[28] OEF/OIF combat zone medical treatment facilities US Navy Bureau of Medicine & Surgery Sampling method: 1) All eligible injuries in US Expeditionary Medical Encounter Database (2004-2007) 2) Matched to alcohol abuse diagnoses from Standard Inpatient and Ambulatory Data Records	Sample size: 3,123 (mTBI: 1,413, No mTBI: 1,710) Median age: 23 Male (%): 100 Race/ethnicity (%): NR Time since TBI: Followed for 2 years from date of injury; Time since discharge: NA Method of TBI diagnosis: ICD-9 codes meeting CDC criteria Multiple TBI: excluded TBI etiology: 100% blast Eligibility: Male service members treated for combat-related blast injuries in combat zone medical facilities, single injury events, no alcohol abuse disorders prior to injury	**PTSD**	NR	NR		NR	NR	
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	ICD-9-CM Alcohol abuse diagnosis 6% (86/1,413)	ICD-9-CM Alcohol abuse diagnosis 5% (84/1,710)	.15	NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
Hoge, 2008[29] Maryland Washington, D.C. Military Operation Medicine Research Area Directorate Sampling Method: 1) US Army combat infantry brigades (active and reserve) after 1-year deployment were provided time to attend study recruitment briefing 2) Anonymous surveys conducted 3-4 months after deployment	Sample size: 2,525 (mTBI with LOC: 124, mTBI with altered state: 260, other injury: 435, no injury: 1,706) Age (% <30 years): 55 Male (%): 95 Race/ethnicity (%): NR Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: Positive response to losing consciousness, being dazed and confused, or not remembering injury Multiple TBI: NR TBI etiology (%): Blast/explosion 75, Bullet 2, Fragment/ Shrapnel 21, Fall 29, Vehicle accident 22 Eligibility: recent return from deployment, attended recruitment briefing and completed questionnaire	**PTSD**	PCL (DSM-IV criteria and total score ≥50) *LOC* 44% (54/123) *Altered State* 27% (71/260)	PCL (DSM-IV criteria and total score ≥50) *Other Injury* 16% (70/433) *No Injury* 9% (155/1,701)	*LOC vs Other Injury* <.001 *Altered State vs Other Injury* <.001	PCL *LOC* 47 (19) *Altered State* 40 (16)	PCL *Other Injury* 35 (15) *No Injury* 29 (13)	*LOC vs Other Injury* <.001 *Altered State vs Other Injury* <.001
		Depressive Disorders	PHQ-9 (DSM-IV criteria and "very difficult" functioning) *LOC* 23% (27/118) *Altered State* 8% (21/250)	PHQ-9 (DSM-IV criteria and "very difficult" functioning) *Other Injury* 7% (28/423) *No Injury* 3% (55/1,673)	*LOC vs Other Injury* <.001 *Altered State vs Other Injury* .39 NS	NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
King, 2017[30] Five VA medical centers and one community-based outpatient clinic in Upstate New York VA HSR&D Sampling method: secondary analysis of data from longitudinal study of OEF/OIF Veterans recruited from clinical referrals for polytrauma or neuropsychology and VISN 2 registry; oversampling of women and minority backgrounds	Sample size: 291 (TBI: 153, no TBI: 138) Mean age: 31 Male (%): 92 Race/ethnicity (%): Caucasian 83, African American 7, Hispanic 5, Asian American 1, Native American 1 Time since TBI: NR Time since discharge: NR Method of TBI diagnosis: 22-item clinical interview Multiple TBI: NR TBI etiology: NR Eligibility: OEF/OIF Veterans intending to stay in Upstate New York for 18-month parent study who had sleep data available (58% of parent study participants)	**PTSD**	PCL-M Probable PTSD (≥50) 57% (87/153)	PCL-M Probable PTSD (≥50) 34% (47/138)	<0.001	PCL-M score 53 (15)	PCL-M score 42 (15)	<0.001
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	NR	NR		AUDIT-C score (≥3 (women) or ≥4 (men): hazardous drinking) 4.0 (3.2)	AUDIT-C score (≥3 (women) or ≥4 (men): hazardous drinking) 5.0 (3.1)	0.008
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
MacDonald, 2014[33] Landstuhl Regional Medical Center (LRMC), Germany	Sample size: 65 (mTBI: 47, No mTBI: 18) Median age: mTBI: 25, No mTBI: 32 Male (%): 100	**PTSD**	CAPS-IV 61% (29/47)	CAPS-IV 28% (5/18)	.01	CAPS-IV (from graph) ~60	CAPS-IV (from graph) ~40	.002
		Depressive Disorders	MADRS (>19) 51% (24/47)	MADRS (>19) 44% (8/18)	.63 (NS)	MADRS (from graph) 19 (11)	MADRS (from graph) 14 (10)	.05

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
Congressionally Directed Medical Research Program, NIH Sampling method: Screened for TBI at LRMC (2008-2009)	Race/ethnicity (%): White 75, Hispanic/Latino 11, African American 11, Asian 3 Time since TBI: median 14 days (1-90) Time since discharge: NA Method of TBI diagnosis: Self-report of blast exposures with alterations of neurologic function Multiple TBI: NR TBI etiology (%): Blast plus other impact Eligibility: Screen for TBI at LRMC, injury from blast with or without additional mechanisms of injury within 90 days of enrollment, US military, no contraindications to MRI, no history of moderate to severe TBI, no history of major psychiatric disorder, agreement to complete study follow up	**Substance Use Disorders**	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
MacDonald, 2014[32] Landstuhl Regional Medical Center (LMRC), Germany Congressionally Directed Medical Research Program Sampling method: Screened for TBI at LRMC (2010-2013)	Sample size: 178 (mTBI plus impact: 53, non-blast mTBI: 29, No mTBI plus blast: 27, No TBI plus non-blast: 69) Median age: mTBI plus impact: 6 non-blast mTBI: 28, No mTBI plus blast: 34, No TBI plus non-blast: 31 Male (%): 93 Race/ethnicity (%): White 73, African American 17, Hispanic/Latino 8 Asian 2 Time since TBI (days): Blast plus impact TBI 12 (10), Non-blast TBI 14 (10) Time since discharge: NA Method of TBI diagnosis: Self-report of blast exposures with alterations of neurologic function Multiple TBI: NR TBI etiology (%): Blast plus impact 65 Non-blast 35 Eligibility: same as MacDonald 2014[33]	**PTSD**	CAPS-IV *Blast* 42% (22/53) *Non-blast* 48% (14/29)	CAPS-IV *Blast* 22% (6/27) *Non-blast* 6% (4/69)	*Blast* .09 NS *Non-blast* <.001	CAPS-IV (from graph) *Blast* ~48 *Non-blast* ~48	CAPS-IV (from graph) *Blast* ~31 *Non-blast* ~16	*Blast* .06 NS *Non-blast* <.001
		Depressive Disorders	NR	NR		MADRS (from graph) *Blast* ~15 *Non-blast* ~16	MADRS (from graph) *Blast* ~11 *Non-blast* ~9	*Blast* .24 NS *Non-blast* <.001
		Substance Use Disorders	NR	NR		MAST (from graph) *Blast* ~3 *Non-blast* ~2	MAST (from graph) *Blast* ~3 *Non-blast* ~2	NS
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
MacDonald, 2017[31] Kandahar Air Field or Camp Leatherneck, Afghanistan Congressionally Directed Medical Research Program, Defense Advanced Research Projects Agency, NIH Sampling method: 1) Screened for TBI at Kandahar Air Field or Camp Leatherneck (March 2012-Sept 2012) 2) Remained in-theater	Sample size: (blast mTBI: 38, No TBI/non-blast: 34) Median age: blast mTBI: 26, No TBI/non-blast: 28 Male (%): 87 Race/ethnicity (%): White 71, Hispanic/ Latino 19, African American 10, Asian 0 Time since TBI (days): All 0-7 days Time since discharge: NA Method of TBI diagnosis: Clinical diagnosis - criteria from American Congress of Rehabilitation Multiple TBI: NR TBI etiology (%): Blast +impact 100% Eligibility: Clinical diagnosis of TBI, US military, no contraindications to MRI, no history of moderate to severe TBI, no pre-deployment history of major psychiatric disorder, agreement to complete study follow up	**PTSD**	NR	NR		CAPS-IV (from graph) *Blast+impact* ~40	CAPS-IV (from graph) *Non-blast* ~23	<.0001
		Depressive Disorders	NR	NR		MADRS (from graph) *Blast+impact* ~15	MADRS (from graph) *Non-blast* ~8	<.0001
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
MacGregor, 2013[34] National US Navy Bureau of Medicine Sampling method: Queried Expeditionary Medical Encounter Database for personnel injured during OIF (March 2004-April 2008) who completed the PDHA and PDHRA	Sample size: 992 (mTBI: 334, No TBI/non-head injury: 658) Mean age: mTBI 23, no TBI 25, P<.001 Male (%): TBI 99.7, no TBI 93, P<.001 Race/ethnicity (%): NR Time since TBI: 255 days (for PDHRA) Time since discharge: NA Method of TBI diagnosis: TBI ICD-9-CM codes corresponding with AIS values of 1 or 2 Multiple TBI: NR TBI etiology (%): Battle, blast 89, Battle, non-blast 2, Non-battle 9 Eligibility: Minor to moderate injuries sustained during OIF March 2004 to April 2008, completed a PDHA and PDHRA within one year of injury	**PTSD**	PDHRA (PC-PTSD) (+ on ≥3 of 4 items) 28% (93/334)	PDHRA (PC-PTSD) (+ on ≥3 of 4 items) 17% (113/658)	<.001	NR	NR	
		Depressive Disorders	PDHRA (based on PHQ) (+ on ≥1 of 2 items) 21% (69/334)	PDHRA (based on PHQ) (+ on ≥1 of 2 items) 13% (87/658)	.002	NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
MacGregor, 2010[35] National	Sample size: 762 (mTBI: 105, No TBI/other head injury:	**PTSD**	ICD-9 codes 12% (13/105)	ICD-9 codes *Head Injury* 15% (40/273)	*mTBI vs Head Injury:* .62[d]	NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
US Navy Bureau of Medicine and Surgery Sampling method: 1) Identified in Expeditionary Medical Encounter Database 3) Registered in Career History Archival Medical and Personnel System (CHAMPS)	273, No TBI/non-head injury: 384) Mean age: 24 Male (%): 100 Race/ethnicity (%): NR Time since TBI: NR Time since discharge: NA Method of TBI diagnosis: TBI ICD-9-CM codes corresponding with AIS values of 1 or 2 Multiple TBI: NR TBI etiology (%): IED 72, Grenade 1, Blast 23, Gunshot wound 2, Fragment/shrapnel <1 Eligibility: Male OIF combatants, presented to forward deployment medical treatment facilities for battle injury Sept 2004-Feb 2005, registered in the EMED and CHAMPS databases, military discharge >90 days into follow-up period			*Non-head Injury* 19% (72/384)	*vs Non-head injury:* .15[d]			
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	ICD-9 codes 9 % (9/105)	ICD-9 codes *Head Injury* 4% (11/273) *Non-head Injury* 8% (31/384)	*mTBI vs Head Injury:* .12[d] *vs Non-head injury:* .84[d]	NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	ICD-9 codes 11% (11/105)	ICD-9 codes *Head Injury* 12% (32/273) *Non-head Injury* 15% (57/384)	*mTBI vs Head Injury:* .86[d] *vs Non-head injury:* .34[d]	NR	NR	
Mora, 2009[36]	Sample size: 110 (mTBI: 19, No mTBI: 91)	**PTSD**	PCL-M (≥44) 37% (7/19)	PCL-M (≥44) 21% (19/91)	.15	NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
US Army Institute of Surgical Research (USAISR) Burn Center, Texas Funding NR Sampling Method: 1) Retrospective review of clinical records of combat casualties injured in explosions and treated at USAISR (March 2003-March 2006) 2) Joint Theater Trauma Registry	Mean age: 26 Male (%): 93 Race/ethnicity (%): NR Time since TBI (days): 196 Time since discharge: NA Method of TBI diagnosis: Loss of consciousness based on ICD codes and AIS scores Multiple TBI: NR TBI etiology (%): Blast/explosion 100 Eligibility: OIF/OEF service members with explosion injury, PCL-M assessment 30 days post-injury	**Depressive Disorders**	NR	NR		NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
Pietrzak, 2009[37] Connecticut State of Connecticut, National Center for PTSD, Private donation Sampling Method: 1) Participants identified alphabetically by	Sample size: 277 (mTBI: 52, No TBI: 225) Mean age: 33 Male (%): 90 Race/ethnicity (%): White 80, Hispanic 6, Black 7, Other 7 Time since TBI: NR Time since last deployment (months): 23	**PTSD**	PCL-M (≥50) 65% (34/52)	PCL-M (≥50) 24% (55/225)	<.001	NR	NR	
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
to obtain 1000 names and addresses 2) Surveys mailed by CT Veterans Affairs to main confidentiality NOTE: 28.5% response rate	Method of TBI diagnosis: VA TBI screening instrument Multiple TBI: NR TBI etiology (%): NR Eligibility: Received and completed Wave 2 of Connecticut OEF/OIF Veterans Needs Assessment Survey, served Jan 2003-Mar 2007	**Anxiety Disorders**	NR	NR		NR	NR	
Polusny 2011[38] US National Guard Brigade Combat Team Veterans Health Administration Office of Research and Development Sampling Method: Recruited at redeployment transition briefings 1 month prior to return home from end of 16-month combat deployment (June	Sample size: 937 (mTBI: 86, No mTBI: 851) Mean age: 33 Male (%): 92 Race/ethnicity (%): white 87 Time since TBI: NR Time since discharge: NR Method of TBI diagnosis: self-report of closeness to blast, injuries, feeling dazed/confused Multiple TBI: NR TBI etiology (>1 answer allowed): Fragment 17%, Bullet 1%, Vehicular 21%,	**PTSD**	PCL-M (≥50) 30% (26/86)[b]	PCL-M (≥50) 12% (103/851)[b]	.0001	PCL-M *mTBI only* 34.3 (9.4)[b] *mTBI+PTSD* 63.1 (7.3)[b]	PCL-M *No mTBI/no PTSD* 29.3 (9.2)[b] *PTSD only* 62.5 (8.1)	<.0001[d] .73[d]
		Depressive Disorders (at 1 year)	NR	NR		BDI-II *mTBI only* 11.4 (8.5)[b] *mTBI+PTSD* 25.5 (8.7)[b]	BDI-II *No mTBI/no PTSD* 8.8 (7.2)[b] *PTSD only* 25.0 (8.9)	.008[d] .80[d]
		Substance Use Disorders (at 1 year)	NR	NR		AUDIT *mTBI only* 9.8 (7.1)[b] *mTBI+PTSD* 15.2 (9.3)[b]	AUDIT *No mTBI/no PTSD* 7.2 (5.4)[b] *PTSD only* 12.5 (9.6)	.0005[d] .20[d]

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
2007); invited to follow-up at 1 year after deployment NOTE: 50% response rate at 1 year	Fall 17%, Blast 73%, Other 17% Eligibility: member of US National Guard Brigade Combat Team completing 16-month combat deployment to Iraq; completed in-theater and post-deployment assessments	**Suicidal Ideation**	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
Tsai 2012[39] Hawaii VA HSR&D Sampling Method: Stratified sample from VA Hawaii Program Registry Nov-Dec 2010 NOTE: 52% response rate	Sample size: 233 (TBI: 79, No TBI: 158) Mean age: 37 Male (%): 87 Race/ethnicity (%): Asian/Pacific Islander 55%, Other 45% Time since TBI: NR Time since discharge: NR Method of TBI diagnosis: VA 4-item screen (history of combat-related concussion and persistent post-concussive symptoms) Multiple TBI: NR TBI etiology: NR Eligibility: Veterans Affairs Hawaii Program Registry,	**PTSD**	PCL-C (≥50) 57 (43/75)[a]	PCL-C (≥50) 18 (28/158)	<.001	NR	NR	
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	CAGE (≥2) 38% (27/75)[a]	CAGE (≥2) 17% (26/158)	<.01	NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
	served in Iraq or Afghanistan							
Vanderploeg 2015[40] Florida Veterans Health Administration, Defense and Veterans Brain Injury Center, 2 HSR&D grants Sampling Method: Survey of Florida National Guard 2009-2010; unselected, representative sample of respondents to invitation to participate in survey NOTE: 41% overall response rate **NOTE: Prevalence data obtained from author**	Sample size: 1443 (mTBI: 144, No mTBI: 1,299) Mean age: NR Male (%): 87 Race/ethnicity (%): Minority 34 Time since TBI: NR Time since deployment: 32 months (range 0-95) Method of TBI diagnosis: self-report Multiple TBI: 13% with prior mtBI TBI etiology: NR Eligibility: Florida National Guard members, reported at least 1 deployment, provided usable data and fully completed an anonymous on-line survey	**PTSD**	PCL (≥ 50 +DSM criteria) 25% (36/144)	PCL (≥ 50 +DSM criteria) 5% (64/1,299)	.0001[d]	NR	NR	
		Depressive Disorders	PHQ-9 (DSM-IV criteria and "very" difficult" functioning) 15% (22/144)	PHQ-9 (DSM-IV criteria and "very" difficult" functioning) 2% (25/1,299)	<.0001[d]	NR	NR	
		Substance Use Disorders	AUDIT-C (≥4 for men, ≥3 for women is hazardous 49% (71/144)	AUDIT-C (≥4 for men, ≥3 for women is hazardous 37% (483/1,299)	.005[d]	NR	NR	
		Suicidal Ideation	PHQ-9 (1 item) 20% (29/144)	PHQ-9 (1 item) 4% (51/1,299)	.0001[d]	NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
Walker 2017[41] Virginia and North Carolina (1 VA Medical Center Polytrauma Rehabilitation Center and 3 military bases) US Army Medical Research and Material Command Sampling Method: Recruited via letters, advertisements, and at ambulatory healthcare clinics	Sample size: 216 (mTBI: 40, No mTBI: 176) Mean age: 25 Male (%): 97 Race/ethnicity (%): White 78%, African American 15%, Other 6% Time since TBI: median 9 months (IQR 5-15) since most recent blast; all blast experiences within past 2 years Time since discharge: NR Method of TBI diagnosis: face-to-face interview (n=106) or algorithm based on Blast Experience Screening Questionnaire (n=110) Multiple TBI (blast TBI): 1 mTBI 45%, 2 mTBIs 22%, ≥3 mTBIs 15% TBI etiology: blast TBI prior to current deployment: NR Eligibility: Service Member of Veteran with one or more	**PTSD**	NR	NR		PCL (version not reported) *Baseline* mTBI with PTA: 49 (95%CI 46-52) mTBI w/o PTA: 49 (95%CI 45-52) *6 months* mTBI with PTA: 49 (95%CI 46-53) mTBI w/o PTA: 46 (95%CI 41-51) *12 months* mTBI with PTA: 47 (95%CI 43-50) mTBI w/o PTA: 46 (95%CI 42-51)	PCL (version not reported) *Baseline* 44 (95%CI 40-49) *6 months* 41 (95%CI 35-47) *12 months* 42 (95%CI 36-48)	*Baseline* mTBI with PTA vs no mTBI: .02[e] mtBI w/o PTA vs no mTBI: .04[e] *12 months* mTBI with PTA vs no mTBI: .03[e] mtBI w/o PTA vs no mTBI: .10[e]
		Depressive Disorders	NR	NR		CESD *Baseline:* mTBI with PTA: 19 (95%CI 17-21) mTBI w/o PTA: 18 (95%CI 15-20) *6 months:* mTBI with PTA: 18 (95%CI 16-21)	CESD *Baseline:* 16 (95%CI 13-19) *6 months:* 18 (95%CI 13-22)	*Baseline* mTBI with PTA vs no mTBI: .04[e] mtBI w/o PTA vs no mTBI: .17[e]

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
	blast experiences in past 2 years while deployed in OEF/OIF/OND; excluded severe and moderate TBI					mTBI w/o PTA: 17 (95%CI 13-20) *12 months* mTBI with PTA: 19 (95%CI 16-22) mTBI w/o PTA: 18 (95%CI 14-21)	*12 months* 16 (95%CI 12-20)	*12 months* mTBI with PTA vs no mTBI: .09[e] mtBI w/o PTA vs no mTBI: .40[e]
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
Wilk, 2012[42] Three brigade combat teams from one Active Component infantry division Sampling method: Unit commanders made Army soldiers available for group recruitment briefings (Nov	Sample size: 1502 (mTBI: 260, No mTBI: 1242) Mean age: NR (70% <30 yr) Male (%): 91 Race/ethnicity (%): NR Time since TBI: NR Time since return from deployment: 4-6 months Method of TBI diagnosis: DOD & VA	**PTSD**	PCL-17 (≥ 50) All 37% (96/260) With LOC 52% (45/86) With AOC 29% (51/174)	PCL-17 (≥ 50) All 12% (143/1242) Other injuries 17% (67/396) No injuries 9% (76/846)	<.05	NR	NR	
		Depressive Disorders	PHQ-9 (DSM-IV criteria and "very" or "extremely" difficult" functioning) All	PHQ-9 (DSM-IV criteria and "very" or "extremely" difficult" functioning) All	<.05	NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
2008-Dec 2008); soldiers voluntarily elected to complete the questionnaire packet NOTE: 86% of soldiers attending recruitment briefing consented to participate; approximately half randomly selected for different study	Brain Injury Center Brief TBI Screen Multiple TBI: 59% of those reporting concussion TBI etiology: blast/ explosion, bullet, fragment/shrapnel, fall, vehicle crash, or other means (% NR) Eligibility: Iraq or Afghanistan deployment experience, provided complete responses to injury and concussion-related questions		18% (48/260) With LOC 23% (20/86) With AOC 16% (28/174)	6% (70/1242) Other injuries 9% (36/396) No injuries 4% (34/846)				
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	
		Anxiety Disorders	NR	NR		NR	NR	
Yurgil 2014[43] Southern California VA HSR&D, Marine Corps, Navy Bureau of Medicine and Surgery Sampling method: Prospective longitudinal study; active duty Marine and Navy servicemen; data	Sample size: 1648 (TBI: 327 [87% mTBI] No TBI: 1321) Mean age: 22 Male (%): 100 Race/ethnicity (%): Hispanic 23%, White 85% Time since TBI: all within past 10 months Time since discharge: NA Method of TBI diagnosis: face-to-face interview Multiple TBI: NR TBI etiology: NR	**PTSD**	CAPS-IV (≥65) 6 (21/327)[a] CAPS-IV (40-64) 19 (61/327)[a]	CAPS-IV (≥65) 1 (18/1321) CAPS-IV (40-64) 6 (81/1321)	Both <.001	NR	NR	
		Depressive Disorders	NR	NR		NR	NR	
		Substance Use Disorders	NR	NR		NR	NR	
		Suicidal Ideation	NR	NR		NR	NR	

Study, year (ref) Location Funding	Study Characteristics	Condition	Prevalence of Psychiatric Conditions % (n/N)			Severity or Persistence Based on Symptom Scores (mean (SD) unless noted)		
			mTBI	No mTBI	P value	mTBI	No mTBI	P value
from assessments 1 week before 7-month deployment, 1 week and 3 months after deployment (June 2008-May 2012) NOTE: 671 lost to follow-up and 188 with missing data)	TBI prior to current deployment: 57% (66% of TBI group, 55% of No TBI group) Eligibility: Marine and Navy serviceman from 4 infantry battalions of the First Marine Division; excluded Officers	**Anxiety Disorders**	NR	NR		NR	NR	

AIS=Abbreviated Injury Scale; AOC=alteration of consciousness; AUD=alcohol use disorder; AUDIT-C=Alcohol Use Disorders Identification Test-Consumption Questions; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; BHM-20=Behavioral Health Measure-20; CAGE=Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers; CAPS=Clinician Administered PTSD Scale; CBTIE=Comprehensive TBI evaluation; CESD=Center for Epidemiologic Studies Depression; CT=computerized tomography; FY=fiscal year; GAD-7=Generalized Anxiety Disorders Questionnaire; HAM-A=Hamilton Rating Scale for Anxiety; HSR&D=Health Services Research and Development; ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; IQR=interquartile range; ISS=Injury Severity Score; LOC=loss of consciousness; MADRS=Montgomery-Asberg Depression Rating Scale; MAST=Michigan Alcohol Screening Test; MDD=major depressive disorder; mTBI=mild traumatic brain injury; MVRI=Minnesota Veterans Research Institute; NA=not applicable; NR=not reported; ODOD=other drug use disorder; OEF=Operation Enduring Freedom; OIF=Operation Iraqi Freedom; OND=Operation New Dawn; PCL=PTSD Checklist; PCL-C=PTSD Checklist-Civilian Version; PCL-M= PTSD Checklist-Military Version; PC-PTSD=Primary Care PTSD screen; PDHA=Post-Deployment Health Assessment; PDHRA=Post-Deployment Health Reassessment; PHQ=Patient Health Questionnaire; PNS=Polytrauma Network Sites; PTSD=Posttraumatic Stress Disorder; SBQ-R=Suicide Behaviors Questionnaire-Revised; SCID= Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder (DSM-IV-TR); STDI=Structured TBI Diagnostic Interview; TBI=traumatic brain injury; USAISR=United States Army Institute of Surgical Research; VA=Veterans Affairs; VISN=Veterans Integrated Service Network

[a]Any TBI
[b]At 1 year post-deployment
[c]Lenient criteria (CAPS): score of "yes" for at least 1 re-experiencing symptom, at least 3 avoidance and numbing symptoms, and at least 2 hyperarousal symptoms
[d]Calculated, not reported in manuscript
[e]Calculated, not reported in manuscript; n completing 12-month assessment not reported; baseline n used in calculations

Table 3. Risk of Bias for Prevalence Studies (KQ1)

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Adams 2017[10]	Army only; included those who completed 2 post-deployment forms (61%); reported no large differences between those completing both questionnaires vs initial only	Adequate	Self-report (American Congress of Rehabilitation Medicine criteria)	Self-report (PC-PTSD, PDHRA)	N/A	**Moderate**
Baldassarre 2015[21]	Recruited via letter from OEF/OIF registries at 3 VA PNSs or presenting for care at the sites; study of sensitivity and specificity of mTBI screening measures	Limited information about service	STDI	Psychology technician administered (CAPS-IV, BDI-II, BAI, AUDIT-C)	25% of Veterans contacted consented and 71% of consented completed assessments; no information on *a priori* sample size estimation	**Moderate**
Brenner 2010[22]	US Army Brigade Combat Team from 1 military base in US; self-reported injury during recent deployment	Limited demographic information	Clinician confirmed based on interview, service member self-report, data from medical records	Self-report (PDHA)	N/A	**Moderate**
Bryan 2013, Bryan 2013[23,24]	Outpatient TBI clinic at combat support hospital in Iraq	Adequate	Licensed clinical psychologist using DoD and VA criteria	Self-report (SBQ-R, BHM-20, PCL-M)	N/A	**Moderate**
Bryant 2015[25]	Military combat theater hospital in Iraq	Limited demographic information	Documented injury to head, meeting LOC and PTA criteria; normal CT	Unclear if self-report (PCL-M)	N/A	**Moderate/high**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Carlson 2010[26]	VA administrative data for VISN23 including databases for demographics, diagnosis codes, clinic type	Limited demographic information	Assigned 1 or more ICD-9 codes for TBI in rehabilitation, neurology, mental health, or primary care clinics	ICD-9 codes	N/A	**Moderate**
Cifu 2013[11]	OEF/OIF/OND Veterans receiving VHA care FY2009-FY2011	Limited to information in Patient Care Database	ICD-9 codes	ICD-9 codes	N/A	**Moderate**
Fonda 2017[12]	OEF/OIF/OND Veterans receiving VHA care 2007-2012; excluded 44% due to inconclusive TBI data	Limited to information in VA electronic medical records databases	Confirmed diagnosis from VA CTBIE	ICD-9 code for suicide or self-inflicted injury recorded in emergency room visit or inpatient hospital admission (VA or facility reimbursed by VA)	N/A	**Moderate**
Gaines 2016[27]	Recruited at VA health care locations in California	Limited information about service	Unclear (prior diagnosis of mTBI or mild concussion)	Unclear if self-report (BDI-II)	N/A	**High**
Grossbard 2017[13]	Documented OEF/OIF service, AUDIT-C in 2012, used VA services in year before AUDIT-C	Limited to information in electronic medical record	ICD-9 code in EMR 365 days before to 30 days after AUDIT-C date	EMR (AUDIT-C administered by physician and ICD-9 codes)	N/A	**Moderate**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Heltemes 2011[28]	EMED; Navy, Marine Corps, & Army; treated for combat injury at forward-deployed medical facilities; excluded non-blast injuries	Adequate	ICD-9 codes	ICD-9 codes	N/A	**Moderate**
Hoge 2008[29]	Survey of Army soldiers from 2 combat infantry brigades (1 Active Component, 1 Reserve)	Adequate	Self-report of injury characteristics	Self-report (PHQ-15, PCL [version not reported])	59%; noted that some soldiers were transferred to other units or involved in training/military school	**Moderate**
Jaramillo 2015[14]	OEF/OIF Veterans receiving VHA care at least once per year in FY2010-FY2011	VA files plus OEF/OIF Roster Files for additional demographic data but limited reporting	ICD-9 codes	ICD-9 codes	N/A	**Moderate**
Johnson 2015[15]	Defense Medical Surveillance System data 2008-2010; active duty; all branches; 10% sample of those without TBI	Adequate	ICD-9 codes with DoD extender codes specific to military service	ICD-9 codes	N/A	**Low**
King 2017[62]	5 VA Medical Centers & 1 community-based outpatient clinic in Upstate NY; clinical referrals for polytrauma or neuropsychology and local OEF/OIF registry	Limited information about service	Clinical interview (developed for the study) administered by neuro-psychologists	Self-report (AUDIT-C, PCL-M)	N/A	**Moderate/high**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Kontos 2013[16]	Limited to US Army Special Operations Command personnel	Limited reporting	Unclear (self-report of post-concussion symptoms); no information on time since exposure	Self-report (PCL [version not reported])	N/A	**Moderate/high**
MacDonald 2014[33]	US military evaluated at medical center in Germany following evacuation from Iraq or Afghanistan	Adequate	Screened based on US military clinical criteria; medical record review	Clinician administered assessments (CAPS-IV, MADRS)	N/A	**Moderate**
MacDonald 2014[32]	US military evaluated at medical center in Germany following evacuation from Iraq or Afghanistan	Adequate	Self-report of alteration of neurological function	Clinician administered assessments (CAPS-IV, MADRS, MAST)	N/A	**Moderate**
MacDonald 2017[31]	Kandahar Air Field and Camp Leatherneck in Afghanistan	Adequate	US military clinical criteria including self-report of injury or clinical diagnosis based on criteria from American Congress of Rehabilitation 1993	Clinician administered assessments (CAPS-IV, MADRS)	N/A	**Moderate**
Macera 2012[17]	Navy/Marine Corps; PDHA and PDHRA forms completed 2008-2009; reported combat experience; excluded women and non-blast TBI	Adequate	Self-report of ≥1 injury item and ≥1 alteration/loss of consciousness or posttraumatic amnesia item on PDHA or PDHRA)	Self-report (PDHA)	N/A	**Moderate**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
MacGregor 2013[34]	EMED; OIF, completed PDHA and PDHRA; minor to moderate injury	Adequate	ICD-9 codes with injury severity codes for minor injury	Self-report (PDHRA)	N/A	**Moderate**
MacGregor 2010[35]	EMED; OIF male combatants who presented to forward deployed medical treatment facility for battle injury	Adequate	ICD-9 codes and narrative completed by provider at point of injury	ICD-9 codes	N/A	**Moderate**
Mora 2009[36]	OEF/OIF combat casualties injured in explosions and treated at US Army Burn Center; records from Joint Theater Trauma Registry;	Limited reporting	ICD codes and Abbreviated Injury Scale scores	Self-report (PCL-M)	N/A	**Moderate**
Pietrzak 2009[37]	Survey of subset of Connecticut OEF/OIF Veterans	Adequate	Self-report; VA 4-question screen	Self-report (PCL-M)	28.5%; respondents were older than non-respondents	**High**
Pogoda 2016[18]	OEF/OIF Veterans completing CTBIE 2007-2009; deployment TBI and complete data; VA/DoD databases for demographics and health information	Adequate	Clinician administered CTBIE	Clinician rating on CTBIE	N/A	**Moderate**
Polusny 2011[38]	US National Guard Brigade Combat Team; 1 month prior to return from deployment and 1 year after deployment	Adequate	Self-report; 3-items from DVBIC screen (injury with altered mental status or LOC)	Self-report (PCL-M, BDI-II, AUDIT)	50.4% for follow-up questionnaire; some differences between returners/non-returners	**Moderate**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Seal 2016{Seal, 2016 #232	OEF/OIF Veterans in CTBIE database; definitive TBI finding; complete data; other databases for demographics and utilization	Adequate	Clinician administered CTBIE	ICD-9 codes	N/A	**Moderate**
Taylor 2015[20]	Iraq and Afghanistan War Veterans using VHA FY2014; other databases for demographics, utilization, and health information	Adequate	ICD-9 codes	ICD-9 codes	N/A	**Moderate**
Tsai 2012[39]	Survey of Veterans in VA Hawaii Program Registry for OEF/OIF/OND (stratified sample – rural/urban, proportion of female Veterans)	Adequate	Self-report; VA 4-item screen (combat-related concussion and persistent postconcussive symptoms	Self-report (PCL-C and CAGE)	52%; respondents similar to others in Hawaii Registry but some differences from national samples of OEF/OIF Veterans	**Moderate**
Vanderploeg 2015[40]	Survey of Florida National Guard (deployed group returned from deployment a mean of 2.7 yrs prior)	Adequate	Self-report of event(s) resulting in LOC, "blacking out," or memory gaps and duration of memory gaps	Self-report (PCL, PHQ-9, GAD-7, AUDIT-C)	41.3%; 22% of respondents excluded after validity checks on responses	**Moderate**
Walker 2017[41]	Recruited by letters, advertisements, and ambulatory clinics at 1 VA PRC and 3 military bases; ≥1 blast experiences in past 2 years	Adequate	~50% interviewed by research staff with data reviewed by physicians; ~50% extrapolated from BESQ information	Self-report (PCL [version not reported], CESD)	N/A	**Moderate**

Author, year	Sampling appropriate[a]	Subject/setting details[b]	TBI identification[c]	Psychiatric measures[d]	Response rate[e]	Overall risk of bias rating
Wilk 2012[42]	3 Brigade Combat Teams from 1 Active Component Infantry Division; 4-6 months post-deployment; randomly selected ~50% for inclusion	Limited demographic information	Self-report of injury event resulting in concussion-related items (*eg*, dazed, not remembering the injury) based in DOD and VA TBI Screen	Self-report (PCL-17, PHQ-9)	N/A	**Moderate/high**
Yurgil 2014[43]	Data from longitudinal study of Marine and Navy servicemen from 4 infantry battalions stationed in S California	Adequate	Interview about head injury history	Clinician administered (CAPS-IV)	N/A	**Low**

[a]Was the sampling appropriate to achieve a nationally representative population of Service Members and Veterans? [b]Were the study subjects and the setting described in sufficient detail? [c]Were valid, standard methods used for the identification of mTBI for all participants? [d]Were valid, standard methods used to assess the mental health conditions for all participants? [e]Was the response rate adequate, and if not, was the low response rate managed appropriately?

Adapted from JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (Available at: http://joannabriggs.org/research/critical-appraisal-tools.html) Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

Shaded cells indicate nationally representative samples.

AUDIT-C=Alcohol Use Disorders Identification Test-Consumption Questions; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; BESQ=Blast Experience Screening Questionnaire; BHM-20=Behavioral Health Measure-20; CAGE=Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers; CAPS-IV=Clinician Administered PTSD Scale for DSM-IV; CESD=Centers for Epidemiological Studies Depression scale; CT=computed tomography; CTBIE=Comprehensive TBI Evaluation; DVBIC=Defense and Veterans Brain Injury Center; EMED=Expeditionary Medical Encounter Database; EMR=electronic medical record; GAD-7=Generalized Anxiety Disorders Questionnaire; LOC=loss of consciousness; MADRS=Montgomery-Asberg Depression Rating Scale; MAST=Michigan Alcohol Screening Test; N/A=not applicable; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; PCL=PTSD Checklist; PCL-M=PTSD Checklist-Military Version; PDHA=Post-Deployment Health Assessment; PDHRA= Post-Deployment Health Reassessment; PHQ-15 (-9)=Patient Health Questionnaire-15 item (-9 item); PNS=Polytrauma Network Site; PRC=Polytrauma Rehabilitation Center; PTA=posttraumatic amnesia; SBQ-R=Suicidal Behaviors Questionnaire-Revised; STDI=Structured TBI Diagnostic Interview; VHA=Veterans Health Administration

Table 4. Overview of Treatment Studies (KQ2)

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Bomyea, 2017[44] Design: Secondary analysis of a randomized controlled trial Funding: Department of Defense	Inclusion: Veterans with ≥1 anxiety or depressive disorders (including PTSD) based on DSM-IV, psychiatric diagnoses (Mini-International Neuropsychiatric Interview) and cognitive impairment (Montreal Cognitive Assessment) screened Exclusion: Interfering neurocognitive impairments, psychosis, bipolar illness, imminent suicidality or self-injury, anticipated change in pharmacologic treatment, concurrent psychotherapy for presenting complaint, or anticipation of inability to complete all study procedures	N=129 Mean age: 35 Male (%): 78% (TBI+ 87% vs TBI- 63%, P<.01) Race/ethnicity: Caucasian/white 77%; African American 9%; Asian 7%; Native American 3%; Biracial/Other 4% History of TBI (%): 64 Time since TBI: NR Time since discharge: NR Multiple TBI: NR TBI etiology: NR PTSD: NR History of depression: NR	Patient centered therapy (PCT): 12 sessions of individual PCT treatment Duration: 1-hour weekly	Acceptance and commitment therapy (ACT): 12 sessions of individual ACT treatment Duration: 1-hour weekly

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Chard, 2011[45] Design: Pre-post Funding: NR Psychiatric Condition: PTSD and depression	Inclusion: Veterans with current PTSD (CAPS-IV) using worst reported trauma, and history of TBI (severity definitions of TBI based on guidelines provided by DoD and VA; severity determined by examination of available medical records and patient interview) Exclusion: NR	N=28 mTBI, an additional 14 participants had moderate/ severe TBI Mean age: 34 Male (%): 100 Race/ethnicity: white 79% Time since TBI: ≥1 year Time since discharge: NR Multiple TBI (for all 47 – see note below): 81% TBI etiology (for all 47 – see note below): blast 62%, 36% motor vehicle accidents, 128% falls, other 47% (fights, sports) PTSD: 100% History of depression: 75%	Cognitive processing therapy-cognitive (CPT-C) in combined group and individual format as primary focus of active-trauma treatment; group held twice a week; individual CPT-C sessions a minimum of twice a week Duration: 7-weeks (residential) Note: Participants assessed posttreatment by independent evaluators who did not conduct their individual psychotherapy	NR

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Harch, 2012[46] Design: Pre-post, proof-of-concept Funding: NR Psychiatric Condition: PTSD	Inclusion: Service members and Veterans;18–65 years, ≥1 mild/moderate TBI (loss of consciousness due to blast injury, ≥1 year old, occurred after 9/11/01); prior diagnosis of chronic TBI/PCS or TBI/PCS/PTSD by military or civilian specialists, no acute cardiac arrest or hemorrhagic shock at time of TBI; Disability Rating Scale score 0–3, negative urine screen for drugs of abuse, <90% on Percent Back to Normal Rating Scale Exclusion: Pulmonary disease precluding HBO_2, unstable medical conditions contraindicated in HBO_2, severe confinement anxiety, participation in another trial with active interventions, inability to complete protocol, history of hospitalization for past TBI, stroke, non-febrile seizures or seizure history outside of TBI, mental retardation, alcohol or drug abuse, or systemic illness impacting central nervous system	N=16 Mean age: 30 Male (%): 100 Race/ethnicity: NR Time since TBI: 2.8 years Time since discharge: NR, 8 were active duty Multiple TBI: average was 2.7 (range 1-7) TBI etiology: blast 100% PTSD: 100% (DSM-IV) History of depression: NR	Hyperbaric oxygen therapy (HBO_2) Patients compressed and decompressed at 1–2 pounds per square inch on 100% oxygen; rate depended on patient comfort and preference; depth of pressurization was 1.5 ATA; total dive time 60 min Duration: 40 sessions in 30 days; treatment twice/day, 5 days/week, with 3- to 4-h surface interval between treatments; protocol goal was 40 sessions.	

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Ragsdale, 2016[47] Design: Pre-post, Retrospective data analysis Funding: NR Psychiatric Condition: PTSD	Inclusion: 41 OEF/OIF/OND Veterans, had completed either individual PE or individual CPT, assessed for PTSD by semi-structured interview based on DSM-IV, TBI status assessed by retrospective medical record reviews Exclusion: Veterans who received group therapy	N=41, 19 with TBI Mean age: 33 Male (%): 88 Race/ethnicity: Caucasian/white 85%; African American 7%; Hispanic/Latino 7% History of TBI (%): 46 Time since TBI: NR Time since discharge: NR Multiple TBI: NR TBI etiology: NR PTSD: 100% History of depression: NR, likely many also had depressive symptoms	Prolonged exposure (PE) therapy (n=21, 9 with TBI (43%)) Standard treatment in clinic provided by licensed psychologists or social workers (or trainees they supervised) who had completed or were engaged in VA certification for PE and CPT PE participants completed 6-15 (*mean*=10) sessions Duration: NR Note: Treatment providers were not necessarily blind to TBI status based on how TBI status was determined	Cognitive processing therapy (CPT**)** (n=20, 10 with TBI (50%)) CPT participants completed 7-16 (*mean*=12) sessions
Sripada, 2013[48] (Study 2) Design: Secondary data (post-hoc examination) from randomized controlled trial Funding: NR Psychiatric Condition: PTSD	Inclusion: Veterans in randomized trial diagnosed with PTSD using CAPS-IV Exclusion: NR	N=22, 8 (36%) with a TBI (most mild) Mean age: 33 Male (%): 91 Race/ethnicity: Caucasian/White 73; African American 23; Asian 4 History of TBI (%): 36 Time since TBI: NR Time since discharge: NR Multiple TBI: NR TBI etiology: NR PTSD (%): 100 History of depression (%): 57	Prolonged exposure (PE) therapy (a) psychoeducation (b) repeated in vivo exposure to commonly avoided trauma-related situations and cues (c) repeated imaginal exposure to traumatic memories and (d) subsequent discussion after imaginal exposures to facilitate emotional processing and corrective learning	Present centered therapy (PCT) Present centered and problem solving oriented approach to facilitate adaptive responses to ongoing stress and difficulties Duration: 10-12 sessions

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Wolf 2015[49] Design: Pre-post, retrospective clinical data review Funding: James V. Haley and Durham VA Medical Centers Psychiatric Condition: PTSD	Inclusion: Veterans or active duty service members referred for clinical treatment of PTSD, history of TBI by CTBIE, ongoing cognitive deficits based on self-report and corroborated by medical observation following injury, and neuropsychologic or neuroimaging Exclusion: Psychosis, unstable bipolar disorder, imminent suicidal or homicidal ideation, and recent aggressive behavior, self-harm, or severe substance dependence	N=69 (complete data for 44) Active duty (%): 26, 36% for completers Mean age: 34 Male (%): 94 Race/ethnicity (%): Caucasian/White 67; African American 19; Hispanic/Latino 12; Other 3 History of TBI (%): 100, 75% with mTBI, 71% for completers Time since TBI (years): 4.7, 4.8 (3.1) for completers Time since discharge: NR Multiple TBI: mean 2.8, 2.6 for completers TBI etiology (%): Blast 51, 52% for completers Non-blast 48 PTSD: 100% History of depression: 83%, 86% for completers	Prolonged exposure (PE) therapy (a) psychoeducation (b) repeated in vivo exposure to commonly avoided trauma-related situations and cues (c) repeated imaginal exposure to traumatic memories and (d) subsequent discussion after imaginal exposures to facilitate emotional processing and corrective learning Modifications (*ie,* memory-enhancing strategies (phones, digital assistants) and increased structure) were incorporated Duration: Bi-weekly sessions for 6-8 weeks (inpatient program); weekly sessions for 3-6 months (residential polytrauma program)	

Study, year (ref) Design Funding	Inclusion/Exclusion Criteria	Study Characteristics	Intervention 1 (describe)	Intervention 2 (describe)
Wolf, 2012[50] Pilot study Design: Prospective observational study Funding: Minneapolis and James V. Haley VA Medical Centers Psychiatric Condition: PTSD	Inclusion: Veterans with current diagnosis of PTSD using CAPS-IV and PCL-M, documented history of TBI by CTBIE, ongoing cognitive deficits based on self-report and corroborated by medical observation following injury, and neuropsychologic or neuroimaging Exclusion: Active psychosis, un-medicated bipolar disorder, imminent suicidal or homicidal ideation or self-harm, and severe uncontrolled substance dependence	*Pilot study* N=10 Mean age: 33 Male (%): 100 Race/ethnicity (%): Caucasian/White 40; Hispanic/Latino 50; Asian 10 History of TBI (%): 100 Time since TBI: NR Time since discharge: NR Multiple TBI: NR TBI etiology: NR PTSD: 100% History of depression: 40% with a prior suicide attempt	Prolonged exposure (PE) therapy (a) psychoeducation (b) repeated in vivo exposure to commonly avoided trauma-related situations and cues (c) repeated imaginal exposure to traumatic memories and (d) subsequent discussion after imaginal exposures to facilitate emotional processing and corrective learning Modifications (*ie,* memory-enhancing strategies (phones, digital assistants), increased structure, and additional session time) were incorporated Duration: Average of 13 sessions (range 8-18) for 120 minutes NOTE: PE initiated after window of expected recovery for TBI was lapsed	

ATA=atmospheres absolute; CAPS-IV=Clinician-Administered PTSD Scale for DSM-IV; CTBIE=Comprehensive TBI Evaluation; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders- 4th Edition; NR=not reported; PCL=PTSD checklist (M=Military version); PCS=post-concussive syndrome; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury

Table 5. Outcomes from Treatment Studies (KQ2)

Study, year (ref) Treatment(s)	Outcome 1 (describe) (n) Mean (SD)	Outcome 2 (describe) (n) Mean (SD)	Outcome 3 (describe) (n) Mean (SD)	Outcome 4 (describe) (n) Mean (SD)
Bomyea, 2017[44] Present Centered Therapy and Acceptance and Commitment Therapy	NR	NR	*Present Centered Therapy* **BSI-18 (≥63=clinical elevation)** *Anxiety or depressive disorder and TBI (n=42)* Pre-treatment: 74.7 (7.7) Post-treatment: ~69 (figure) P NS *Without TBI* (n=25) Pre-treatment: 72.6 (7.6) Post-treatment: ~64 (figure)	*Acceptance and Commitment Therapy* **BSI-18 (≥63=clinical elevation)** *Anxiety or depressive disorder and TBI (n=41)* Pre-treatment: 73.3 (8.5) Post-treatment: ~68 (figure) P NS *Without TBI* (n=21) Pre-treatment: 72.5 (8.0) Post-treatment: ~65 (figure)
Chard, 2011[45] Cognitive Processing Therapy-Cognitive	**CAPS-IV** (n=28) **(cut-off NR)** Pre-treatment: 75.1 (5.9) Post-treatment: 49.0 (22.3) P<.01 vs baseline	**PCL (version not reported)** (n=28) **(cut-off NR)** Pre-treatment: 61.8 (10.3) Post-treatment: 46.5 (16.1) P<.01 vs baseline	**BDI-II** (n=28) **(cut-off NR)** Pre-treatment: 32.6 (10.7) Post-treatment: 23.7 (11.0) P<.01 vs baseline	NR
Harch, 2012[46] Hyperbaric oxygen therapy *Proof-of-concept study*	**PCL-M** (n=16) **(cut-off=50)** Pre-treatment: 67.4 (10.5) Post-treatment: 47.1 (16.0) Mean difference -20.3 [95%CI -30.4 to -10.2] P<.0001 vs baseline	NR	**PHQ-9 Depression** (n=16) **(cut-off NR)** Pre-treatment: 16.6 (4.9) Post-treatment: 8.2 (4.7) Mean difference -8.4 [95%CI -12.5 to -4.3] P<.0001 vs baseline	**GAD-7 Anxiety** (n=16) **(cut-off NR)** Pre-treatment: 12.7 (5.8) Post-treatment: 7.9 (5.3) Mean difference -4.8 [95%CI -8.0 to -1.6] P<.007 vs baseline

Study, year (ref) Treatment(s)	**Outcome 1 (describe) (n) Mean (SD)**		**Outcome 2 (describe) (n) Mean (SD)**	**Outcome 3 (describe) (n) Mean (SD)**		**Outcome 4 (describe) (n) Mean (SD)**
Ragsdale, 2016[47] Cognitive Processing Therapy and Prolonged Exposure Therapy	*Prolonged exposure therapy* **PCL-S (cut-off=50)** *PTSD+TBI* (n=9) Pre-treatment: 62.7 (11.4) Post-treatment: 32.9 (16.0) Change: -29.8 (13.7) *PTSD only* (n=12) Pre-treatment: 63.8 (8.4) Post-treatment: 29.2 (11.6) Change: -34.6 (10.3)	*Cognitive processing therapy* **PCL-S cut-off=50)** *PTSD+TBI* (n=10) Pre-treatment: 59.3 (12.1) Post-treatment: 42.9 (13.8) Change: -16.4 (8.8) *PTSD only* (n=10) Pre-treatment: 55.3 (11.5) Post-treatment: 43.8 (18.4) Change: -11.5 (14.1)	NR	*Prolonged exposure therapy* **BDI-II (clinical cut off NR)** *PTSD+TBI* (n=9) Pre-treatment: 28.3 (15.2) Post-treatment: 12.1 (14.6) Change: -16.2 (8.7) *PTSD only* (n=12) Pre-treatment: 30.1 (11.9) Post-treatment: 12.8 (13.8) Change: -17.3 (10.4)	*Cognitive processing therapy* **BDI-II (clinical cut off NR)** *PTSD+TBI* (n=10) Pre-treatment: 26.1 (11.1) Post-treatment: 19.8 (15.0) Change: -6.3 (7.9) *PTSD only* (n=10) Pre-treatment: 26.6 (7.4) Post-treatment: 19.8 (12.6) Change: -6.8 (10.0)	NR

Study, year (ref) Treatment(s)	**Outcome 1 (describe) (n) Mean (SD)**	**Outcome 2 (describe) (n) Mean (SD)**		**Outcome 3 (describe) (n) Mean (SD)**	**Outcome 4 (describe) (n) Mean (SD)**
Sripada, 2013[48] (Study 2) Present Centered Therapy and Prolonged Exposure Therapy	*Combined present centered and prolonged exposure therapy groups* **CAPS-IV** (n=22) **(reduction of 10 points=clinically significant reduction in PTSD)** Pre-treatment: 78.4 (11.3) Post-treatment: 41.4 (26.0) P<.001 vs pre-treatment **CAPS-IV (reduction of 10 points=clinically significant reduction in PTSD)** *TBI only* (n=8) Pre-treatment: 82.4 (11.7) Post-treatment: 45.5 (32.5) P<.001 vs pre-treatment *PTSD only* (n=14) Pre-treatment: 76.1 (10.8) Post-treatment: 39.1 (22.5) P NR	*Present centered therapy* **CAPS-IV (reduction of 10 points=clinically significant reduction in PTSD)** *PTSD+TBI* Pre-treatment: 82.0 (9.3) Post-treatment: 66.3 (27.3) P NS between treatments at either time point	*Prolonged exposure therapy* **CAPS-IV (reduction of 10 points=clinically significant reduction in PTSD)** *PTSD+TBI* Pre-treatment: 82.8 (15.3) Post-treatment: 24.8 (23.8)	NR	NR
Wolf 2015[49] Prolonged Exposure Therapy	**PCL (version not reported)** (n=69) **(cut-off=49)** Pre-treatment: 64.8 (10.1) Post-treatment: 43.5 (16.8) **PCL for completers** (n=44) Pre-treatment: 63.5 (9.2) Post-treatment: 34.8 (10.7)	NR		**BDI-II** (n=69) **(cut-off=14)** Pre-treatment: 29.6 (9.5) Post-treatment: 18.1 (12.6) **BDI-II for completers** (n=44) Pre-treatment: 29.1 (8.6) Post-treatment: 13.9 (10.3)	NR

Study, year (ref) Treatment(s)	Outcome 1 (describe) (n) Mean (SD)	Outcome 2 (describe) (n) Mean (SD)	Outcome 3 (describe) (n) Mean (SD)	Outcome 4 (describe) (n) Mean (SD)
Wolf, 2012[50] Prolonged Exposure Therapy *Pilot study*	**PCL-M** (n=10) **(cut-off=49.5)** Pre-treatment: 69.2 (8.1) Post-treatment: 38.0 (9.0) P<.001 Note: Based on a cut-off score of 49.5, 90% of participants achieved a clinically significant change	NR	**BDI-II** (n=10) **(cut-off=14.9)** Pre-treatment: 34.4 (9.7) Post-treatment: 17.7 (8.6) P<.001 Note: Based on a cut-off score of 14.9, 40% of participants achieved a clinically significant change	NR

AUDIT=Alcohol Use Disorders Identification Test; BDI-II=Beck Depression Inventory-II; BSI-18=Brief Symptom Inventory-18; CAPS=Clinician-Administered PTSD Scale; CPT=Cognitive Processing Therapy; GAD-7=Generalized Anxiety Disorder 7-item scale; EO=education only; PE=Prolonged Exposure Therapy; PCL=PTSD Checklist; PCL-M=PTSD Checklist-Military Version; PCL-S=PTSD Checklist-Specific; PCT=Present Centered Therapy; PHQ-9=9-item Patient Health Questionnaire; PST=problem-solving treatment; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury

Table 6. Risk of Bias for Treatment Studies (KQ2)

Author, year	Sampling appropriate[a]	Follow-up complete[b]	Standard assessment methods[c]	Manual-based/fidelity monitored[d]	Independent outcome assessment[e]	Overall rating
Bomyea 2017[44]	Yes, secondary analysis of an RCT	Unclear, but the RCT notes all were analyzed	Yes, DSM-IV	Unclear, but the RCT notes fidelity was monitored independently	Unclear	Moderate
Chard 2011[45]	No control	Yes, completers only in analyses but reasons for non-completion stated	Yes, CAPS-IV	Yes/No, lack of treatment fidelity data	Yes, by "independent evaluators who did not conduct their individual psychotherapy"	Moderate
Harch 2012[46]	No control	Completers only, 1 (6%) withdrawal	Yes, DSM-IV	Not applicable	Unclear	Moderate
Ragsdale 2016[47]	No control, retrospective analysis	Unclear, completers only with no further details	Yes, interview based on DSM-IV diagnostic criteria	Yes/No, lack of treatment fidelity data	No, treatment providers were not necessarily blind to TBI status	Moderate/High
Sripada 2013[48]	No control (sample characteristics combined, post-hoc data from RCT)	Unclear, completers only with no further details	Yes, CAPS-IV	Yes/No, "treatment sessions were not coded for treatment fidelity"	Unclear, none noted	Moderate
Wolf 2015[49]	No control, retrospective analysis	Yes, differences between completers and non-completers addressed	Unclear ("evaluated by a psychiatrist or psychologist to confirm the diagnosis")	Yes/No, lack of treatment fidelity data ("no formal monitoring of the delivery of PE, and it was clear that there were nonstandard elements added for many participants")	Unclear, none noted	Moderate/High
Wolf 2012[50]	No control, possible selection bias	Yes, follow-up for all 10 participants	Yes, CAPS-IV	Yes/No fidelity data reported; noted that "very few modifications to the treatment manual were necessary …with exception of memory-enhancing strategies"	Unclear, none noted	Moderate/High

[a]Were the participants included in any comparisons similar at baseline? [b]Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? [c]Were standard methods used to assess the psychiatric conditions for all participants? [d]If applicable, was the therapy manual-based and was treatment fidelity monitored? [e]Were the outcomes of participants included in any comparisons measured by outcomes assessors independent of the intervention?

Adapted from JBI Critical Appraisal Tool for Quasi-Experimental Studies (experimental studies without random allocation) (Available at: http://joannabriggs.org/research/critical-appraisal-tools.html)

Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017.