
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 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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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

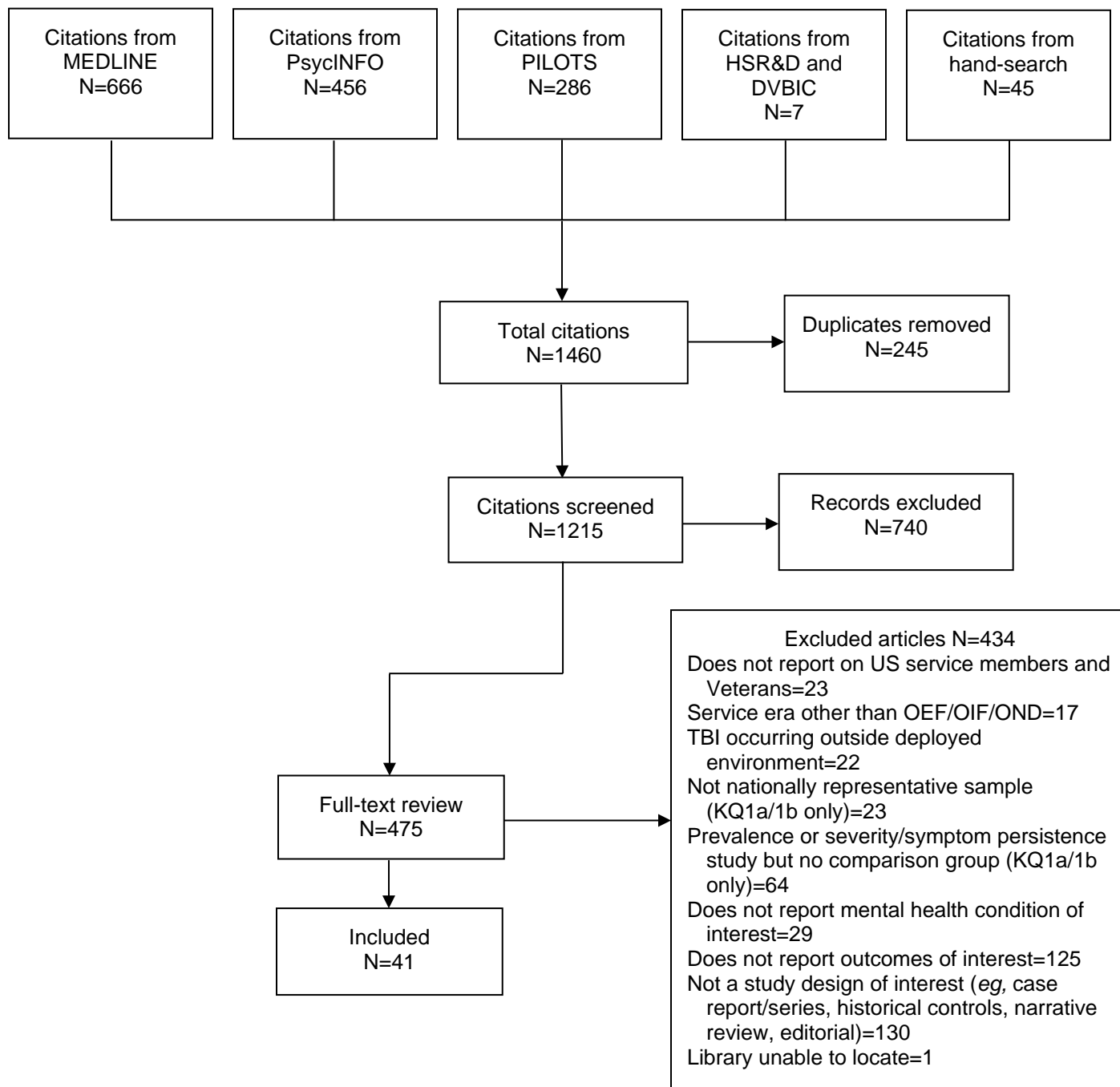
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C and the report was modified as needed.

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 sample¹⁰⁻²⁰ 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 Army¹⁰ or US Army Special Operations Command personnel¹⁶ 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 months⁴⁰) and one reported time since discharge (430 days²⁶). 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
<i>GEOGRAPHICALLY DIVERSE SAMPLES (k=22)</i>														
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

^aReported 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 study¹⁹ 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).

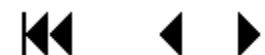
Geographically Diverse Samples

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 scores³⁶ 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

^aHigher 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	<ul style="list-style-type: none"> · 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	<ul style="list-style-type: none"> · Severity of symptoms rarely reported
Depressive disorders	0		
Substance use disorders	1		
Suicidal ideation	0		
Anxiety disorders	0		

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

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=postraumatic 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 Questionnaire¹⁷ 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 unspecified²⁶ 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} 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 tobacco¹² or drug abuse¹³ 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 unspecified²⁶ 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 abuse²⁸ or any substance disorder³⁵ 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 mTBI¹² 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 unspecified²⁶ or mTBI²¹ 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 (HBO₂) 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]

^aMean number of sessions completed in TBI group = 8.9 (not reported by intervention)

^bParticipants 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	<i>History of TBI</i> Change from Pre-treatment mean (SD); n	<i>No History of TBI</i> Change from Pre-treatment mean (SD); n	Effect Size (ES) [95%CI] Based on mean change from baseline for each group
<i>CPT, Veterans with TBI+PTSD vs PTSD only</i>				
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]
<i>PE, Veterans with TBI+PTSD vs PTSD only</i>				
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]
<i>CPT combined with PE, Veterans with TBI+PTSD vs PTSD only</i>				
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]
<i>PCT, Veterans with TBI vs no TBI history</i>				
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
<i>ACT, Veterans with TBI vs no TBI history</i>				
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
<i>PE combined with PCT, Veterans with TBI+PTSD vs PTSD only</i>				
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	<ul style="list-style-type: none"> • 4 small nonrandomized studies with a pre- and post-study design and 2 small post-hoc analysis of RCTs were evaluated; risk of bias was moderate to high • Improvements in PTSD and depressive symptom scale scores were observed with all therapies and were consistent across studies where multiple studies existed but lack of usual care or wait-list control group limits interpretation of the effect • No differences in outcomes regardless of TBI status (history or no history; data from 3 studies) however studies were not specifically designed to examine differential effectiveness by TBI status and were likely underpowered to do so
Prolonged Exposure Therapy (PE)	3		
Acceptance and Commitment Therapy	1		
Present Centered Therapy	1		
PE combined with Present Centered Therapy (PCT)	1		
Non-behavioral Therapies			
Hyperbaric oxygen therapy	1	Insufficient	<ul style="list-style-type: none"> • One small pre- and post-study, moderate risk of bias • Improvement in PTSD symptom scale
Pharmacological	0	Insufficient	<ul style="list-style-type: none"> • No studies identified

PTSD=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-PTSD 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 HBO₂ 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 HBO₂ 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 (HBO₂) for post-concussion syndrome (PCS) and PTSD in service members and Veterans with a history of mild to moderate blast-related TBI. No studies reported on treatments for substance use disorders or suicidal ideation 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 HBO₂ for PCS and PTSD among service members and Veterans with mild to moderate TBI reported a significant reduction in PCL-M scores following treatment (insufficient evidence, 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 HBO₂ for service members with a history of TBI and PTSD. Other reviews have looked at HBO₂ 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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