
Chronic Pain in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury: A Systematic Review

August 2020

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:

Evidence Synthesis Program (ESP) Center
Portland VA Medical Center
Portland, OR
Devan Kansagara, MD, MCR, Director

Authors:

Principal Investigator:

Maya E. O'Neil, PhD
Kathleen F. Carlson, PhD

Co-Investigators:

Haley K. Holmer, PhD
Chelsea K. Ayers, MPH
Benjamin J. Morasco, PhD
Devan Kansagara, MD, MCR
Karli Kondo, PhD



U.S. Department of Veterans Affairs

Veterans Health Administration
Health Services Research & Development Service



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 three 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.

Recommended citation: O'Neil ME, Carlson KF, Holmer HK, Ayers CK, Morasco BJ, Kansagara D, Kondo K. Chronic Pain in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #05-225; 2020. Available at: <https://www.hsrd.research.va.gov/publications/esp/reports.cfm>.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the VA Portland Healthcare System, Portland, OR, 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 the VHA Committee on the Care of Veterans with Traumatic Brain Injury (TBI) for an evidence review on the epidemiology, assessment, and treatment of chronic pain complicated by co-occurring mild traumatic brain injury (mTBI) in combat veterans. 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 Robin Paynter, MLIS, and 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.

Stuart Hoffman, PhD

Scientific Program Manager, VA Office of Research and Development
Veterans Health Administration, Washington, DC

Ralph DePalma, MD, FACS

Special Operations Officer, VA Office of Research and Development
Veterans Health Administration, Washington, DC

Audrey Kusiak, PhD

Scientific Program Manager, VA Office of Research and Development
Veterans Health Administration, Washington, DC

David Cifu, MD

Senior TBI Specialist, VA Office of Research and Development
Veterans Health Administration, Washington, DC

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:

Friedhelm Sandbrink, MD
George Washington University & VA Central Office
Washington, DC

Joel Scholten, MD
Georgetown University & VA Central Office
Washington, DC

Linda Picon, MCD, CCC-SLP
VA Central Office
Washington, DC

Lisa Brenner, PhD, ABPP
VA Eastern Colorado Health Care System
Aurora, CO

Mary Jo Pugh, PhD, RN
The University of Utah School of Medicine & Salt Lake City VA Health Care System
Salt Lake City, UT

Erin Krebs, MD, MPH
University of Minnesota & Minneapolis VA Health Care System
Minneapolis, MN

Robert Kerns, PhD
Yale University
New Haven, CT

Jason Sico, MD, MHS
Yale School of Medicine & VA Connecticut Healthcare System
New Haven, CT

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.

TABLE OF CONTENTS

PREFACE	I
ACKNOWLEDGMENTS	II
ABSTRACT	1
EXECUTIVE SUMMARY	2
Aim	2
Methods.....	2
Results.....	3
Figure i. Number of studies reporting prevalence of chronic pain in Veterans/Service members with history of mTBI, by pain type	3
Figure ii. Range of chronic pain prevalence estimates by pain type across studies	5
Conclusion	9
Abbreviations Table.....	10
EVIDENCE REPORT	13
INTRODUCTION	13
METHODS	15
Topic Development.....	15
Search Strategy	16
Study Selection	16
Data Abstraction	20
Quality Assessment.....	20
Data Synthesis.....	20
Rating the Body of Evidence	20
RESULTS	22
Key Question 1: What is the prevalence of chronic pain in US Veterans or Service members with a history of mTBI?	24
Summary of Findings.....	24
Detailed Results	38
Key Question 2: What is the risk of suicide in US Veterans or Service members with chronic pain and a history of mTBI?	63
Summary of Findings.....	63

Key Question 3. What are the benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI?.....	64
Summary of Findings.....	64
Detailed Results	64
DISCUSSION	71
Conclusion	78
REFERENCES.....	80

TABLES

Table 1. PICOTS by Key Question.....	18
Table 2. Characteristics of studies reporting prevalence of chronic pain in Veterans/Servicemembers with a history of mTBI.....	25
Table 3. Prevalence estimates of general chronic pain from studies of Veterans/Servicemembers with a history of mTBI.....	39
Table 4. Prevalence estimates of head pain from studies of Veterans/Servicemembers with a history of mTBI.....	42
Table 5. Prevalence estimates of other chronic pain from studies of Veterans and Servicemembers with a history of mTBI.....	49
Table 6. Prevalence of Chronic Pain in Veterans and Servicemembers with a History of mTBI by mTBI Etiology	57
Table 7. Characteristics of studies of interventions for headaches in participants with a history of mTBI.....	65
Table 8. Findings of studies of interventions for headaches in participants with a history of mTBI.....	68
Table 9. Risk of bias in trials of interventions for chronic pain in Veterans with a history of mTBI.....	70
Table 10. Criteria used in quality assessment of randomized controlled trials	93
Table 11. Quality ratings for studies reporting prevalence of chronic pain in Veterans/Servicemembers with history of mild traumatic brain injury.....	94

FIGURES

Figure 1. Analytic Framework.....	16
Figure 2. Literature Flow Chart	23
Figure 3. Prevalence of general chronic pain in Veterans/Servicemembers with a history of mTBI by study and pain measurement tool	60

Figure 4. Prevalence of head pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool..... 61

Figure 5. Prevalence of back pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool..... 62

Figure 6. Prevalence of neck pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool..... 62

Figure 7. Prevalence of arm, leg, and/or joint pain in Veterans and Servicemembers with a history of mTBI by study and pain measurement tool..... 63

Figure 8. Number of studies reporting prevalence of chronic pain in Veterans and Servicemembers with mTBI by pain type 71

Figure 9. Range of chronic pain prevalence estimates by pain type across studies..... 73

APPENDIX A. SEARCH STRATEGIES..... 85

APPENDIX B. STUDY SELECTION 91

APPENDIX C. QUALITY ASSESSMENT..... 93

APPENDIX D. STUDIES EXCLUDED AT FULL TEXT LEVEL..... 99

APPENDIX E. PEER REVIEW COMMENTS/AUTHOR RESPONSES..... 111

EVIDENCE REPORT

INTRODUCTION

The post-9/11 military operations in and around Afghanistan and Iraq (Operations Enduring Freedom, Iraqi Freedom, and New Dawn, or OEF/OIF/OND) have served to highlight the high prevalence of mild traumatic brain injury (mTBI) in Servicemembers (SMs) and Veterans, often referred to as the “signature injury” of these conflicts.¹⁵ Approximately 413,000 SMs have experienced a traumatic brain injury (TBI) since the year 2000, and over 80% of those were classified as mild in severity.¹⁶

Mild TBI often resolves completely and quickly, without the need for much or any intervention. However, up to one-third of individuals who experience an mTBI have a longer and/or more severe symptom course.^{17,18} It is not clear why some individuals experience long-term sequelae from mTBI events while others experience complete resolution.¹⁹ Among SMs and Veterans in particular, it is also unclear whether symptoms and sequelae that are attributed to mTBI are due to the mTBI itself or, rather, are physical and mental health outcomes related to the same exposures (*ie*, related to combat) that led to the mTBI.

Regardless of the source, it is important to provide rehabilitative services to individuals with a history of mTBI to maximize functional outcomes.¹⁹ To meet Veterans’ needs, the Department of Veterans Affairs (VA) Veterans Health Administration (VHA) developed a comprehensive system of care to ensure that those exposed to mTBI and who may be experiencing long-term sequelae are referred for appropriate services. This TBI/Polytrauma System of Care involves a brief screen, used universally with nearly all OEF/OIF/OND Veterans, to detect potential history of mTBI plus current symptoms that may be related; a follow-up clinical evaluation (the Comprehensive TBI Evaluation, or CTBIE) with a specialist to confirm whether symptoms are or are not related to mTBI, and to provide referrals for related care needs; and a network of polytrauma providers and clinics to ensure Veterans’ TBI-related needs are met.²⁰ The TBI/Polytrauma System of Care has been lauded for ensuring that Veterans with mTBI-related symptoms and sequelae are identified and receive care that maximizes functioning and quality of life.²¹ However, the screening and evaluation program has also been criticized for causing inflated symptom reporting, reduced recovery expectations, and leading to other iatrogenic effects among Veterans who may not otherwise experience long-term effects of mTBI.^{22,23}

Common sequelae and health conditions that are associated with mTBI include mental health concerns such as posttraumatic stress disorder (PTSD) and depression, cognitive problems, sensory sensitivity, and chronic pain,^{17,18,24} which are often associated with significant functional limitations. Due to the common co-occurrence of mTBI, PTSD, and chronic pain among SMs and Veterans, clinicians and researchers have described these comorbidities as the polytrauma clinical triad.²⁵ The extent to which these comorbidities interact to further increase the risk of functional limitations or other adverse outcomes beyond mTBI history alone is unknown, but the number of patients meeting the polytrauma clinical triad definition, and the potential for poor outcomes among these individuals, warrants close attention. While some recent clinical intervention research has targeted comorbid mTBI and PTSD (*eg*, Pagulayan et al, 2017²⁶), there

is very limited research on interventions specifically targeting chronic pain among individuals with a history of mTBI (*eg*, Irvine, 2018²⁷) or targeting the triad of conditions.

The rate of suicide among military SMs and Veterans is higher than among the general US population and continues to increase annually.²⁸ Although the reasons for increased risk of suicide among SMs and Veterans, relative to others, are not well understood, both mTBI and pain have been identified as risk factors in both Veteran and non-Veteran populations.^{10,11,29,30}

Whether or not comorbid mTBI and pain would interact to increase risk of suicide beyond the risk associated with either condition alone is unknown, but it stands to reason that SMs and Veterans with a history of both mTBI and pain are a potentially high-risk population.

Understanding this risk and developing therapies or other interventions that can reduce it, in this population or among SMs and Veterans more generally, is critical.

Because these complexities and additional clinical complications may be present when mTBI and pain are co-occurring, there is a need to better understand both the epidemiology of these conditions and their potential impact on risk of suicide and suicide-related behaviors. There is also a need for a comprehensive understanding of the effectiveness of intervention research targeting chronic pain among individuals with a history of mTBI. The purpose of this systematic review is to address these epidemiologic and clinical research questions by identifying and synthesizing existing literature on mTBI and chronic pain, highlighting research gaps and future research needs, as well as describing evidence specifically related and relevant to Veterans and SMs.

METHODS

TOPIC DEVELOPMENT

This topic was nominated by the VHA Committee on the Care of Veterans with TBI. The scope was refined through a process that included a preliminary review of published peer-reviewed literature and consultations with our operational partners and a technical expert panel (TEP). Our approach was guided by a conceptual framework developed in consultation with our operational partners and TEP (Figure 1. Analytic Framework).

The Key Questions (KQs) for this systematic review were:

KQ1: What is the prevalence of chronic pain in US Veterans or Servicemembers with a history of mTBI?

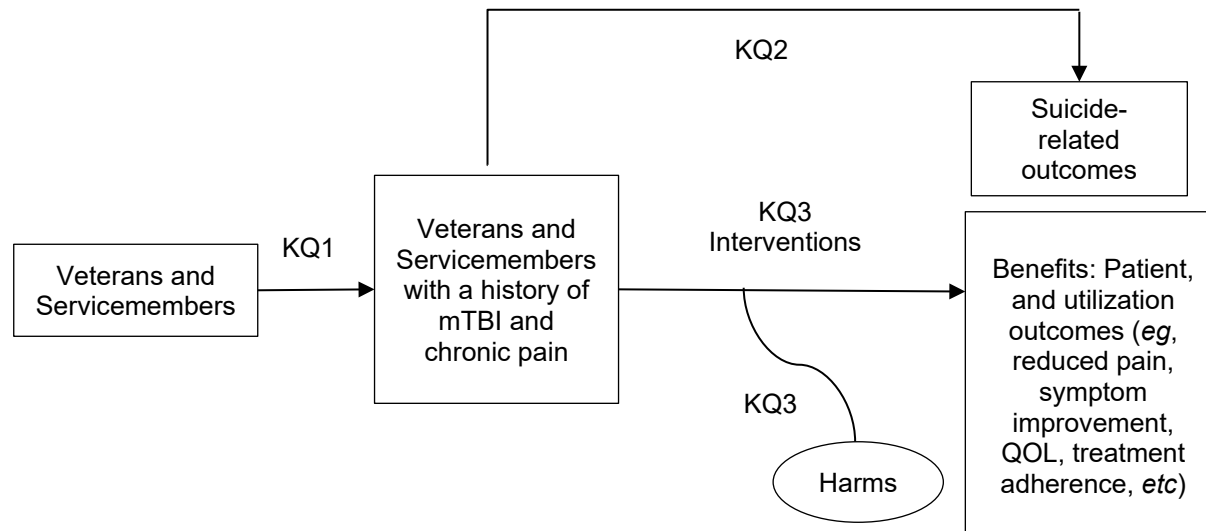
- a. What are the most common types of chronic pain in US Veterans or Servicemembers with a history of mTBI?
- b. Do the prevalence or types of chronic pain experienced by US Veterans or Servicemembers with a history of mTBI differ by mTBI etiology?
- c. How do estimates of the prevalence of chronic pain and mTBI in US Veterans or Servicemembers differ according to pain measurement methods or definitions?

KQ2: What is the risk of suicide in US Veterans or Servicemembers with chronic pain and a history of mTBI?

- a. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with a history of mTBI and chronic pain compare to US Veterans or Servicemembers with no mTBI history and/or no chronic pain?
- b. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and history of mTBI compare to civilians with chronic pain and history of mTBI?
- c. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and a history of mTBI vary depending on mTBI etiology?
- d. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and a history of mTBI vary depending on prescription opioid use or opioid use disorder?

KQ3: What are the benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI?

- a. Do the benefits or harms differ by mTBI etiology, type of chronic pain, mental health comorbidities, intervention setting, and demographics?
- b. How is pain assessed in clinical trials for comorbid chronic pain and history of mTBI in Veterans and Servicemembers?

Figure 1. Analytic Framework

Abbreviations: KQ=Key Question; mTBI=Mild traumatic brain injury; QOL=Quality of Life

SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian and were peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS).³¹ We conducted a review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the research questions. To identify relevant studies, we searched Ovid Medline; Ovid EBM Reviews: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews; Ovid PsycINFO; CINAHL; Scopus (conference abstracts only); Google Scholar; and Epistemonikos. We searched all available years of publication from database inception (1946 for Ovid MEDLINE®) through February 7, 2020 (March 4, 2020 for Medline). In the Medline database, we were able to further limit the population with search terms to identify Veterans and/or Servicemembers, and we also conducted a supplementary search with Veteran/Servicemember terms in PsycINFO. We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; See Appendix A for full search strategies).

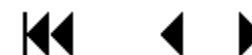
STUDY SELECTION

Criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS) were developed in collaboration with our operational partners and TEP (see Table 1). Two investigators independently reviewed the first 42% of titles and abstracts for relevance in order to establish consistency in application of inclusion and exclusion criteria. The remaining titles and abstracts did not contain relevant keywords and were assessed for inclusion by 1 reviewer. Two reviewers then independently assessed the full text of all citations included at the abstract screening phase. All discordant results were resolved through consensus or consultation with a third reviewer. Articles meeting eligibility criteria were included for data abstraction.

For Key Questions 1 and 2, we included primary studies reporting chronic pain prevalence estimates in US Veterans and/or SMs with a history of mTBI. For Key Question 3, we included randomized and non-randomized controlled trials on interventions for chronic pain in Veterans and/or SMs with a history of mTBI from any country. Cohort, prospective, and retrospective studies were also includable for KQ3. Chronic pain was defined as pain lasting or recurring for more than 3 months.¹ We considered any pain measure that was not clearly described as measuring acute pain to be chronic pain (*eg*, pain over last 30 days, headaches, *etc*), along with proxies for chronic pain such as diagnosis codes in healthcare records, analgesic medication use, and conditions usually accompanied by chronic pain (*eg*, arthritis). We included prevalence estimates for these definitions of chronic pain from any study population that was defined as having a history of mTBI, granted that a clear definition of mTBI was provided. For this report, mild TBI was defined using the VA and Department of Defense common definition of an external force to the head followed by immediate neurological symptoms as indicated by ≤ 30 minutes of loss of consciousness, 0-1 days of posttraumatic amnesia, or up to 24 hours of altered mental status; individuals had to have normal structural imaging, if completed.² We excluded studies that reported results for a mixed TBI population (mild plus moderate and/or severe) based on the definition of mTBI (See Table 1 and Appendix B for details). Citation lists of included systematic reviews were reviewed for relevant studies. For each key question of interest, we used a “best evidence” approach to guide additional study design criteria depending on the question under consideration and the literature available.³²

Table 1. PICOTS by Key Question

<p>Key Questions:</p>	<p>KQ1: What is the prevalence of chronic pain in US Veterans or Servicemembers with a history of mTBI?</p> <p>a. What are the most common types of chronic pain in US Veterans or Servicemembers with a history of mTBI?</p> <p>b. Do the prevalence or types of chronic pain experienced by US Veterans or Servicemembers with a history of mTBI differ by mTBI etiology?</p> <p>c. How do estimates of the prevalence of chronic pain and mTBI in US Veterans or Servicemembers differ according to pain measurement methods or definitions?</p>	<p>KQ2: What is the risk of suicide in US Veterans or Servicemembers with chronic pain and a history of mTBI?</p> <p>a. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with a history of mTBI and chronic pain compare to US Veterans or Servicemembers with no mTBI history and/or no chronic pain?</p> <p>b. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and history of mTBI compare to civilians with chronic pain and history of mTBI?</p> <p>c. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and a history of mTBI vary depending on mTBI etiology?</p> <p>d. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with chronic pain and a history of mTBI vary depending on prescription opioid use or opioid use disorder?</p>	<p>KQ3: What are the benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI?</p> <p>a. Do the benefits or harms differ by mTBI etiology, type of chronic pain, mental health comorbidities, intervention setting, and demographics?</p> <p>b. How is pain assessed in clinical trials for comorbid chronic pain and history of mTBI in Veterans and Servicemembers?</p>
<p>Population</p>	<p>US Veterans or Servicemembers with mTBI and chronic pain or headaches; studies reporting a mixed sample of mild and moderate/severe TBI will be excluded if mTBI results are not reported separately</p>		<p>Veterans or Servicemembers from any country with mTBI and chronic pain or headaches; studies reporting a mixed sample of mild and moderate/severe TBI will be excluded if mTBI results are not reported separately</p>
<p>Intervention</p>	<p>NA</p>		<p>Pharmacologic, nonpharmacologic, and complementary and integrative health interventions</p>
<p>Comparator</p>	<p>mTBI injury type, direct comparisons to those with no mTBI history and/or no chronic pain, direct comparisons of US Veterans or Servicemembers and civilians</p>		<p>Placebo, active comparator, usual care, wait-list control, pre-post</p>
<p>Outcome</p>	<p>Prevalence, demographics, chronic pain types</p>	<p>Suicide-related outcomes (including suicide, suicidal ideation/intent/plan, and suicidal self-directed harm)</p>	<p>Benefits: Intermediate and patient outcomes, utilization (eg, reduced pain, mental health diagnosis/symptoms,</p>



			opioid use; better QOL, functioning, treatment adherence) Harms: AEs, SAEs, withdrawals due to AEs
Timing	Any		
Setting	United States		Any
Study Design	Primary studies that include frequencies; Systematic reviews*. Exclude: Case studies/reports, non-systematic reviews, modeling studies.		RCT, NRCT, cohort, prospective, retrospective studies; Systematic reviews*. Exclude: Case studies/reports, non-systematic reviews, modeling studies.

* Reference lists from relevant systematic reviews were reviewed.

Abbreviations: AE=adverse event; mTBI=mild traumatic brain injury; NA=not applicable; NRCT=non-randomized controlled trial; PICOTS=population, interventions, comparators, timing, setting, and study design; QOL=quality of life; RCT=randomized controlled trial; SAE=severe adverse event; US=United States

DATA ABSTRACTION

Data from studies meeting inclusion criteria were abstracted by 1 reviewer and confirmed by at least 1 additional reviewer. From each study, we abstracted the following *a priori*-defined categories of data when reported in the publications: study design, sample size, setting, population characteristics (including demographics, military service characteristics, and mental health comorbidities where available), definitions and operationalizations of mTBI and pain, participant inclusion and exclusion criteria, and results. In studies where comparison data were presented for groups without mTBI, these pain prevalence estimates were also abstracted. For intervention studies, we also abstracted intervention and comparator characteristics including dosage, timing, and duration of treatment, duration of follow-up, adjunctive interventions (if applicable), and behavioral and health outcomes, as well as relevant harms.

QUALITY ASSESSMENT

Two reviewers independently assessed the methodological quality of each study using established methods for each study design. To assess risk of bias (RoB), we used the Cochrane Risk-of-Bias 2.0 criteria³³ for RCTs and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I)³⁴ for non-randomized intervention studies. We adapted the Newcastle-Ottawa Scale³⁵ supplemented with another critical appraisal tool for prevalence studies³⁶ for all other study designs (see Appendix C). Ratings of quality were specific to the outcome of interest (*ie*, prevalence of chronic pain or suicide for KQs 1 & 2 and treatment of chronic pain in KQ3). Disagreements were resolved by consensus of a third reviewer and/or the entire review team.

DATA SYNTHESIS

We qualitatively synthesized the evidence for all key questions and presented the findings in tables. We were not able to conduct quantitative meta-analyses for prevalence estimates because of the heterogeneity of study populations and chronic pain and mTBI measures across studies. Neither were we able to combine intervention studies due to the small number of studies and heterogeneity of interventions and outcomes.

RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence (SOE) for KQ3 outcomes using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).³⁷ The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials (RCTs) and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect and strength of association, as well as separate guidance for applicability.³⁸ Ratings were based on the following criteria:

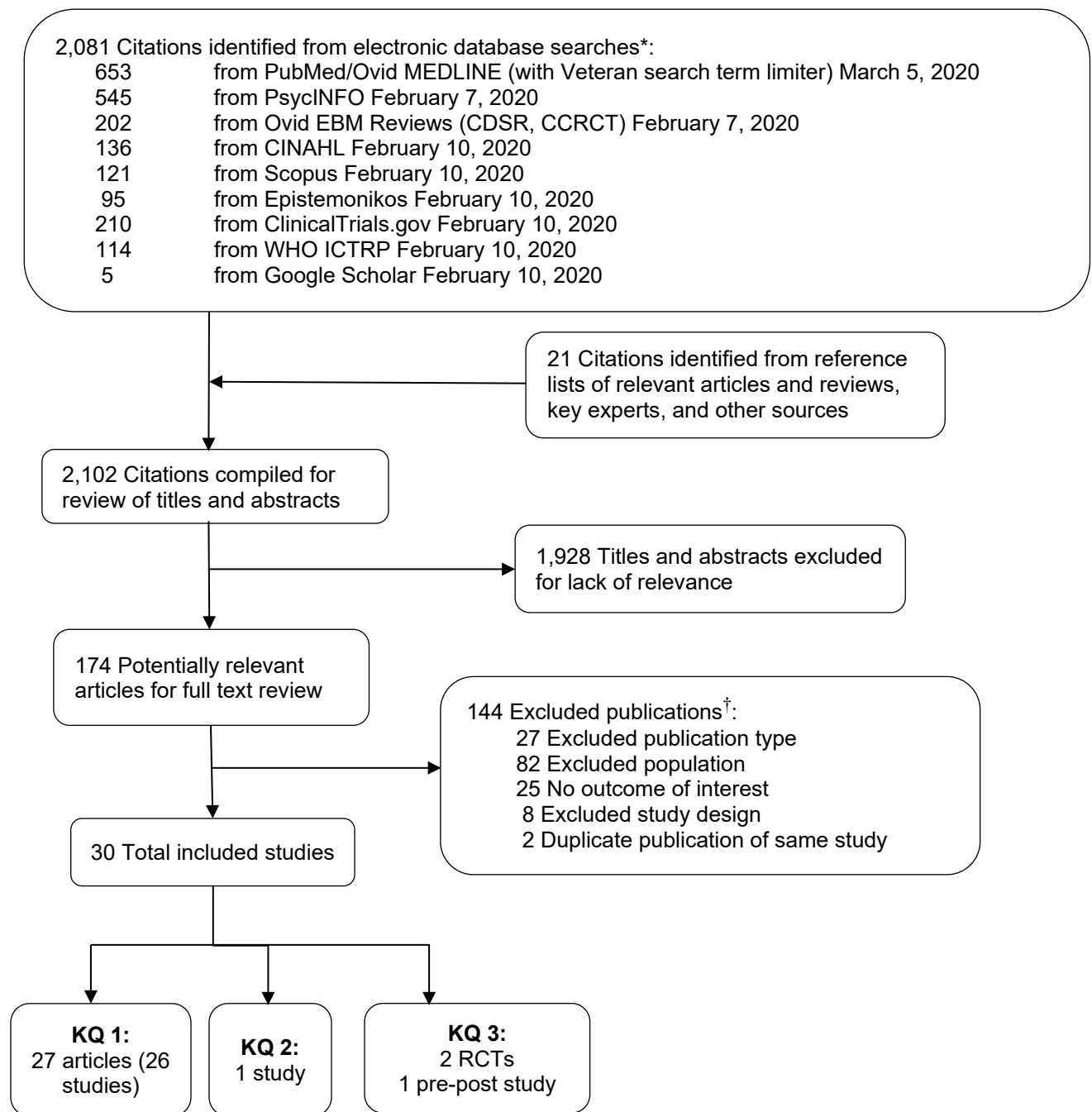
- High: Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.

- Moderate: Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.
- Low: Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient: No evidence, unable to estimate an effect, or no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

RESULTS

We reviewed a total of 2,081 studies. After title and abstract review, 174 met inclusion criteria. Upon full-text review, we included a total of 27 prevalence studies, 2 RCTs, and 1 pre-post study (see Figure 2).

Figure 2. Literature Flow Chart



*after deduplication. KQ = Key Question
 †See Appendix D for full list of excluded publications.
 Note: KQ2 study is also included in KQ1.

KEY QUESTION 1: What is the prevalence of chronic pain in US Veterans or Servicemembers with a history of mTBI?

Summary of Findings

We found 27 articles that reported chronic pain prevalence estimates for Veterans and/or Servicemembers (SMs) with a history of mTBI. General chronic pain prevalence was reported in 8 studies,^{4,25,39-44} and head pain (*eg*, headaches and/or migraines) in 23 studies.^{6,7,15,39,40,42,44-60} Other types of chronic pain for which prevalence estimates were reported included: back pain (10 studies^{7,15,40,44,49,52,53,56,59,60}); neck pain (5 studies^{7,40,44,52,53}); arm, leg, and/or joint pain (9 studies^{15,39,42,49,52,53,56,59,60}); abdominal/stomach pain (5 studies^{15,40,56,59,60}); chest pain (3 studies^{15,59,60}); sexual pain/problems (3 studies^{15,59,60}), prescription pain medication use (4 studies^{40-42,54,61}), arthritis (2 studies^{40,57}); and other pain (4 studies^{7,39,40,42}). Three articles included data from the 4-site VA/Department of Defense (DoD) Chronic Effects of Neurotrauma Consortium (CENC) longitudinal study,^{41,57,61} albeit with different subsets of the total sample, and therefore we only included data that was not duplicative from those articles – taking the prevalence estimate with the largest denominator when more than 1 estimate for the same measure was available. Sample sizes ranged from 40⁴⁷ to 102,055⁴⁵ Veterans or SMs with history of mTBI. Studies also varied widely in target population (*eg*, SMs or Veterans, geographic region, era served, comorbidities) and definitions and measures used to classify mTBI and chronic pain. Characteristics of the studies are in Table 2. Prevalence estimates from these studies are provided in Tables 3 through 5.

Table 2. Characteristics of studies reporting prevalence of chronic pain in Veterans/ Servicemembers with a history of mTBI

Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed										
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other
Beswick- Escanlar, 2016 ⁴⁵ N=222,036 Multi-site: Military Health System 2006-2015 Cohort – retrospective.		N=102,055 EHR (based on incident ICD diagnosis codes) between 2006 and 2014, with 1-year follow-up period (2006-2015).	Active component Army, Navy, Air Force, and Marine Corps SMs with no prior history of medical care for TBI, headache, or migraine documented in EHR.	Age: 55.2% <24 yrs; 33.3% 25-24 yrs; 9.8% 35-44 yrs; 1.6% 45-54 yrs; 0.1% 55+ yrs. Female: 8.1%. Race: 76.4% White; 12.1% African-American/Black; 11.5% other. 100% SMs. PTSD: 22.2%.		X									
Brickell, 2014 ⁴² N=167 1 site: WRAMC Dates NR Cohort – prospective.		N=167 Routine comprehensive clinical evaluation by healthcare professional; mTBI=PTA<24 hrs and LOC<15 mins (could have intracranial abnormality).	SMs with mTBI and polytrauma sustained during deployment (combat or other) who had undergone a TBI clinical evaluation within the first 3 months of injury and participated in ≥1 follow-up telephone interview.	Age: 27.6 (7.0) yrs. Female: 3.6%. 100% SM. Blast: 74.3%. Wounded OIF: 79.6%. Wounded OEF: 13.2%. Wounded Other: 7.2%.	X	X			X				X		X
Couch, 2016 ⁴⁶ N=110 1 Site: Oklahoma City VA outpatient clinic designed to assist		N=55 mTBI with LOC: n=23 mTBI with AOC: n=20	Male post-deployment, Post-9/11 Veterans that participated in this specialty clinic. All were age 20-60, confirmed to have deployment-	LOC: Age: 20-29=35%; 30- 39=39%, ≥40=26.2%. AOC: Age: 20-29=35%; 30- 39=40%; ≥40=25%. Female: 0%.			X								



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed											
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other	
Veterans in return to civilian life. 7/2012 - 8/2014. Case-control.		VA/DoD common definition, based on TBI screen followed by TBI clinic evaluation.	related TBI (cases), and 4-11 years post-TBI.	Race NR. 100% Veterans.												
Farrell-Carnahan, 2015 ⁴⁷ N=112 4 sites: VA Polytrauma Rehabilitation Centers (PRC). Jan 2009–Mar 2013. Cross-sectional.		N=40 VA/DoD common definition, based on VA PRC TBI Model System Form 1 inpatient data collection at time of study enrollment.	Veterans 18+ yrs receiving care for TBI and/or TBI-related issues in VA inpatient rehabilitation program and enrolled in VA PRC TBI Model System within 1-year of injury. Also required TBI severity information and at least partial completion of a 1-year follow-up assessment (including NSI and/or patient proxy).	Age: 29 (13) yrs. Female: 7%. Race: 70% White. 100% Veteran. Cause of injury: motor-vehicle related 10/40 (25%); other violence (blast) 21/40 (53%); all other 9/40 (23%). Injured during deployment: 26/40 (65%).		X										
Hoge, 2008 ¹⁵ N=2,525 Single-site: Walter Reed Army Institute of Research. 2006. Cross-sectional.		N=384 (LOC=124; AOC=260) Screening questionnaire consistent with VA/DoD common definition.	SMs (active or reserve US Army combat infantry brigade) 3-4 months after return from combat deployment to Iraq. Exclusions: missing data from injury questions or reported having had a head	LOC vs AOC: Female: 1/123 (0.8%) vs 3/258 (1.2%). Age<30 yrs: 79/123 (64.2%) vs 149/257 (58.0%). 100% SMs. PTSD: 54 (43.9%) vs 71 (27.3%).		X	X		X	X	X	X				



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed											
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other	
			injury without LOC or AOC.	Major depression: 27 (22.9%) vs 21 (6.6%). Mechanism of injury: Blast or explosion 98 (79.0%) vs 189 (72.7%); Bullet 6 (4.8%) vs 2 (0.8%); Fragment or shrapnel 31 (25.0%) vs 48 (18.5%); Fall 38 (30.6%) vs 73 (28.1%); Vehicle accident 38 (30.6%) vs 47 (18.1%); Other 16 (12.9%) vs 23 (8.8%).												
Hoot, 2018 ⁴¹ N=454 4 sites: VAMCs in Richmond, VA; Tampa, FL; San Antonio, TX; and Houston, TX. 2016-2017. CENC. Cross-sectional.	N=379	DoD/VA common definition. Each potential concussive event identified was investigated via the VCU rCDI.	Post-9/11 Veterans/SMs with combat exposure. Exclusion: (1) history of moderate or severe TBI; (2) history of major neurologic or psychiatric disorder.	Median age: 36.0 (range 22-64). Female: 11.6%. Race: 67.3% White; 22.7% African-American/Black; 10.0% other. Ethnicity: 23.6% Hispanic/Latino. PTSD (MINI): 31.2%. Depression (PHQ-9): 43.1%.	X									X		
Jackson, 2016 ⁴⁸ N=1,312 Numerous: Nationally dispersed Veterans	N=612	VA/DoD common definition, based on VA 4-item TBI screen plus clinical	Post-9/11 reserve or active duty (Army and Marine) Veterans with history of mTBI (with or without LOC)	Age: 37.1 (9.8) yrs. Female: 52.8% female. Race/Ethnicity: 66.5% White; 15.6% African American/Black; 13% other. 100% Veterans.											X	



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed													
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other			
enrolled in Project VALOR 2009-2012 Cohort – retrospective.		interview by doctoral-level clinician.	required to have undergone a mental health evaluation at a VA facility, indicated by a diagnostic interview or psychotherapy procedure code July 2008-Dec 2009. Must not have been participating in a clinical trial at the time of enrollment or have moderate/severe TBI, or TBI of unknown severity. Individuals with probable PTSD were oversampled at a 3:1 ratio; females were oversampled at a 1:1 ratio.	Major depression: 38.5%. Current PTSD: 51.9%. PTSD + Depression: 30.9%.														
King, 2014 ⁴⁰ N=842 Multi-site: VA Integrated Service Network 2 (upstate NY + parts of northern PA). Oct 2001-Sept 2011. Cross-sectional.		N=421 ≥1 encounter with ICD code 310.2 (post-concussion syndrome).	Post-9/11 Veterans who used VA primary care.	Age: 30.3 (7.6) yrs. Female: 4%. 100% Veterans.	X	X	X	X		X			X	X	X			



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed												
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other		
Kulas, 2018 ³⁹ N=164,884 Multi-site: National data (VA EHR) 10/1/2011 - 9/30/2012. Cohort – retrospective.		N=32,316 (23,063 mTBI+PTSD; 9,253 mTBI no PTSD)	All Post-9/11 Veterans who received care in VHA and had ≥1 ICD diagnosis code for mTBI.	mTBI + PTSD group: Age: 32.8 (8.3) yrs. Female: 5%. mTBI no PTSD group: Age: 32.1 (8.6) yrs. Female: 8%.	X	X				X						X	
Lew, 2009 ²⁵ N=340 Single-site: VA level 2 polytrauma clinic. Jan 1, 2007 - Oct 27, 2008 (22 months). Cross-sectional.		N=227 Clinical determination of mTBI on CTBIE based on VA/DoD common definition.	All Post-9/11 Veterans with persistent post- concussive symptoms seen at the polytrauma clinic.	NR	X												
MacGregor, 2013 ⁴⁹ N=992 Multi-site: Navy/Marine deployment health database. Mar 2004 – Apr 2008. Cohort – retrospective.		N=334 EHR: ICD diagnosis codes indicative of TBI with corresponding Abbreviated Injury Score values of 1 or 2.	Iraq War SMs (Navy/Marines) who sustained minor to moderate injuries and completed a PDHRA after deployment (within 1 year of injury).	Age: 23.3 yrs (range 18- 45). Female: 0.3%. Race: NR. Mechanism of injury: Battle, blast: 297 (88.9%). Battle, nonblast: 8 (2.4%). Nonbattle: 29 (8.7%).		X	X		X								



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed										
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other
Patil, 2011 ⁵⁰ N=246 Single-site: large, midwestern polytrauma network site. June 15, 2007 - July 15, 2009. Cohort – retrospective.		N=246 (56 evaluated in Neurology) VA/DoD common definition, based on VA CTBIE.	Post-9/11 combat Veterans receiving care at a VA polytrauma network site with combat-related mTBI.	Age: 27.9 (6.3) yrs. Female: 7.7%. Race: 85.8% White. Ethnicity: 19.1% Hispanic. Mechanism of injury: 1+ blast exposure: 65%.		X									
Powell, 2015 ⁴³ N=171 Single-site: Boston VA TRACTS Center of Excellence. Cross-sectional.		N=171 Clinical interview by doctoral-level psychologist (reviewed by 3+ doctoral-level psychologists for consensus diagnosis).	Post-9/11 Veterans. Excluded: (a) a history of seizures; (b) prior serious medical illness; (c) current active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; (d) DSMIV-TR diagnosis of current bipolar disorder, schizophrenia, or other psychotic disorder (except psychosis not otherwise specified [NOS] due to trauma- related hallucinations); or (e) cognitive disorder due to general medical condition other than	Age: 33.3 (8.6) yrs. Female: 13.5%. Race/Ethnicity: Black/African-American 10.5%; Hispanic/Latino 17%; White 68.4%. Current mood disorder: 30.4%. Current anxiety disorder: 22.2%.		X									



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed											
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other	
			TBI. Participants with any history of moderate to severe TBI were excluded.													
Pugh, 2019 ⁷ N=527,381 Multi-site: VA EHR data. Oct 1, 2001 - September 30, 2011. Cross-sectional.	N=93,003 VA/DoD common definition, based on comprehensive algorithm using DoD trauma data, VA CTBIE data, and ICD diagnosis codes.	Veterans who met criteria for mTBI. Included: (a) entered VA care Oct 1, 2001-September 30, 2011; (b) received ≥5 years of VA care (inpatient, outpatient, or pharmacy) before Sept 30, 2014; and (c) received ≥1 year of care after 2007.	Age: 29.8 (7.8) yrs. Female: 6.0%. Race/Ethnicity: White 69.6%; Black/African American 13.3 %; Hispanic 12.6%; Asian 2.1%; Native American/Pacific Islander 1.7%. 100% Veteran.		X	X	X									X
Romesser, 2012 ⁴⁴ N=433 2 sites: VAMC polytrauma clinics. Cohort – retrospective.	N=354 Clinical interview: Self-reported history of mTBI based on VA/DoD common definition and identifying a mechanism of injury.	Post-9/11 Veterans with mTBI referred to VA polytrauma clinic. Excluded: Incomplete demographic and/or injury severity characteristics, missing pain or headache data, or with ≥2 items missing on PTSD Checklist.	Age: 31.0 (8.2) yrs. Female: 4.6%. Race/Ethnicity: Black/African-American 15%; White 63.7%; Hispanic 17.3%; other 3.9%.	X	X	X	X									
Ruff, 2008 ⁶ N=126 Single-site: Cleveland, OH	N=126 VA/DoD common definition, based on VA CTBIE.	Post-9/11 combat Veterans receiving care at a VA polytrauma network site with	Demographics NR. 100% Veteran.		X											



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed											
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other	
VA polytrauma network site. Dates NR. Cross-sectional.			deployment- and blast- related mTBI.													
Schwab, 2017 ⁵¹ N=1,567 2 sites: Fort Carson, CO, and Fort Bragg, NC. Cohort – prospective.		N=557 at baseline; 358 with mTBI completed 3-month follow-up. VA/DoD common definition, based on screening followed by OSU TBI-ID interview.	Post-9/11 Army SMs recently returned from Iraq/Afghanistan with positive TBI screen. Excluded: having been medically evacuated from theater, determined that likely incurred more than a mild TBI, and likely symptom exaggeration.	Age: 27 (6) yrs. Female: 8%. Race/ethnicity: 65.8% White; 13.6% Hispanic; 11.2% African American/Black; 9.4% multiple. Experienced blast: 67%. PTSD screen: 15% positive.		X										
Seal, 2017 ⁴ N=116,913 Multi-site: VA CTBIE database. October 2007- March 2015. Cohort – retrospective.		N=65,675 Clinical determination of mTBI on CTBIE based on VA/DoD common definition.	Post-9/11 Veterans with determinate TBI finding on CTBIE, VA EHR data during year before or after CTBIE, sufficient CTBIE data to classify TBI severity, complete data.	Age: mean NR. Female: 6.1%. Race: 39.9% Other-than- white. 100% Veteran. PTSD: 65.8%. Depression: 39.4%. Alcohol Use Disorder: 15.9%. Drug Use Disorder: 8.7%.		X										
Suri, 2019 ⁵² N=36,880 Multi-site: VA CTBIE database		N=23,703 VA/DoD common definition, based on CTBIE.	Post-9/11 Veterans aged 18-65 years who had: (1) complete data for the presence and/or	Age: 33.3 (7.7) yrs. Female: 5.1%. Race: Asian 2.0%; Black/African-American		X	X	X	X							

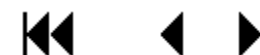


Author, Year N total pts*	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed										
				General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other
7/1/2009 - 9/30/2013. Cohort – prospective.		duration of the most severe episodes of deployment-related LOC, PTA, and/or AOC experienced; (2) complete data for the CTBIE clinician's overall assessment of deployment-related TBI history (Y/N); (3) agreement between #1 and #2; and (4) no self- reported occurrences of pre-deployment or post- deployment TBI.	13.2%; Hawaiian/Pacific Islander 1.5%; American Indian/Alaska Native 1.3%; White/caucasian 69.7%; Unknown/NR 12.4%. Depression: 37.0%. PTSD: 67.7%. Alcohol abuse/dependence: 7.2%. Drug abuse/dependence: 2.4%. Non-blast TBI only: 21.8%. Blast TBI only: 46.6%. Blast+non-blast TBI: 31.6%.											
Suri, 2017 ⁵³ N=2,187 24 VA facilities nationwide: CTBIE database. 7/1/2009- 9/30/2013. Cohort – prospective survey ~3 yrs after CTBIE).	N=1,683 VA/DoD common definition, based on CTBIE.	18-65 years; Agreement between clinician TBI impression and expected diagnosis based on VA/DoD criteria for AOC, LOC, and PTA; Past TBI history limited to nondeployment-related TBIs only.	Age: 36.6 (9.2) yrs. Female: 8.7%. Race: NR. 100% Veteran. Depression: 29.8%. PTSD: 48.6%. Alcohol abuse: 4.8%. Drug abuse: 1.6%. Non-blast TBI only: 25.8%. Blast TBI only: 56.4%. Both blast/non-blast TBI: 17.8%.		X	X	X	X						



Author, Year N total pts*	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed										
				General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other
Theeler, 2012 ⁵⁴ N=978 Single-site: Madigan Army Medical Center. Cross-sectional.	N=978 Screening: Initial 2- question screen followed by 10- question screen (scored in a standardized manner from 0 to 39); concussion=score of ≥5 on the 2-plus-10 questionnaire. SMs with positive screen then evaluated in TBI clinic.	SMs who had a deployment-related concussion in Iraq or Afghanistan.	NR.		X								X	
Tsao, 2017 ⁵⁵ N=2,612 3 sites: Camp Lejeune, NC; Twentynine Palms, CA; and Kaneohe Bay, HI. 4/2010 - 6/2013. Cross-sectional.	N=2,612 VA/DoD common definition, based on screening questions.	Male SMs (Marines) were 2-8 weeks post- deployment in Iraq and/or Afghanistan and saw greatest amount of combat but did not sustain injury requiring medical evacuation and were not on restricted duty.	Median age: 22 years (range 19-50) 95% were <33 years 99% were <39 years Female: 0% 100% SMs		X									
Vanderploeg, 2009 ⁵⁶ N=4,462	N=278	Male, Vietnam-era, Army Veterans who had: (1) first entered the military between Jan	Age: 78% <40 yrs. Race: 16% Other-than- white.		X	X		X	X					

Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed									
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis
Randomly-sampled US Veterans flown to VAMC and University of South Florida, Tampa, FL. Mid-1980s. Cross-sectional.	Those who had a head injury with AOC. Interview: (1) Since your discharge from active duty, have you injured your head? and (2) Did you lose consciousness as a result of the head injury? (If participants were unclear if they had lost consciousness, they were asked if they had “blacked out” in the accident.).	1965-Dec 1971; (2) been on active duty for ≥4 months; (3) served only 1 tour of duty; (4) obtained a military occupational specialty; and (5) achieved a pay grade ≤E-5 (sergeant) on discharge. Excluded: Participants that required hospitalization after their head injury.	100% Veteran; Approximately half the sample had served in Vietnam, whereas the other half had served elsewhere (ie, United States, Korea, Germany).											
Walker, 2018a ⁵⁷ N=492 4 sites: VAMCs in Richmond, VA; Tampa, FL; San Antonio, TX; and Houston, TX. Consented for study (CENC) prior to Sept. 2017.	N=414 VA/DoD common definition. Each potential concussive event identified was investigated via the VCU rCDI.	Post-9/11 Veterans/SMs with combat exposure. Exclusion: (1) history of moderate or severe TBI; (2) history of major neurologic or psychiatric disorder.	Age: 36.0 yrs (31.0, 47.0). Female: 11.8%. Race: 66.2% White; 23.4% African-American/Black; 10.4% other. Ethnicity: 23.4% Hispanic or Latino.		X								X	



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed																	
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other							
Cross-sectional.																						
Webb, 2015 ⁵⁸ N=513,893 Multi-site: Military Health System. 2001-2008. Cohort – retrospective.	N=5,065	EHR (based on ICD diagnosis codes).	Air Force SMs who served on active duty for ≥180 days between Oct 1, 2001 -Sept 30, 2008 with incident cases of mTBI. Excluded: history of mTBI or other head injuries in the 2 years prior to entering the study.	Born before 1965: 6.7%. 1966-1975: 15.7%. 1976 and later: 77.6%. Female: 18%. Race/ethnicity: 75.1% White; 11.6% African- American/Black; 2.5% Asian/Pacific Islander; 6.5% Hispanic; 0.7% Native American; 3.7% Other/Unknown. 100% SMs.		X																
Wilk, 2012 ⁵⁹ N=1,502 Single-site: Walter Reed Army Institute of Research. Nov-Dec 2008. Cross-sectional.	N=260 (LOC=86; AOC=174)	Screening questionnaire consistent with VA/DoD common definition.	SMs (3 Army brigade combat teams from 1 Active Component infantry division) 4-6 months after return from combat deployment to Iraq or Afghanistan who met criteria for mTBI.	72% <30 yrs. Female: 9%. LOC vs AOC: PTSD (PCL-17): 52% vs 29% . Depression (PHQ-9): 23% vs 16%.		X	X		X	X	X	X										
Wilk, 2010 ⁶⁰ N=3,952 Single-site: Walter Reed Army Institute of Research. 2006-2007. Cross-sectional.	N=587 (LOC=201; AOC=373)	Screening questionnaire consistent with	SMs (1 Army National Guard and 2 Active Duty infantry brigades) 3-6 months after return from combat deployment in Iraq who met criteria for mTBI.	66.9% <30 yrs. Female: 1.7%. LOC blast vs non-blast: AOC blast vs non-blast: PTSD: 44.7% vs 38.5%. 30.0% vs 29.1%. Major depression:		X	X		X	X	X	X										



Author, Year N total pts*	Setting Dates	mTBI N pts with history of mTBI	Eligibility study inclusion/exclusion criteria	Demographics Age: mean (SD) Female: % Race: % SMs or Veterans Mental health comorbidities, mTBI injury details (mechanism, # of mTBIs)	Type(s) of CP assessed															
					General	Head	Back	Neck	Arm/leg/joint	Stomach/ abdominal	Chest	Sexual	Pain medication use	Arthritis	Other					
		VA/DoD common definition.		21.2% vs 15.8%. 10.2% vs 16.0%. Alcohol misuse: 39.0% vs 42.1%. 28.2% vs 37.4%.																
Total Studies:					8	23	10	5	9	5	3	3	4	2	3					

*may include those without TBI history and/or with moderate/severe TBI
 Abbreviations: AOC=Alteration of consciousness; CA=California; CENC=Chronic Effects of Neurotrauma Consortium; CO=Colorado; DoD=Department of Defense; DVBIC=Defense and Veterans Brain Injury Center; FL=Florida; HI=Hawaii; LOC=Loss of consciousness; MINI=Mini-International Neuropsychiatric Interview; mTBI=Mild Traumatic Brain Injury; NC=North Carolina; NR=Not reported; OH=Ohio; OSU TBI-ID=Ohio State University Traumatic Brain Injury Identification Method; P=P-value; PDHA=Post-Deployment Health Assessment; PDHRA=Post-Deployment Health Re-Assessment; PHQ-9=9-item Patient Health Questionnaire scale; PNS=Polytrauma Network Site; PTS=Posttraumatic Stress; PTSD=Posttraumatic Stress Disorder; SD=Standard Deviation; SM=Servicemember; TBI=Traumatic Brain Injury; TRACTS=Translational Research Center for TBI and Stress Related Disorders; TX=Texas; US=United States; VA=Virginia; or Veterans Affairs; VALOR=Veterans' After-discharge Longitudinal Registry; VAMC=Veterans Affairs Medical Center; VCU-rCDI=Virginia Commonwealth University retrospective Concussion Diagnostic Interview; WRAMC=Walter Reed Army Medical Center



Detailed Results

General Chronic Pain

There were 8 studies that reported prevalence of general (or any) chronic pain among Veterans with mTBI: 3 were retrospective cohort studies based on VA administrative data (*ie*, EHR data) for Veterans who used VA healthcare,^{4,39,40} 1 was a study of injured SMs evaluated at different time points for approximately 5 years post-injury,⁴² and 4 were VA-based studies that either enrolled Veterans for testing or utilized chart review of patients who had been seen in TBI clinics.^{25,41,43,44} All 8 studies focused on Post-9/11 Veterans.

A relatively robust estimate of the prevalence of general chronic pain among Veterans was identified by Seal et al⁴ in a study of 65,675 Veterans with a confirmed history of mTBI based on the VA's CTBIE. In this study, the prevalence of chronic pain diagnoses (defined as those with 2 or more International Classification of Diseases [ICD] diagnosis codes for pain, greater than 90 days apart, in the year before or after their CTBIE) was 59%. This compared to 53% among those whose CTBIE did not confirm mTBI history. The strengths of this study are that it is broadly representative of the large population of Veteran VA users who have been diagnosed with mTBI by a specialist clinician using the CTBIE. Additionally, the criteria used to identify pain using ICD codes were relatively stringent compared to other studies that use administrative data. However, Veterans who complete the CTBIE are generally seeking treatment for a variety of post-deployment health symptoms that may or may not be related to mTBI, or pain, and thus symptoms may be overreported. Additionally, the use of ICD diagnosis codes in EHR data to estimate the prevalence of health disorders such as chronic pain may lead to over- (or even under-) estimation due to a variety of reasons.^{3,5} Therefore, pain data from this study and other studies relying on CTBIE or EHR diagnosis data may not represent the true prevalence of chronic pain in the population of Veterans and SMs with mTBI.

The Seal et al study⁴ also captured rates of pain disability, which was examined with a 5-item Likert scale from none to very severe interference in daily functioning and quality of life. Moderate-to-very severe interference qualified as pain disability, and the prevalence of pain interference (defined as moderate-to-severe interference in daily functioning) was 75%.⁴ This pain interference finding was consistent with a smaller study (n=354) of Veterans treated consecutively at 2 VA polytrauma program sites, in which 70% had reported moderate-to-extreme pain interference (defined as functional limitations secondary to pain).⁴⁴

The remaining studies were based on a variety of Veteran samples, measures of mTBI history, and definitions/measures of pain. A study by Kulas and Rosenheck³⁹ was similar to the Seal et al study in its use of VA EHR data for a large number of Veterans; however, rather than the CTBIE, this study used ICD diagnosis codes to identify Veterans with mTBI. It also examined comorbid PTSD. In this study, 82% of Veterans with both mTBI and PTSD diagnoses also carried a pain diagnosis, while 71% of those with mTBI but no PTSD had been diagnosed with pain (compared to 62% of those with PTSD only). This was consistent with a study by King et al in which 2 or more ICD diagnosis codes for pain, assigned ≥ 90 days apart, were identified in 76% of Veterans with mTBI (versus 52% of those without mTBI).⁴⁰ Similar figures were presented in a polytrauma clinic chart review study by Lew et al,²⁵ in which 86% of Veterans diagnosed with both mTBI and PTSD had been diagnosed with chronic pain, while 71% of those with mTBI but no PTSD had been diagnosed with chronic pain, and in a longitudinal survey of

SMs with mTBI by Brickell et al, in which 67% to 89% of respondents in each wave reported bodily pain.⁴² Powell et al⁴³ used cross-sectional data from clinical interviews of 171 Veterans enrolled in the VA Translational Research Center for TBI and Stress Disorders (TRACTS) longitudinal study at 1 VA site. Among Veterans with mTBI as confirmed via clinical interview, 38% met study criteria for chronic pain. Hoot et al⁴¹ reported the prevalence of chronic pain among 379 Veterans enrolled in the CENC study with confirmed history of mTBI; 59% of Veterans reported moderate, severe, or extreme pain or discomfort based on a validated measure of pain intensity, compared to 65% of Veterans with no TBI history. (Brickell et al also reported pain severity among respondents in a longitudinal study of SMs and identified moderate or greater pain intensity among 37% to 59% of respondents across survey time points.⁴²)

Additional detail of these and other studies presenting general chronic pain data can be found in Table 3.

Table 3. Prevalence estimates of general chronic pain from studies of Veterans/ Servicemembers with a history of mTBI

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Seal, 2017 ⁴ n=65,675 Post-9/11 Veterans.	EHR data	Presence: Having ≥2 of the same pain ICD diagnosis code more than 90 days apart, 1 year before or after CTBIE.	38,591/65,675 (58.8%)
	CTBIE	Pain interference presence: Ascertained during the CTBIE and defined as an individual's appraisal of the degree to which pain interferes with their daily functioning and quality of life. Veterans are prompted to endorse level on a 5-item scale, and responses were dichotomized as moderate-to-extreme versus none-to-mild.	75%
Kulas, 2018 ³⁹ n=32,316 Post-9/11 Veterans.	EHR data	Presence: Y/N of ICD diagnosis code for pain in EHR.	mTBI+PTSD: 81.5% mTBI no PTSD: 70.8%
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Presence: If treated for conditions commonly associated with pain for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	320/421 (76.0%)
Hoot, 2018 ⁴¹ n=379 Post-9/11 Veterans/SMs. CENC sample.	EQ-5D-5L	Intensity: Level of pain or discomfort. <i>[Note that we considered "No or slight pain or discomfort" = no chronic pain, while "Moderate, Severe, or Extreme pain or discomfort" = chronic pain.]</i>	Moderate: 166/378 (43.9%) Severe: 54/378 (14.3%) Extreme: 4/378 (1.1%) Moderate-to-extreme: 224/378 (59.3%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Romesser, 2012 ⁴⁴ n=354 Post-9/11 Veterans assessed at 2 polytrauma clinics.	Self-report	Interference: Asked how much pain interfered with life in the past 30 days (moderately, severely, or extremely versus not at all or mild).	mTBI with no LOC (n=210) vs mTBI with LOC (n=144): Moderately: 72 (34.3%) vs 58 (40.3%) [Total mTBI=36.7%] Severely: 52 (24.8%) vs 40 (27.8%) [Total mTBI=26.0%] Extremely: 15 (7.1%) vs 12 (8.3%) [Total mTBI=7.6%] Severely to extremely: 67 (31.9%) vs 52 (36.1%) [Total mTBI=33.6%] Moderately to extremely: 139 (66.2%) vs 110 (76.4%) [Total mTBI=70.3%]
Lew, 2009 ²⁵ n=227 Post-9/11 Veterans seen at polytrauma clinic.	EHR data	Presence: Chronic pain was defined as persisting reports of pain in ≥ 1 body part for ≥ 3 months after onset.	Total mTBI: 81.9% mTBI with PTSD: 86.2% mTBI no PTSD: 70.5%
Powell, 2015 ⁴³ n=171 Post-9/11 Veterans enrolled in VA TRACTS.	EHR/self-report	Presence: Veterans were determined to have chronic pain if pain diagnosis was listed as an active problem in VA EHR and dated prior to TRACTS testing day (n=45); if they were referred to a chronic pain specialist after determined to have chronic pain via clinical interview (n=17); or if they had discussed pain that had lasted ≥ 3 months during their interview (n=3).	65/171 (38.0%)
Brickell, 2014 ⁴² n=167 Post-9/11 SMS.	Self-report telephone interview with open- ended questions	Bodily pain (other than headache) presence: Any pain in past month. The telephone follow-up interview is an unpublished, 10-15 min, semi-structured interview developed specifically for this study.	6 mos: 78.3% 12 mos: 76.4% 24 mos: 88.9% 36 mos: 78.6% 48 mos: 66.7% 60 mos: 80.0%
		Bodily pain (other than headache) frequency: Daily/almost daily in past month.	6 mos: 34.8% 12 mos: 41.6% 24 mos: 37.0% 36 mos: NR 48 mos: 50.0% 60 mos: Unclear
		Bodily pain (other than headache) intensity: Moderate or greater in past month.	6 mos: 37.0% 12 mos: 39.3% 24 mos: 59.3% 36 mos: NR 48 mos: 36.7% 60 mos: NR

Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; EQ-5D-5L=EuroQol Group 5-dimension 5-level version; ICD=International Classification of Diseases; LOC=Loss of consciousness; mTBI=Mild Traumatic Brain Injury; NR=Not reported; OEF=Operation Enduring Freedom; OIF=Operation Iraqi Freedom; PTSD=Posttraumatic Stress Disorder; SM=Servicemember; TRACTS=Translational Research Center for TBI and Stress Related Disorders; VA=Veterans Affairs

Head Pain

We identified 23 studies reporting prevalence of head pain in Veterans with a history of mTBI.^{6,7,15,39,40,42,44-60} Headaches and/or migraines were assessed across a range of study populations using a variety of pain assessment tools, including EHR data, the Neurobehavioral Symptom Inventory (NSI), the 15-item Patient Health Questionnaire (PHQ-15), the 6-item Headache Impact Test (HIT-6), and the Post-deployment Health Assessment and Re-assessment (PDHA/PDHRA), with prevalence estimates ranging from 3%⁵⁸ to 98%.⁵⁴ Two studies, 1 larger multi-site study in Air Force SMs (n=5,065)⁵⁸ and 1 very small study in OEF/OIF Veterans from a single site (n=43),⁴⁶ specifically reported the prevalence of migraines independent of headache. The presence of migraines or headaches was combined in 1 large study using administrative data (n=102,055).⁴⁵ All other studies reported prevalence of headaches, although only 9 addressed the severity and/or frequency of headaches.^{15,42,46,47,51,53,54,57}

Five studies may best inform prevalence estimates of headache and/or migraine in Veterans with mTBI.^{7,39,45,52,53} These studies were conducted in broad population samples and are most generalizable to the population of SMs/Veterans with mTBI; however, the range of pain prevalence values was broad, from 15% of a SM sample receiving head pain diagnosis codes in a 1-year time period (compared to 3% among those without mTBI diagnosis),⁴⁵ to 94% of Veterans with confirmed mTBI indicating they experience headaches when asked by a clinician completing the CTBIE (compared to 86% of those without confirmed mTBI).⁵³ A large (n=102,055) retrospective cohort study of surveillance data from the Defense Medical Surveillance System (DMSS)⁴⁵ estimated a 15% prevalence of headaches or migraines in SMs with a history of mTBI. This was the lowest prevalence estimate among all included studies, with the exception of a smaller study (n=5,065) that reported a prevalence estimate of 3% among SMs in the 31-179-day period post-mTBI.⁵⁸ A similarly large, multi-site, cross-sectional study of 93,003 Veterans estimated a 20% prevalence of headaches among Veterans with mTBI history, compared to 6% of those without.⁷ The prevalence estimate was higher in a multi-site retrospective cohort study of 32,316 Post-9/11 Veterans: 36% of those with mTBI history had a headache diagnosis.³⁹ Among Veterans with comorbid mTBI and PTSD diagnosis, the prevalence of headache increased to 48% (compared to 16% among those with PTSD and no mTBI).³⁹ In another large study (n=23,703) of Post-9/11 Veterans who were confirmed with mTBI via a completed CTBIE, 70% reported headache pain in the past 30 days, compared to 55% of those without confirmed mTBI.⁵² A smaller study (n=1,683) across 24 VA facilities nationwide also utilized CTBIE data to estimate headache prevalence by intensity and found that approximately 94% of participants experienced any headaches and 82% of participants reported experiencing moderate to very severe headaches (compared to 86% and 61%, respectively, among those without confirmed mTBI).⁵³

See Table 4 for additional details of headache/migraine pain measurement and prevalence outcomes for all included studies.

Table 4. Prevalence estimates of head pain from studies of Veterans/ Servicemembers with a history of mTBI

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Beswick-Escanlar, 2016 ⁴⁵ n=102,055 SMs.	EHR data	Headache or migraine presence (incident diagnosis; yes/no): Presence/absence of ICD diagnosis code for headache or migraine in EHR during the post-TBI 1-year follow-up period.	15,519/102,055 (15.2%)
Pugh, 2019 ⁷ n=93,003 Post-9/11 Veterans.	EHR data	Headache presence (yes/no): ICD diagnosis code in health record during first year of VA care.	18,929/93,003 (20.4%)
Kulas, 2018 ³⁹ n=32,316 Post-9/11 Veterans.	EHR data	Headache presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 47.7% mTBI no PTSD: 36.0%
Suri, 2019 ⁵² n=23,703 Post-9/11 Veterans.	CTBIE	Headache presence (yes/no): CTBIE questionnaire item inquires about headache pain in the last 30 days.	16,534/23,703 (69.8%)
Webb, 2015 ⁵⁸ n=5,065 Post-9/11 SMs.	EHR data	Headache presence (yes/no): ICD diagnosis code in health record after mTBI diagnosis.	31-179 days post-mTBI: 142/5,065 (2.8%) ≥180 post-mTBI: 371/5,065 (7.3%)
		Migraine presence (yes/no): ICD diagnosis code in health record after mTBI diagnosis.	31-179 days post-mTBI: 79/5,065 (1.6%) ≥180 days post-mTBI: 211/5,065 (4.2%)
Suri, 2017 ⁵³ n=1,683 Post-9/11 Veterans.	CTBIE (headache item from NSI)	Headache presence (yes/no) and severity: Presence and severity were evaluated at the baseline CTBIE assessment using the NSI 5-level headache item ranging from 0 ("none") to 4 ("very severe") interference in past 30 days.	Any headache: 94.1% Severity: Mild: 12.5% Moderate: 26.8% Severe: 33.7% Very severe: 21.1% Total Mod-Severe: 81.6%
Tsao, 2017 ⁵⁵ n=1,022 Post-9/11 SMs.	Self-report	Headache presence (yes/no): Survey asked if respondents experienced headaches (yes/no).	1 mTBI: 499/892 (55.9%) ≥2 mTBI: 96/130 (73.8%) Total any # of mTBI: 595/1,022 (58.2%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Theeler, 2012 ⁵⁴ n=978 Post-9/11 SMS.	Self-report	Headache presence (yes/no): Assessed using 13-item self-administered headache questionnaire in TBI clinic. Chronic daily headaches (CDH; defined as headaches occurring ≥15 days per month for the previous 3 months); episodic headaches were <15 days/month. Also measured headaches meeting criteria for migraine, post-traumatic headache (PTHA), and headaches that disrupt functioning.	Total headache: 957/978 (97.9%) CDH: 196/978 (20.0%) Episodic headache: 761/978 (77.8%) Migraine: 504/978 (51.5%) PTHA: 360/978 (36.8%) Disrupt functioning: 397/978 (40.6%)
Jackson, 2016 ⁴⁸ n=612 Post-9/11 Veterans.	EHR data/Self-report	Headache presence (yes/no): Assessed as part of the VA TBI Clinical Reminder and Screening Tool (endorsed symptoms after injury and currently).	Total mTBI: 196/592 (33.1%) mTBI+PTSD: 151/384 (39.3%) mTBI no PTSD: 45/208 (21.6%)
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMS.	PHQ-15	Headache presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 144/563 (25.6%) LOC: 72/197 (36.5%) AOC: 72/366 (19.7%)
Schwab, 2017 ⁵¹ n=557 Post-9/11 SMS.	NSI	Headache intensity: Proportion that rated item on the NSI for headaches as a 3 or 4 (severe or very severe) on a 0-4 scale, 3-months post-deployment (and post-TBI screening).	15% of 358 who completed 3-month follow-up.
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Headache presence (yes/no): If treated for headache conditions for ≥3 months based on ICD diagnosis codes (ie, if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 160/421 (38.0%) mTBI+PTSD: 145/283 (51.2%)
Walker, 2018a ⁵⁷ n=414 Post-9/11 Veterans/SMS. CENC sample.	HIT-6	Headache impact on function, categorized as: No headaches lately; Little to no impact; Some impact; Substantial impact; Very severe impact.	Some impact: 44/407 (10.8%) Substantial impact: 50/407 (12.3%) Very severe impact: 172/407 (42.3%) Some to very severe headache impact: 266/407 (65.4%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMS.	PHQ-15	Headache presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 84/375 (22.4%) LOC: 39/121 (32.2%) AOC: 45/254 (17.7%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Romesser, 2012 ⁴⁴ n=354 Post-9/11 Veterans assessed at 2 polytrauma clinics.	Self-report	Headache presence (yes/no): If Veteran reported problems with pain in the past 30 days, self-reported information about pain characteristics was used to classify the individual with head pain/headaches.	Total mTBI: 266/354 (75.1%) LOC: 116/144 (80.6%) No LOC: 150/210 (75.1%)
MacGregor, 2013 ⁴⁹ n=334 Post-9/11 SMs.	PDHRA	Headache presence (yes/no): Asked to endorse whether they currently have headache pain that they feel is related to their deployment.	Total mTBI: 111/334 (33.2%) mTBI with LOC: 37/103 (35.9%) mTBI no LOC: 43/150 (28.7%)
Vanderploeg, 2009 ⁵⁶ n=278 Vietnam-era Veterans.	Self-report	Headache presence (yes/no): Medical history interview and questionnaire: "During the past year, have you had unusually frequent or severe headaches?"	27.0%
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Headache presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 85/260 (32.7%) LOC: 40/86 (46.5%) AOC: 45/174 (25.9%) mTBI+PTSD: 53/96 (55.2%) mTBI no PTSD: 31/163 (19.0%)
Patil, 2011 ⁵⁰ n=246 Post-9/11 Veterans seen in Polytrauma clinic.	CTBIE and EHR	Headache presence (yes/no): Asked if they experienced headache pain within the 30 days preceding the CTBIE. Among Veterans who were referred to and attended a Neurology clinic evaluation, diagnoses of migraine, chronic daily headache (CDH), and post-traumatic headache (PTHA) were measured.	CTBIE: 182/246 (74.0%) Received and attended Neurology clinic referral: 56/246 (22.8%) Migraine: 25/56 (44.6%) CDH: 11/56 (19.6%) PTHA: 4/56 (7.1%)
Brickell, 2014 ⁴² n=167 Post-9/11 SMs.	Telephone interview with open- ended questions	Headache presence (yes/no): Any in past month. (the telephone follow-up interview is an unpublished, 10-15 min, semi-structured interview developed specifically for this study.)	6 mos: 73.9% 12 mos: 67.4% 24 mos: 85.2% 36 mos: 83.3% 48 mos: 83.3% 60 mos: 92.0%
		Headache frequency: Daily or weekly in past month.	6 mos: 58.7% 12 mos: 56.2% 24 mos: 64.8% 36 mos: 64.3% 48 mos: 70.0% 60 mos: 76.0%

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
		Headache intensity: Moderate or higher in past month.	6 mos: 52.2% 12 mos: 41.6% 24 mos: 53.7% 36 mos: 59.5% 48 mos: 63.3% 60 mos: 68.0%
		Pain location: Any (non-headache) head or neck pain in past month.	6 mos: 17.4% 12 mos: 18.0% 24 mos: 16.7% 36 mos: 7.1% 48 mos: 20.0% 60 mos: 4.0%
Ruff, 2008 ⁶ n=126 Post-9/11 Veterans seen in a polytrauma clinic.	Neurological exam	Headache presence (yes/no): Present and associated with Post-9/11 deployment. Among Veterans with headache, proportions with diagnoses of migraine, tension, or mixed headache presented.	Any headache: 80/126 (63.5%) Migraine: 14/126 (11.1%) Tension: 36/126 (28.6%) Mixed: 30/126 (23.8%)
Couch, 2016 ⁴⁶ n=43 Post-9/11 Veterans.	Self-report during clinical assessment	Headache frequency: Chronic daily headaches (CDH; defined as ≥ 15 days/month) or frequent headaches (defined as 10-14 days/month) in 6 months prior to telephone questionnaire. (Used detailed headache questionnaire which has been used in the University of Oklahoma Headache Clinic since 1996.)	All mTBI: CDH: 18/43 (41.9%) Frequent headache: 16/43 (37.2%) Either CDH or FH: 34/43 (79.1%) mTBI with LOC: CDH: 11/23 (47.8%) Frequent headache: 6/23 (26.1%) mTBI with AOC: CDH: 7/20 (35.0%) Frequent headache: 10/20 (50.0%)
	Self-report during clinical assessment.	Tension headache presence (yes/no): Determined by headache questionnaire and based on the hierarchical method of the ICDH-3 system.	All mTBI: 4/43 (9.3%) mTBI with LOC: 2/23 (8.7%) mTBI with AOC: 2/20 (10.0%)
	Self-report during clinical assessment.	Migraine (with & without aura) presence (yes/no): Determined by headache questionnaire and based on the hierarchical method of the ICDH-3 system.	All mTBI: 38/43 (88.4%) mTBI with LOC: 21/23 (91.3%) mTBI with AOC: 17/20 (85.0%)
Farrell-Carnahan, 2015 ⁴⁷ N=40 VA PRC TBIMS.	NSI	Headache intensity: NSI Item 4 'severely'/'very severely' disturbed by headaches in the last 2 weeks.	11/40 (27.5%)

Abbreviations: AOC=Alteration of consciousness; CDH=Chronic daily headaches; EHR=Electronic Health Record; FH=Frequent headaches; HIT-6=Headache Impact Test; ICDH-3=The International Classification of Headache

Disorders 3rd edition; LOC=Loss of consciousness; mTBI=Mild Traumatic Brain Injury; NSI=Neurobehavioral Symptom Inventory; OEF=Operation Enduring Freedom; OIF=Operation Iraqi Freedom; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire scale; PRC=Polytrauma Rehabilitation Center; PTHA=Posttraumatic headaches; SM=Servicemember; TBI=Traumatic Brain Injury; TBIMS=Traumatic Brain Injury Model Systems; VA=Veterans Affairs; VALOR=Veterans' After-discharge Longitudinal Registry

Back pain

We included 10 studies that reported measures of back pain prevalence among Veterans and SMs with mTBI.^{7,15,40,44,49,52,53,56,59,60} These studies ranged in size from clinical samples of 260 to large database studies of 93,003. Pain assessment varied broadly across studies and included validated measures of pain presence, standardized measures used in surveillance and screening instruments, and ICD diagnosis codes from healthcare records.

Three studies involved similar Post-9/11 SM populations and methodology, including assessment of pain using the PHQ-15, and may provide the most consistent evidence for prevalence of chronic back pain.^{15,59,60} Prevalence levels of back pain among SMs with mTBI in these 3 studies ranged from 32% to 44%. These studies also reported prevalence levels stratified by mTBI with loss of consciousness (LOC) versus alteration of consciousness (AOC); the prevalence of back pain was consistently higher among those with LOC than those with AOC, but only slightly so. Wilk et al, 2012⁵⁹ also stratified prevalence levels by mTBI with, versus without, comorbid PTSD and prevalence of back pain was considerably higher among those with comorbid PTSD (56% versus 36%).

Using data from the VA CTBIE, which asks about pain in the past 30 days, 2 studies by Suri et al^{52,53} also report relatively consistent findings. In these 2 samples, 13%⁵² and 16%⁵³ of Veterans with mTBI reported the presence of upper back pain (versus 11%, in both studies, among those without confirmed mTBI) and 53%⁵² and 58%⁵³ reported the presence of lower back pain (versus 48%, in both studies, of those without confirmed mTBI). Romesser et al reported somewhat similar, although higher, figures for a sample of Post-9/11 Veterans treated at 2 polytrauma clinics.⁴⁴ Based on a clinical questionnaire used with these treatment-seeking Veterans, 21% experienced upper back pain and 61% experienced lower back pain. This compared to 13% and 56% among those who did not have a history of mTBI.

Two studies were based on VA EHR data and reported prevalence of back pain diagnoses among Post-9/11 Veterans.^{7,40} Pugh et al used data for only the first year of Veterans' VA use and reported a prevalence of 27% among 93,003 Veterans with mTBI (compared to 18% among Veterans without any indication of mTBI history).⁷ King et al used data for multiple years of VA use and reported a prevalence of 46% among 421 Veterans with mTBI history (versus 23% of those without).⁴⁰

Additional details of these and other studies presenting back pain data are presented in Table 5.

Neck pain

Five studies reported data on prevalence of neck pain among Veterans with mTBI; all 5 involved Post-9/11 VA patients.^{7,40,44,52,53} Two studies were based on VA EHR data and reported prevalence of neck pain diagnoses.^{7,40} Pugh et al used data for only the first year of Veterans'

VA use and reported a prevalence of 6% among 93,003 Veterans with mTBI history (and 3% among 434,378 Veterans without mTBI),⁷ while King et al used data for multiple years of VA use and reported a prevalence of 14% among 421 Veterans (and 6% among a matched sample of 421 Veterans without mTBI).⁴⁰ Two studies by Suri et al^{52,53} used data from the VA CTBIE, which asks about pain in the past 30 days. In these 2 samples, 23%⁵² and 30%⁵³ of those with clinician-confirmed mTBI reported the presence of neck pain, while only 19% and 21% of those without clinician-confirmed mTBI reported neck pain. The highest prevalence of neck pain was observed in a sample of 354 Veterans seeking care in VA polytrauma clinics,⁴⁴ in which 40% reported that they had experienced neck pain in the past 30 days on a clinical questionnaire (45% among those who experienced LOC with their mTBI and 37% among those who did not; in comparison, 29% of Veterans without mTBI history reported neck pain).

Arm, leg, and/or joint pain

Arm, leg and/or joint pain were reported in 9 studies.^{15,39,42,49,52,53,56,59,60} Outcomes were assessed differently across studies, both in terms of what qualified as chronic arm, leg, or joint pain and the specific parts of the arms, legs, and/or joints that the studies assessed.

The largest study involved 32,316 Post-9/11 Veterans and used 1 year of VA EHR data to estimate prevalence of musculoskeletal pain among patients with mTBI.³⁹ Almost 39% of Veterans diagnosed with mTBI were diagnosed with musculoskeletal pain; among Veterans diagnosed with both mTBI and PTSD, 47% were also diagnosed with musculoskeletal pain (versus 35% of those with PTSD diagnoses only). This study defined both mTBI and pain (and PTSD) as any single instance of a respective ICD diagnosis code in the Veterans' health record.

Three studies^{15,59,60} assessed pain using the PHQ-15, which asks about "Arm/leg/joint pain" intensity in the past month. For the purposes of these studies, those who ranked their pain intensity as "bothered a lot" were considered to have chronic pain. All 3 studies reported prevalence levels of arm/leg/joint pain between 40% and 50%. These studies stratified the mTBI sample by those who had experienced an LOC at the time of their mTBI versus those who experienced AOC.^{15,59,60} In 2 of the studies,^{59,60} prevalence estimates were slightly higher for those with LOC versus those with AOC; the opposite was observed in the third study.¹⁵ One study also stratified the sample by whether comorbid PTSD was present.⁵⁹ As with other types of chronic pain, reports of arm/leg/joint pain were considerably more prevalent among those with comorbid PTSD than among those without (66% and 41%, respectively).

Two large studies using CTBIE data reported on "other joint pain," defined as pain experienced in the legs, arms, hands, feet, or "other" locations in the past 30 days.^{52,53} Prevalence levels in these studies were fairly similar for those with clinician-confirmed mTBI (48% and 53%), with both estimates slightly higher than among those without confirmed mTBI (44% and 43%). These 2 studies also reported on shoulder pain and, again, presented similar results (25% and 30%, versus 21% and 22%).

Several smaller studies reported on pain in various joints and parts of the arms and legs (*eg*, shoulders, knees, hips). See Table 5 for details of pain measurement and prevalence outcomes in these and all other included studies.

Abdominal/stomach pain

Five studies reported prevalence of abdominal or stomach pain among Veterans and SMs with mTBI.^{15,40,56,59,60} All reported prevalence levels that were, in general, 10% or less. Among these studies, 3 involved similar Post-9/11 SM study populations and methodology,^{15,59,60} prevalence ranged from 7% to 9% (these estimates were slightly higher than those provided in the 2 studies that also reported prevalence among participants without mTBI). These studies also reported prevalence stratified by mTBI with LOC versus mTBI with AOC and, in general, abdominal pain prevalence was slightly higher among those with LOC versus AOC. A study by Wilk et al⁵⁹ also stratified prevalence levels by mTBI with, versus without, comorbid PTSD and prevalence was considerably higher among those with comorbid PTSD (12% versus 5%). Another study examined VA healthcare records for Post-9/11 Veterans⁴⁰ and reported that 3% of those diagnosed with post-concussion syndrome had also been diagnosed with abdominal pain. Finally, a 1980s study of Vietnam-era Veterans reported abdominal pain in 10% of those with a history of mTBI (versus 12% among those with other injuries but without mTBI).⁵⁶

Arthritis

Two studies reported prevalence of arthritis (considered an indicator of chronic pain) among individuals with mTBI.^{40,57} Both were smaller studies with similar sample sizes, 414⁵⁷ and 421,⁴⁰ and reported fairly consistent prevalence estimates of 44% and 41% respectively. These estimates were higher than estimates among participants in these studies without mTBI (30% and 33%, respectively). The smaller study used CENC data for prevalence of arthritis,⁵⁷ and the larger used VA EHR data to estimate the presence of arthritis for at least 3 months.⁴⁰

Chest pain

Three studies involving similar Post-9/11 SM study populations and methodology reported on chest pain.^{15,59,60} Prevalence levels among SMs with mTBI in these 3 studies ranged from 6% to 12%. Two studies included estimates for comparison groups with other (non-mTBI) injuries (4% and 5%) or with no injuries (4% and 2%). These studies also reported prevalence levels stratified by mTBI with LOC versus AOC; as reported above, the prevalence of chest pain was consistently slightly higher among those with LOC than those with AOC. Wilk et al, 2012⁵⁹ also stratified prevalence levels by mTBI with, versus without, comorbid PTSD and prevalence was 2 times higher among those with comorbid PTSD (19% versus 8%).

Pain medication use

Use of pain medications, abstracted as an indicator of chronic pain, was reported in 4 articles.^{40-42,54} Three studies were clinic-based and enrolled Post-9/11 Veterans/SMs,^{41,42,54} while the other study was based on EHR data for Post-9/11 Veterans.⁴⁰ In an analysis of CENC study data, Hoot et al⁴¹ reported that 50% of 379 participants with mTBI were using analgesic pain medications, compared to 32% of those without a history of mTBI. Brickell et al⁴² queried 167 Post-9/11 SMs with mTBI and polytrauma who participated in follow-up telephone interviews. Among the 46 participants interviewed within 6 months of their injury, 30% reported using prescription opioid medications and 100% reported using non-opioid pain medications. Finally, in a clinical study of 978 SMs who screened positive for mTBI and were evaluated in a TBI program,⁵⁴ 50% of the 196 with chronic daily headaches (and 11.6% of the entire mTBI sample) reported using abortive headache medications for 15 or more days per month in the prior 3 months. A study based on

VA EHR data for Post-9/11 Veterans with diagnosed post-concussion syndrome in the Northeast region of the US reported that 78% had received any kind of pain control prescription medication; 49% were prescribed opioid analgesics, 29% non-opioid analgesics, 58% non-steroidal anti-inflammatory drugs (NSAIDs), and 17% anti-migraine agents.⁴⁰ This study also stratified medication receipt by comorbid PTSD diagnosis status and, with the exception of NSAID medications, pain medication prescriptions were more prevalent among Veterans with comorbid PTSD than those without.

Sexual pain/problems

The 3 studies involving similar Post-9/11 SM study populations and methodology also reported on sexual pain/problems.^{15,59,60} The prevalence levels among SMs with mTBI in these studies ranged from 5% to 9%. These estimates were slightly higher than those from the 2 studies that provided an injured (but no mTBI) comparison group (5% and 4%) and a non-injured (2% and 1%) comparison group. These studies also reported prevalence levels stratified by mTBI with LOC versus AOC and, again, the prevalence of sexual pain/problems was consistently slightly higher among those with LOC than those with AOC. Wilk et al 2012⁵⁹ also stratified prevalence levels by mTBI with, versus without, comorbid PTSD and prevalence was considerably higher among those with comorbid PTSD (22% versus 3%). Of note, the vast majority (91% to 99%) of participants in these 3 studies were male.

Other pain

A small number of studies reported other pain types not otherwise categorized above.^{7,39,40,42} Data from these studies are presented in Table 5.

Table 5. Prevalence estimates of other chronic pain from studies of Veterans and Servicemembers with a history of mTBI

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Back Pain			
Pugh, 2019 ⁷ n=93,003 Veterans.	EHR data	Back pain presence (yes/no): ICD diagnosis code in health record during first year of VA care.	25,255/93,003 (27.2%)
Suri, 2019 ⁵² n=23,703 Post-9/11 Veterans.	EHR data	Back pain presence (yes/no): VA health care use for back pain in past year.	8,661/23,703 (36.5%)
	CTBIE	Back pain presence (yes/no): Indicate whether experienced in last 30 days.	13,303/23,703 (56.1%)
		Low back pain (yes/no)	12,498/23,703 (52.7%)
Suri, 2017 ⁵³ n=1,683 Post-9/11 Veterans.	CTBIE	Back pain presence (yes/no): Indicate whether experienced in last 30 days.	60.9%
		Low back pain (yes/no)	57.5%
		Upper back pain (yes/no)	15.6%
Wilk, 2010 ⁶⁰ n=587	PHQ-15	Back pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 205/562 (36.5%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Post-9/11 SMs.			LOC: 85/197 (43.1%) AOC: 120/365 (32.8%)
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Back pain presence (yes/no): If treated for back pain conditions for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 193/421 (45.8%) mTBI+PTSD: 170/283 (60.1%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMs.	PHQ-15	Back pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 118/374 (31.6%) LOC: 40/121 (33.1%) AOC: 78/253 (30.8%)
Romesser, 2012 ⁴⁴ n=354 Post-9/11 Veterans assessed at 2 polytrauma clinics.	Self-report	Low back pain presence (yes/no): If Veteran reported problems with pain in the past 30 days, self-reported information about pain characteristics was used to classify the individual with low back pain. Upper back pain presence (yes/no): Same as above.	Total mTBI: 216/354 (61.0%) LOC: 90/144 (62.5%) No LOC: 126/210 (60.0%) Total mTBI: 73/354 (20.6%) LOC: 34/144 (23.6%) No LOC: 39/210 (18.6%)
MacGregor, 2013 ⁴⁹ n=334 Post-9/11 SMs.	PDHRA	Back pain presence (yes/no): Asked to endorse whether they currently have pain that they feel is related to their deployment.	Total mTBI: 110/334 (32.9%) mTBI with LOC: 31/103 (30.1%) mTBI no LOC: 49/150 (32.7%)
Vanderploeg, 2009 ⁵⁶ n=278 Vietnam-era Veterans.	Self-report	Low back pain presence (yes/no): Unusually frequent or severe pain during last year via medical history interview and questionnaire.	36.3%
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Back pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 114/260 (43.8%) LOC: 39/86 (45.3%) AOC: 75/174 (43.1%) mTBI+PTSD: 54/96 (56.3%) mTBI no PTSD: 59/163 (36.2%)
Neck Pain			
Pugh, 2019 ⁷ n=93,003 Post-9/11 Veterans.	EHR data	Neck pain presence (yes/no): ICD diagnosis code in health record during first year of VA care.	5,916/93,003 (6.4%)
Suri, 2019 ⁵² n=23,703	CTBIE	Neck pain presence (yes/no): Indicate whether experienced in last 30 days.	5,428/23,703 (22.9%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Post-9/11 Veterans.			
Suri, 2017 ⁵³ n=1,683 Post-9/11 Veterans.	CTBIE	Neck pain presence (yes/no): Indicate whether experienced in last 30 days.	30.4%
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Neck pain presence (yes/no): If treated for neck pain conditions for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 57/421 (13.5%) mTBI+PTSD: 50/283 (17.7%)
Romesser, 2012 ⁴⁴ n=354 Post-9/11 Veterans assessed at 2 polytrauma clinics.	Self-report	Neck pain presence (yes/no): If Veteran reported problems with pain in the past 30 days, self-reported information about pain characteristics was used to classify the individual with neck pain.	Total mTBI: 143/354 (40.4%) LOC: 65/144 (45.1%) No LOC: 78/210 (37.1%)
Arm/leg/joint pain			
Kulas, 2018 ³⁹ n=32,316 Post-9/11 Veterans.	EHR data	Musculoskeletal pain presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 47.0% mTBI no PTSD: 38.8%
Suri, 2019 ⁵² n=23,703 Post-9/11 Veterans.	CTBIE	Shoulder pain presence (yes/no): Indicate whether experienced in last 30 days. Other joint pain (legs, arms, hands, feet, or "other" location) presence (yes/no): Indicate whether experienced in last 30 days.	5,799/23,703 (24.5%) 11,357/23,703 (47.9%)
Suri, 2017 ⁵³ n=1,683 Post-9/11 Veterans.	CTBIE	Shoulder pain presence (yes/no): Indicate whether experienced in last 30 days. Other joint pain (legs, arms, hands, feet, or "other" location) presence (yes/no): Indicate whether experienced in last 30 days.	30.0% 53.1%
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMs.	PHQ-15	Arm/leg/joint pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 254/559 (45.4%) LOC: 95/196 (48.5%) AOC: 159/363 (43.8%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMs.	PHQ-15	Arm/leg/joint pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 150/373 (40.2%) LOC: 45/121 (37.2%) AOC: 105/252 (41.7%)
Vanderploeg, 2009 ⁵⁶ n=278 Vietnam-era Veterans.	Self-report	Calf pain presence (yes/no): Unusually frequent or severe pain during last year via medical history interview and questionnaire.	4.4%

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Arm/leg/joint pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 129/260 (49.6%) LOC: 47/86 (54.7%) AOC: 82/174 (47.1%) mTBI+PTSD: 63/96 (65.6%) mTBI no PTSD: 66/163 (40.5%)
Brickell, 2014 ⁴² n=167 Post-9/11 SMs.	Telephone interview with open-ended questions.	Lower extremities pain (yes/no): Any pain in past month (the telephone follow-up interview is an unpublished, 10-15 min, semi-structured interview developed specifically for this study).	6 mos: 43.5% 12 mos: 37.1% 24 mos: 55.6% 36 mos: 28.6% 48 mos: 23.3% 60 mos: 28.0%
		Upper extremities pain (yes/no).	6 mos: 26.1% 12 mos: 24.7% 24 mos: 25.9% 36 mos: 19.0% 48 mos: 23.3% 60 mos: 8.0%
MacGregor, 2013 ⁴⁹ n=334 Post-9/11 SMs.	PDHRA	Joint and muscle pain presence (yes/no): Asked to endorse whether they currently have pain that they feel is related to their deployment.	Total mTBI: 78/334 (23.4%) mTBI with LOC: 25/103 (24.3%) mTBI no LOC: 49/150 (32.7%)
Abdominal/stomach pain			
Vanderploeg, 2009 ⁵⁶ n=278 Vietnam-era Veterans.	Self-report	Abdominal pain presence (yes/no): Unusually frequent or severe pain during last year via medical history interview and questionnaire.	10.1%
⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Abdominal pain presence (yes/no): If treated for abdominal pain conditions for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 12/421 (2.9%) mTBI+PTSD: 11/283 (3.9%)
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMs.	PHQ-15	Stomach pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 47/557 (8.4%) LOC: 17/196 (8.7%) AOC: 30/361 (8.3%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMs.	PHQ-15	Stomach pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 34/369 (9.2%) LOC: 14/120 (11.7%) AOC: 20/249 (8.0%)
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Stomach pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 19/260 (7.3%) LOC: 5/86 (5.8%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
			AOC: 14/174 (8.0%) mTBI+PTSD: 11/96 (11.5%) mTBI no PTSD: 8/163 (4.9%)
Arthritis			
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR	Arthritis presence (yes/no): If treated for arthritis conditions for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 173/421 (41.1%) mTBI+PTSD: 152/283 (53.7%)
Walker, 2018a ⁵⁷ n=414 Post-9/11 Veterans/SMs. CENC sample	BRFSS	Arthritis presence (yes/no): This item was asked as in the CDC's Behavioral Risk Factor Surveillance System: "Has a doctor, nurse, or other health professional EVER told you that you had any of the following? For each, tell me 'Yes,' 'No,' or you're 'Not sure.'" Variable was dichotomous.	180/412 (43.7%)
Chest Pain			
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMs.	PHQ-15	Chest pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 46/560 (8.2%) LOC: 28/196 (14.3%) AOC: 18/364 (4.9%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMs.	PHQ-15	Chest pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 24/374 (6.4%) LOC: 17/121 (14.0%) AOC: 7/253 (2.8%)
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Chest pain presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 30/260 (11.5%) LOC: 11/86 (12.8%) AOC: 19/174 (10.9%) mTBI+PTSD: 18/96 (18.8%) mTBI no PTSD: 13/163 (8.0%)
Pain medication use			
Theeler, 2012 ⁵⁴ n=978 Post-9/11 SMs.	Self-report	Abortive headache medication use among those with chronic daily headaches (CDH; ≥15 days/month for past 3 months; n=196) versus those with episodic headaches (<15 days/month; n=761).	Total mTBI: 113/978 (11.6%) CDH: 97/196 (49.5%) Episodic headache: 16/761 (2.1%)
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Any pain control medication prescriptions identified in VA pharmacy records (yes/no).	Total mTBI: 312/400 (78.0%) TBI+PTSD: 277/351 (78.9%) TBI no PTSD: 35/49 (71.4%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
		Opioid analgesic prescriptions identified in VA pharmacy records (yes/no).	Total mTBI: 195/400 (48.8%) TBI+PTSD: 174/351 (49.6%) TBI no PTSD: 21/49 (42.9%)
		Non-opioid analgesics prescriptions identified in VA pharmacy records (yes/no).	Total mTBI: 117/400 (29.3%) TBI+PTSD: 104/351 (29.6%) TBI no PTSD: 13/49 (26.5%)
		Non-steroidal anti-inflammatory drug prescriptions identified in VA pharmacy records (yes/no).	Total mTBI: 231/400 (57.8%) TBI+PTSD: 103/351 (29.3%) TBI no PTSD: 29/49 (59.2%)
		Anti-migraine agent prescriptions identified in VA pharmacy records (yes/no).	Total mTBI: 66/400 (16.5%) TBI+PTSD: 59/351 (16.8%) TBI no PTSD: 7/49 (14.3%)
Hoot, 2018 ⁴¹ n=379 Post-9/11 Veterans/SMs. CENC sample	EHR/Self-report	Analgesic medication use (yes/no): Uses analgesic medications.	188/376 (50.0%)
Brickell, 2014 ⁴² n=167 Post-9/11 SMs.	Telephone interview with open-ended questions	Opioid pain medication use (yes/no): Asked if taking any medications and categorized post hoc. The telephone follow-up interview is an unpublished, 10-15 min, semi-structured interview developed specifically for this study.	6 mos: 30.4% 12 mos: 25.8% 24 mos: 18.5% 36 mos: 19.0% 48 mos: 26.7% 60 mos: 12.0%
		Other (non-opioid) pain medication use (yes/no): Asked if taking any medications for pain and categorized post hoc.	6 mos: 100% 12 mos: 27.0% 24 mos: 18.5% 36 mos: 19.0% 48 mos: 30.0% 60 mos: 8.0%
Sexual pain/problems			
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMs.	PHQ-15	Sexual pain/problems presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 33/560 (5.9%) LOC: 16/196 (8.2%) AOC: 17/364 (4.7%)
Hoge, 2008 ¹⁵ n=384 Post-9/11 SMs.	PHQ-15	Sexual pain/problems presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 18/373 (4.8%) LOC: 10/120 (8.3%)

Author, year N pts with mTBI Population	Pain assessed by	Pain measurement definition/details of assessment tool	Prevalence Results n (%)
			AOC: 8/253 (3.2%)
Wilk, 2012 ⁵⁹ n=260 Post-9/11 SMs.	PHQ-15	Sexual pain/problems presence in past month (yes/no): "Bothered a lot"=yes.	Total mTBI: 23/260 (8.8%) LOC: 9/86 (10.5%) AOC: 14/174 (8.0%) mTBI+PTSD: 21/96 (21.9%) mTBI no PTSD: 4/163 (2.5%)
Other			
Kulas, 2018 ³⁹ n=32,316 Post-9/11 Veterans.	EHR data	Skeletal pain presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 3.1% mTBI no PTSD: 2.1%
		Diabetic pain presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 0.3% mTBI no PTSD: 0.2%
		Fibromyalgia presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 4.1% mTBI no PTSD: 2.2%
		Herpetic pain presence (yes/no): Presence/absence of ICD diagnosis code in EHR.	mTBI+PTSD: 1.1% mTBI no PTSD: 0.6%
Pugh, 2019 ⁷ n=93,003 Post-9/11 Veterans.	EHR data	Other pain presence (arthritis/musculoskeletal pain; yes/no): ICD diagnosis code in health record during first year of VA care.	19,631/93,003 (21.1%)
King, 2014 ⁴⁰ n=421 Post-9/11 Veterans.	EHR data	Other pain presence (yes/no): If treated for other pain conditions for ≥3 months based on ICD diagnosis codes (<i>ie</i> , if the time elapsed between encounters with similarly coded conditions was ≥90 days from the initial encounter).	Total mTBI: 107/421 (25.4%) mTBI+PTSD: 99/283 (35.0%)
Brickell, 2014 ⁴² n=167 Post-9/11 SMs.	Telephone interview with open-ended questions	Body pain (as contrasted with extremities and head and neck pain) presence (yes/no): Any pain in past month (the telephone follow-up interview is an unpublished, 10-15 min, semi-structured interview developed specifically for this study).	6 mos: 43.5% 12 mos: 40.4% 24 mos: 37.0% 36 mos: 38.1% 48 mos: 40.0% 60 mos: 16.0%

Abbreviations: AOC=Alteration of consciousness; BRFSS=Behavioral Risk Factor Surveillance System; CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; ICD=International Classification of Diseases; LOC=Loss of consciousness; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire scale; PTSD=Posttraumatic stress disorder; SM=Servicemember; VA=Veterans Affairs

KQ1a. What are the most common types of chronic pain in US Veterans or Servicemembers with a history of mTBI?

Across studies, back pain, head pain, and arm, leg, and/or joint pain were the most prevalent types of chronic pain observed. For instance, 1 study of 384 SMs with a history of mTBI¹⁵ asked how much they were bothered by physical symptoms in the past month (PHQ-15) including stomach pain, back pain, arm, leg, or joint pain, headache, and chest pain. Of those with a history of mTBI, arm, leg, or joint pain was the most prevalent (40.2% indicated they were “bothered a lot”), followed by back pain (31.6%), then headache (22.4%). See Table 4 and Table 5 for more details.

KQ1b. Do the prevalence or types of chronic pain experienced by US Veterans or Servicemembers with a history of mTBI differ by mTBI etiology?

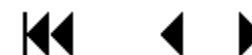
Three studies^{41,46,60} provide evidence for prevalence of chronic pain in Veterans and SMs with a history of mTBI by mTBI etiology. Table 6 summarizes the results of these studies. All included studies examined mTBI due to blast compared to mTBI resulting from non-blast causes; no other etiologies were examined/compared. Overall, blast-related mTBI did not appear to be associated with more frequent or more severe pain in these 3 studies. One exception was the measure of headache prevalence in Wilk et al 2010⁶⁰ which, among Veterans who experienced LOC after their mTBI (but not those who only experienced AOC), was endorsed for 40% of those whose mTBI was associated with blasts versus only 23% of those whose mTBI was not associated with blasts. None of the other pain types assessed in this study differed by mTBI etiology. The study by Hoot et al⁴¹ may also suggest higher pain prevalence among those with blast versus non-blast mTBI; however, this difference was small (eg, 63% versus 56%). None of the studies compared pain prevalence levels by location of mTBI, location of co-occurring injuries, or timing of pain onset relative to the mTBI.

Table 6. Prevalence of Chronic Pain in Veterans and Servicemembers with a History of mTBI by mTBI Etiology

Author, year N pts with mTBI Population	mTBI etiology assessed by	mTBI etiology measurement/ assessment tool	Pain assessed by	Pain measurement definition/details of assessment tool	Pain prevalence results by etiology n (%)
Wilk, 2010 ⁶⁰ n=587 Post-9/11 SMS.	Self-report	The questionnaire (3-6 months after return from deployment) asked soldiers whether they had been injured during deployment by a blast/explosion.	PHQ-15	Stomach pain presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 13/156 (8.3%) vs 4/40 (10.0%); P=0.76 AOC blast vs non-blast: 14/254 (5.5%) vs 16/107 (15.0%); P=0.01
				Back pain presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 71/157 (45.2%) vs 14/40 (35.0%); P=0.29 AOC blast vs non-blast: 84/257 (32.7%) vs 36/108 (33.3%); P=0.90
				Arm/leg/joint pain presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 78/156 (50.0%) vs 17/40 (42.5%); P=0.48 AOC blast vs non-blast: 105/256 (41.0%) vs 54/107 (50.5%); P=0.11
				Headache presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 63/157 (40.1%) vs 9/40 (22.5%); P=0.04 AOC blast vs non-blast: 53/258 (20.5%) vs 19/108 (17.6%); P=0.57
				Chest pain presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 23/156 (14.7%) vs 5/40 (12.5%); P=0.81 AOC blast vs non-blast: 12/258 (4.7%) vs 6/106 (5.7%); P=0.79
				Abdominal pain presence in past month (yes/no): "Bothered a lot"=yes.	LOC blast vs non-blast: 13/156 (8.3%) vs 3/40 (7.5%); P=1.00 AOC blast vs non-blast: 13/257 (5.1%) vs 4/107 (3.7%); P=0.79

Author, year N pts with mTBI Population	mTBI etiology assessed by	mTBI etiology measurement/ assessment tool	Pain assessed by	Pain measurement definition/details of assessment tool	Pain prevalence results by etiology n (%)
Hoot, 2018 ⁴¹ n=379 Post-9/11 Veterans/SMs. CENC sample.	VCU rCDI	Detailed structured diagnostic TBI interview for blast or non-blast TBI.	EQ-5D-5L	Pain presence and intensity: Moderate, severe, or extreme level of pain or discomfort.	mTBI by blast exposure: ≥1 TBI from blast: 123/196 (62.8%) TBI not from blast: 101/182 (55.5%) Severity breakdown: (≥1 TBI from blast vs TBI not from blast): Moderate pain or discomfort: 83/196 (42.3%) vs 83/182 (45.6%) Severe pain or discomfort: 37/196 (18.9%) vs 17/182 (9.3%) Extreme pain or discomfort: 3/196 (1.5%) vs 1/182 (0.5%)
Couch, 2016 ⁴⁶ n=43 Post-9/11 Veterans.	Self-report	Screening questionnaire in TBI clinic: Mode of injury recorded including number of blast injuries versus blunt injury with no blast.	Self-report	Detailed headache questionnaire which has been used in the University of Oklahoma Headache clinic since 1996: Assessed chronic daily headache (CDH, defined as ≥15 days/month) and frequent headache (defined as 10-14 days/month) in the last 6 months prior to telephone contact (questionnaire).	CDH: Blast mTBI: 15/34 (44.1%) Blunt mTBI-only: 4/9 (44.4%) Frequent headache: Blast mTBI: 12/34 (35.3%) Blunt mTBI-only: 3/9 (33.3%)

Abbreviations: AOC=Alteration of consciousness; CDH=Chronic daily headaches; EQ-5D-5L=EuroQol Group 5-dimension 5-level version quality-of-life; LOC=Loss of consciousness; mTBI=Mild traumatic brain injury; PHQ-15=15-Item Patient Health Questionnaire; SM=Servicemember; TBI=Traumatic brain injury; VCU-rCDI=Virginia Commonwealth University retrospective Concussion Diagnostic Interview



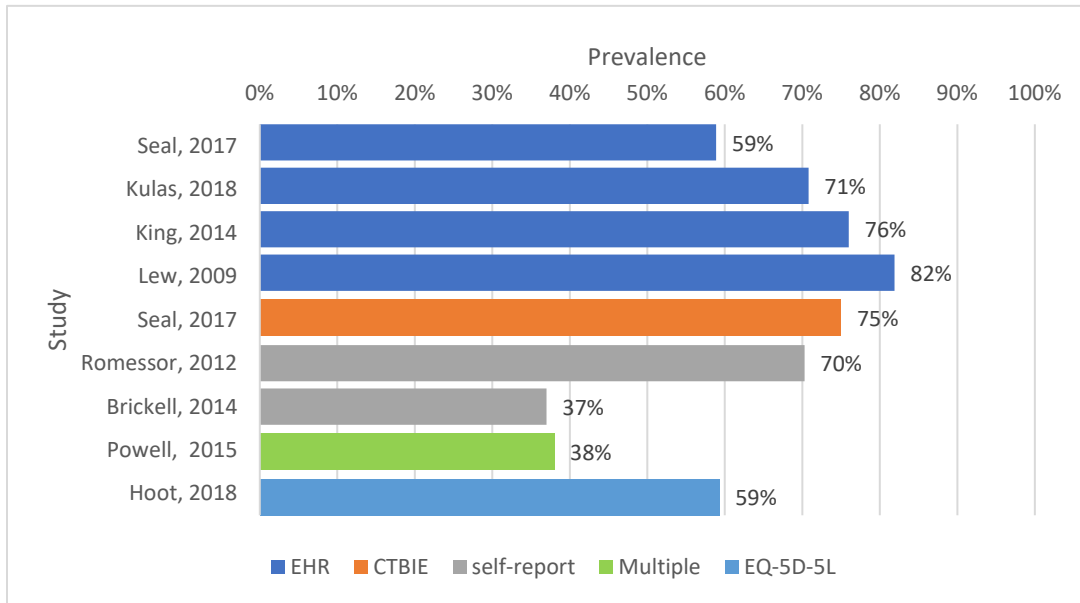
KQ1c. How do estimates of the prevalence of chronic pain and mTBI in US Veterans or Servicemembers differ according to pain measurement methods or definitions?

Studies of pain prevalence in populations with a history of mTBI (*ie*, those included for KQ1) employed a wide variety of strategies to assess pain. These strategies include self-report, use of validated measures, diagnostic data abstraction from the EHR, and evaluation of medication use for pain. Within types of measures used, there was also variability, as some studies required a certain threshold of symptoms (such as endorsement of at least “bothered a lot” on the PHQ-15), whereas other studies identified pain regardless of the level of severity (such as “frequent headache” in the past month). There was also heterogeneity in strategies for identifying pain from the EHR; while some studies indicated pain was present if there was any diagnosis within a given time period, other studies required 2 or more of the same pain diagnosis at least 3 months apart (presumably to match the definition of chronic pain, which requires pain to be present for 3 or more consecutive months).

As summarized for KQ1, studies reported a broad range of pain prevalence estimates, even among those using similar assessment methodology. In general, studies relying on more comprehensive diagnostic assessment methods reported lower pain prevalence estimates than studies using self-report methods of pain assessment. For example, both Seal et al⁴ and Kulas and Rosenheck³⁹ extracted EHR data; however, Seal et al required 2 or more instances of the same diagnostic code, more than 90 days apart, whereas Kulas and Rosenheck reported prevalence based on a singular instance of a pain diagnosis. The different prevalence levels of any chronic pain identified were 59% (Seal et al, 2017) and 71% (Kulas and Rosenheck, 2018). Similarly, in studies of head pain, results derived from the EHR,^{7,40,45,48,58} which are based on diagnostic assessment, generally reported lower prevalence levels than studies that reported self-report data.^{42,44,46,50,55} In 3 different studies using the same self-report measure (the PHQ-15) and same cut-point,^{15,59,60} the authors identified relatively similar pain prevalence levels across studies (*eg*, range of 7.3% to 9.2% with abdominal/stomach pain).

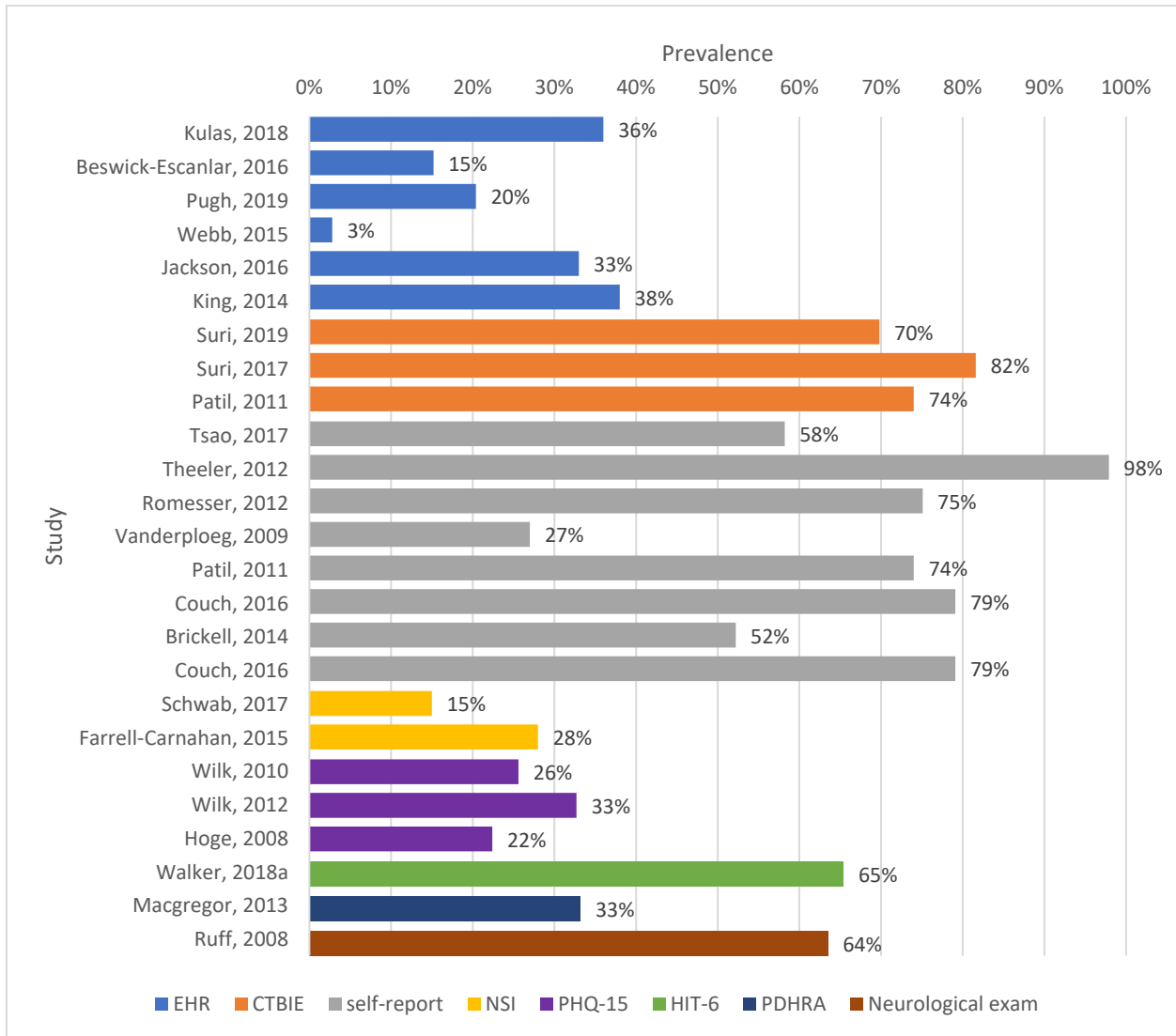
Figures 3-7 portray the range of prevalence estimates by study and tool for some of the most common types of chronic pain. Where severity or frequency data were available, the estimates in these figures reflect more severe pain (in some cases moderate or higher, in others severe to very severe pain), and more frequent pain (most studies that specified used a cutoff of 15 or more days per month in the case of headaches). Some studies also reported prevalence estimates for multiple time frames of follow-up (such as at 6-month intervals, or pain occurring at less than, versus greater than, 180 days post-injury). Where studies reported multiple time frames, we used the more recent in these figures in order to be more comparable to studies that only examined pain in the past 30 days or 3 months.

Figure 3. Prevalence of general chronic pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool



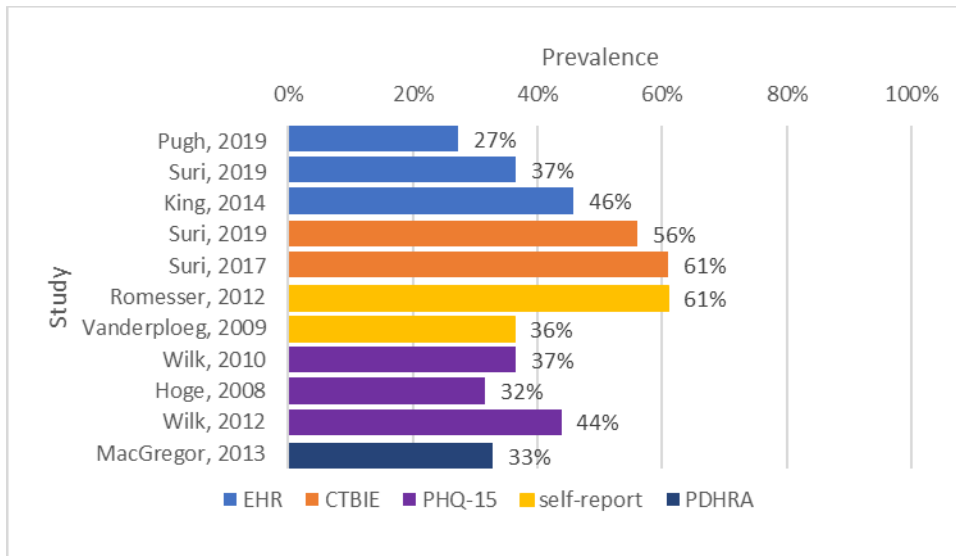
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; EQ-5D-5L=EuroQol Group 5-Dimension 5-Level version

Figure 4. Prevalence of head pain in Veterans/Servicemembers with a history of mTBI by study and pain measurement tool



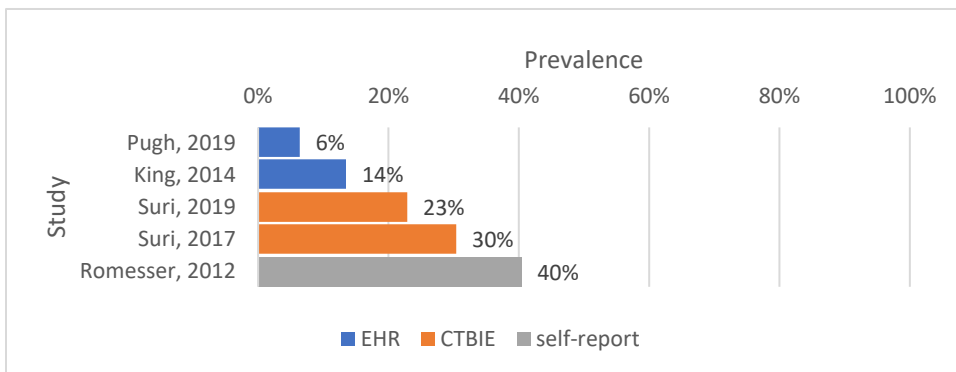
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; HIT-6=6-Item Headache Impact Test; NSI=Neurobehavioral Symptom Inventory; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire

Figure 5. Prevalence of back pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool



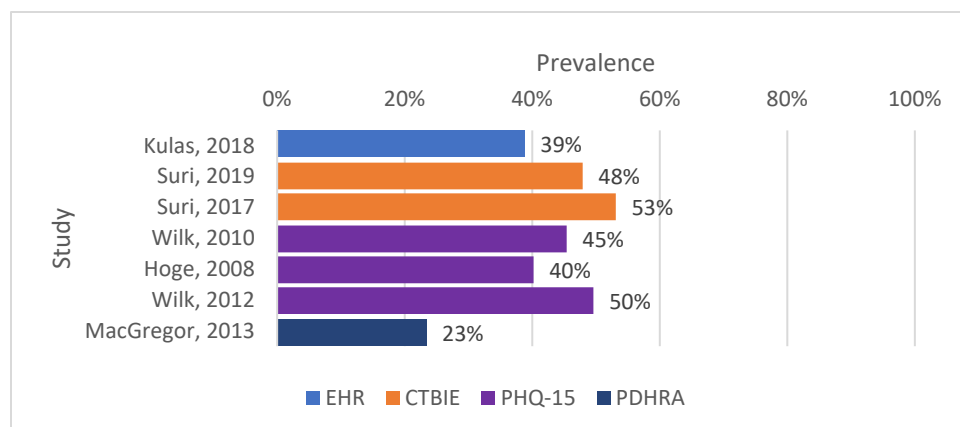
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire

Figure 6. Prevalence of neck pain in Veterans/ Servicemembers with a history of mTBI by study and pain measurement tool



Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record

Figure 7. Prevalence of arm, leg, and/or joint pain in Veterans and Servicemembers with a history of mTBI by study and pain measurement tool



Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire

KEY QUESTION 2: What is the risk of suicide in US Veterans or Servicemembers with chronic pain and a history of mTBI?

Summary of Findings

We found 1 study⁷ that addressed KQ2. It also contributed evidence in KQ1. This study only provided data related to sub-question ‘a.’

a. How does the prevalence of suicide-related outcomes in US Veterans or Servicemembers with a history of mTBI and chronic pain compare to US Veterans or Servicemembers with no mTBI history and/or no chronic pain?

Pugh and colleagues classified Veterans in the study into a number of phenotypes. The Polytrauma phenotype was defined by consistently high comorbidities of mental health disorders, post-concussive symptoms, and pain throughout the study, and therefore we considered this group to represent Veterans in the study with chronic pain and history of mTBI. A second group of interest was the Moderately Healthy + Decline phenotype, characterized by a worsening of symptoms from years 1 to 5. The comparison group is a moderately healthy group of Veterans with a history of mTBI, characterized by “relatively low probabilities of back pain, other pain, mental health and sensory conditions compared to the base-rate in the population.”⁷ The prevalence of suicide-related behaviors (*ie*, suicidal ideation/attempt, identified based on ICD-9-CM diagnosis codes) in Veterans with mTBI classified in the Polytrauma phenotype ($n=11,333$) was 6.1% and in the Moderately Healthy + Decline phenotype ($n=17,706$) was 6.9%, compared to 2.9% in the moderately healthy group of Veterans with a history of mTBI ($n=29,168$).⁷ Compared to the phenotype of relatively healthy Veterans, both the Polytrauma and Moderately Healthy + Decline groups had significantly higher odds of SRB (adjusted OR=1.4 and 1.3 respectively; CI not reported quantitatively).⁷ This study also compared the prevalence of suicide-related behaviors between those with and without a history of mTBI (*eg*, 6.6% versus 2.4%, respectively) but did not likewise directly compare suicide-related behaviors between those with mTBI with and without comorbid pain. This study of the entire population of Post-9/11 VA users defined pain based on ICD diagnosis codes.

KEY QUESTION 3. What are the benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI?

Summary of Findings

Three studies¹²⁻¹⁴ met inclusion criteria and addressed KQ3. All 3 studies were focused on treatment for chronic headaches following mTBI. The studies by Leung et al (2016 and 2018) investigated the efficacy of repetitive transcranial magnetic stimulation (rTMS) in 2 small RCTs (N=29 and 44).^{12,13} Nelson and Esty (2015) conducted a small (N=9) pre-post study to investigate a “brainwave-based intervention” described as “the Flexyx Neurotherapy System (FNS) that involves minute pulses of electromagnetic energy stimulation of brainwave activity.”¹⁴ Table 7 describes study characteristics of the 3 included studies, including descriptions of the study samples and interventions; Table 8 provides additional study details including descriptions of the pain assessment tools used in these trials and outcomes. All 3 studies examined intervention effects in adult US Veterans, many of whom experienced other comorbidities common among Veterans with mTBI history (eg, PTSD, depression, and cognitive dysfunction). Because of the high RoB ratings and small sample sizes of the included studies, the overall body of evidence was rated as having “insufficient” strength of evidence according to AHRQ EPC methods.

Of note is that no studies were identified that compared the efficacy of chronic pain treatments among those with, versus without, mTBI.

Detailed Results

Results from the 3 included studies are summarized in Table 8. Briefly, the 2 Leung et al studies (2016 and 2018)^{12,13} reported significantly greater reduction in persistent headaches in the rTMS group compared to the group randomized to the sham treatment condition. Similar results were obtained for debilitating headache exacerbation, with significantly greater reductions observed in the rTMS group compared to the sham group in both studies. Nonsignificant differences in global pain intensity were reported for both rTMS studies. Nelson and Esty (2015) reported a consistent decrease in mean pain scores over time, with a mean BPI-HA score of 7.3 (SD=1.2) decreasing to 2.9 (SD=2.6) after 20 FNS (neurotherapy) sessions for “worst pain past week” and a mean BPI-HA score of 4.6 (SD=1.6) decreasing to 1.4 (SD=1.2) after 20 sessions for “average pain past week.”¹⁴

Risk of Bias

Using the Cochrane Risk-of-Bias 2.0 criteria³³ for RCTs and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I)³⁴ for non-randomized intervention studies, we conducted a formal rating of the risk of bias (RoB) of the 3 included treatment studies (see Appendix C, Table 10 for full criteria). The Leung RCTs^{12,13} reported similar methods, though the study published earlier (2016) did not report adequate information on randomization, whereas the 2018 publication reported adequate randomization methods. Neither study reported adequate detail on attrition after consent, and the 2018 study reported that only 29 out of 44 consented participants completed the study and were included in analyses. A notable strength, however, was the reliance on a well-designed and implemented sham control condition in these 2 trials, as well as

similar baseline characteristics of treatment and control groups. The study by Nelson and colleagues¹⁴ provides less robust evidence primarily due to its reliance on a pre-post (uncontrolled) study design and the very small (N=9) sample size. Studies failed to provide adequate detail to assess RoB in numerous domains (eg, randomization, masking, attrition, fidelity). Overall, these 3 studies were all rated as having high RoB. Risk of bias ratings by domain are shown in Table 9.

According to AHRQ methods,^{37,38} we considered study limitations, directness, consistency, precision, reporting bias, dose-response association, and plausible confounding that would decrease the observed effect, strength of association, and applicability to classify the strength of evidence for KQ3 outcomes. While all 3 studies investigated the population of interest, high RoB in combination with the very small number of studies (two from the same research team) and small sample sizes of included studies resulted in a strength of evidence rating of “insufficient” according to AHRQ EPC methods. The “insufficient” rating was based on the following AHRQ criteria: unable to estimate an effect, or no confidence in the estimate of effect for this outcome. The body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

KQ3a. Do the benefits or harms differ by mTBI etiology, type of chronic pain, mental health comorbidities, intervention setting, and demographics?

Due to the small number of pain trials on limited populations, generalizations about whether benefits and harms differ by mTBI etiology, type of chronic pain, mental health comorbidities, intervention setting, and demographics were not possible.

KQ3b. How is pain assessed in clinical trials for comorbid chronic pain and history of mTBI in Veterans and Servicemembers?

Table 8 lists measures used to assess pain in clinical trials. Two of the 3 studies examined persistent headaches and debilitating headaches based on headache diaries using numeric rating scales (NRS).^{12,13} These unvalidated headache pain assessments were both based on composite scores of average presence, duration, and intensity. All 3 studies also examined changes on the standardized Brief Pain Inventory (BPI), a validated self-report measure of global pain.

Table 7. Characteristics of studies of interventions for headaches in participants with a history of mTBI

Study design	Intervention	Total N	Selection criteria	mTBI definition and participant characteristics	Intervention	Comparator	Demographics
Leung, 2016 ¹²	RCT	N=24 (but 5 participants dropped out from the study prior to intervention and were not	US Veterans; age 18-80; history of mTBI; diagnosed ICDH-2 posttraumatic headache; average chronic persistent daily (24/7) headache intensity>30 on 0–	Head trauma with: either no LOC, or LOC<30 min duration; GCS score ≥13; symptoms and/or signs diagnostic of concussion.	N=12 Three neuronavigation-guided rTMS study treatments with intertreatment interval at least 24 hours or no	N=12 Sham rTMS	Reported by treatment group; rTMS: Age: 41.2±14.0 yrs. Female: 2/12 (8.3%). Sham: Age: 41.4±11.6 yrs.

Study design Intervention Total N	Selection criteria	mTBI definition and participant characteristics	Intervention	Comparator	Demographics
included in analyses).	100 M-VAS at screening; and average pain intensity >3/10 on NRS reported in the headache diary (between visits 1-2) Also: No prior experience of TMS treatment; no history of daily persistent headache prior to the mTBI incidence.		more than 72 hours apart were administered to the patients within 1 week.		Female: 1/12 (16.7%). Mental health comorbidities: PTSD, depression, cognitive dysfunction.
Leung, 2018 ¹³ RCT N=29 (but 15 participants dropped out from the study prior to intervention and were not included in analyses)	US Veterans; age 18-65; history of mTBI; diagnosed ICDH-2 posttraumatic headache; average chronic persistent daily (24/7) headache intensity >30 on 0-100 M-VAS at screening; and average pain intensity >3/10 on NRS reported in the headache diary (between visits 1-2) Also: No prior experience of TMS treatment; no history of daily persistent headache prior to the mTBI incidence.	Head trauma with: either no LOC, or LOC <30 min duration; GCS score ≥13; symptoms and/or signs diagnostic of concussion. Based on published criteria from the 1993 American Congress of Rehabilitation Medicine, and recent DoD recommendation.	N=14 rTMS: at the left prefrontal cortex delivered at 10 Hz, 80% of resting motor threshold and 2000 pulses per session. 4 sessions at >24 and <72 hours apart	N=15 Sham rTMS	Age: 34.1±7.9 yrs. Female: 6/29 (20.7%). Mental health comorbidities: depression, PTSD, cognitive dysfunction.
Nelson, 2015 ¹⁴ Pre-post N=9	US Veterans with wartime deployments in Afghanistan and/or Iraq; experienced service-connected TBI; other criteria NR.	Majority experienced some LOC (range: a few seconds to a number of minutes); 1 reported having experienced only 1 concussion, the others reported having experienced multiple (typically "many" or "too many to count"), including	N=9 FNS: Brainwave-based biofeedback. Involves subtle, minute pulses of EM stimulation computer-adjusted based on EEG feedback. Total	No comparator	Age: 37.3±12.6 yrs (range: 25-64). Time from end of most recent deployment to 1 st treatment: 6-103 months (median=46). Taking ≥1 Rx: 7/9 (range=1-7; median=2).

Study design	Intervention	mTBI definition and participant characteristics	Intervention	Comparator	Demographics
Total N	Selection criteria	exposures to explosive blasts.	of 4 s of EM stimulation spaced over 4 minutes. 2–3 sessions/week until 20 sessions were completed.		Mental health comorbidities: PTSD (majority of participants); depressive disorders (3 participants).

Abbreviations: DoD=Department of Defense; EEG=Electroencephalogram; EM=electromagnetic energy; FNS=Flexyx Neurotherapy System; GCS=Glasgow Coma Scale; ICDH-2=International Classification of Headache Disorders 2nd Edition; LOC=Loss of consciousness; mTBI=mild traumatic brain injury; M-VAS=Mechanical Visual Analog Scale; NR=Not reported; NRS=Numerical rating scale; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; rTMS=Repetitive transcranial magnetic stimulation; Rx=prescription medication; TBI=traumatic brain injury; TMS=transcranial magnetic stimulation



Table 8. Findings of studies of interventions for headaches in participants with a history of mTBI

Study design T vs C N (T vs C)	Headache definition	Findings		Risk of Bias
		Headache pain	Harms	
Leung, 2016 ¹² RCT rTMS vs sham 12 vs 12	<p>Persistent headaches: Between-visit persistent headache severity averaged (sum of headache rating score/number of days) from daily headache diary.</p> <p>Debilitating headache exacerbation: composite score generated by multiplying average duration (hours/episode) of headache exacerbation by average frequency (episodes/day) and average intensity (NRS)</p> <p>Global Pain Intensity: BPI assessed baseline level of overall pain (total score divided by a factor of 4), the degree of headache relief (%) from the medication, and overall degree of interference (total score divided by 7) of pain on daily functions.</p>	<p>Persistent headaches: ANOVA (Visit × Treatment): (p=0.06; F=3.93; df=1) of treatment by time interaction. rTMS group had significantly (p=0.041; F=4.73; df=1) higher percentage of persistent headache intensity reduction than the sham group at 1-week posttreatment. A significantly (p=0.035; chi-square=4.44, df=1) higher percentage of rTMS participants (58.3%) demonstrated at least 50% headache reduction than the SHAM group participants (16.6%) at 1-week posttreatment.</p> <p>Debilitating headache exacerbation: Debilitating headache exacerbation was significantly (p=0.017, F=6.61; df=1.22) reduced in the rTMS group at 4-weeks posttreatment compared to the sham group.</p> <p>Global Pain Intensity: Visit and treatment interaction for global pain intensity was nonsignificant.</p>	<p>One participant had mild scalp discomfort, no other AEs reported.</p>	High
Leung, 2018 ¹³ RCT rTMS vs sham 14 vs 15	<p>Persistent headaches: Between-visit persistent headache severity=averaged (sum of headache NRS score/number of days) from daily headache diary.</p> <p>Debilitating headache exacerbation: Composite score generated by multiplying average duration (hours/episode) of headache exacerbation by average frequency (episodes/day) and average intensity (NRS)</p>	<p>Persistent Headaches: Two-factor (visit x treatment) ANOVA indicated an overall interaction for average daily persistent headache intensity (F=11.63, DF=1, p=0.002). Significant difference between groups at 1-week (F=21.75, p<0.0001) and 4-weeks (F=11.56, p=0.002) posttreatment. At 4-weeks posttreatment, 57% of the rTMS group no longer experienced persistent headaches compared to 20% of the sham group (F=6.76, p=0.009).</p> <p>Debilitating Headache: Non-significant difference for debilitating headache composite scores (F=3.71, p=0.062). rTMS group decreased 55.1% (SD=29%)</p>	<p>No AEs reported: “Aside from a transient elevation of Perservations score without an overall significant treatment 3 visit interaction or behavioral correlation in the REAL group at post-treatment one-week assessment, the</p>	High

Study design T vs C N (T vs C)	Headache definition	Findings		Risk of Bias
		Headache pain	Harms	
	Global Pain Intensity: BPI assessed baseline level of overall pain (total score divided by a factor of 4), the degree of headache relief (%) from the medication, and overall degree of interference (total score divided by 7) of pain on daily functions.	at 1 week and 58.4% (SD=24.5%) at 4 weeks post-treatment whereas sham group decreased 1.7% (SD=41.2%) and 9.5% (SD=60.0%) at 1 week and 4 weeks post-treatment. Debilitating headache duration (F=4.5, p=0.044) and debilitating HA frequency (F=5.57, p=0.026) had improvements in the rTMS vs sham groups. Global Pain Intensity: No significant interaction between visit and treatment on BPI pain interference.	study cohort reported no other side effects."	
Nelson, 2015 ¹⁴ Pre-post FNS N=9	BPI was modified to indicate 0–10 numeric ratings for pain intensity of headaches in the past week (0=no pain, 10=pain as bad as you can imagine), including worst headache pain and average headache pain . BPI completed at the beginning of treatment and then at sessions 5, 10, 15, and 20 (end of treatment)	Worst pain in past week: t(8)=5.43, p=0.001 (results reported for baseline to end of treatment; means and SDs reported in study for multiple timepoints) Average pain in past week: t(8)=5.86, p<0.001 (results reported for baseline to end of treatment; means and SDs reported in study for multiple timepoints)	"...a few (rarely) reported minor intensifications of their typical symptoms following a treatment session, which was then followed by a more marked reduction in symptom intensity."	High

Abbreviations: AE=Adverse event; ANOVA=Analysis of variance; BPI=Brief Pain Inventory; C=Comparator; df=degrees of freedom; NRS=Numeric Rating Scale; p=p-value; rTMS=Repetitive transcranial magnetic stimulation; SD=Standard deviation; T=Treatment



Table 9. Risk of bias in trials of interventions for chronic pain in Veterans with a history of mTBI

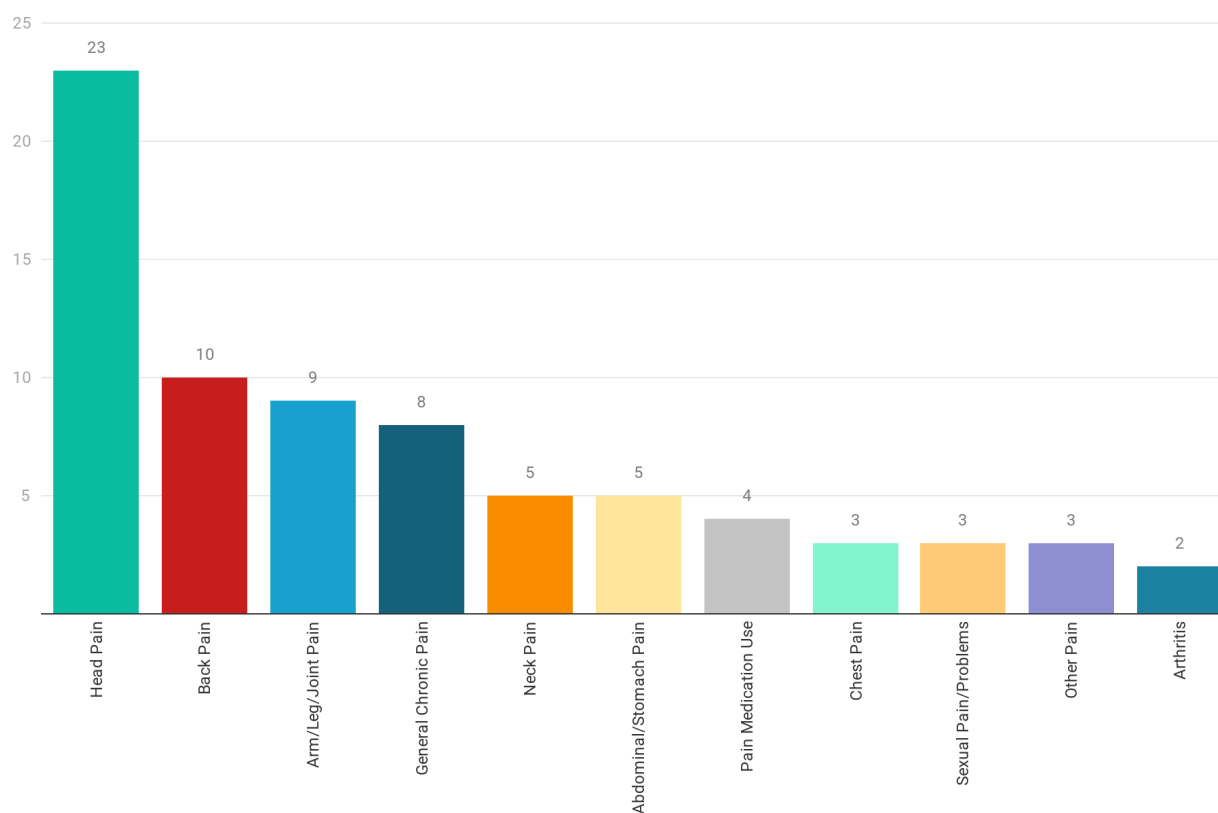
Study	Intervention vs comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias	Comment
Leung, 2016 ¹²	rTMS vs Sham rTMS	High	Some concerns	High	Some concerns	Low	High	Little information about randomization. Masking of providers and assessors was unclear. Analyzed completers only and high attrition. Statistically underpowered.
Leung, 2018 ¹³	rTMS vs Sham rTMS	Low	Some concerns	High	Some concerns	Low	High	Masking of providers and assessors was unclear. Analyzed completers only and high attrition. Statistically underpowered.

Abbreviations: rTMS=Repetitive transcranial magnetic stimulation

DISCUSSION

We identified 27 studies reporting chronic pain prevalence estimates in Veterans and SMs with a history of mTBI, 1 study that reported on prevalence of suicide-related behaviors among Veterans diagnosed with mTBI and chronic pain versus those with mTBI but no chronic pain diagnoses (and those with no mTBI), and 3 studies examining interventions for the treatment of chronic pain in Veterans and SMs with a history of mTBI. Included prevalence studies describe a wide range of chronic pain types, with the most common being head pain (23 studies), followed by back pain (10 studies), and arm, leg, and/or joint pain (9 studies). Four studies reported data on the use of pain medications (*eg*, analgesics including opioids, non-opioid analgesics) among Veterans and SMs with mTBI, which we abstracted as a proxy measure for chronic pain (see Figure 8). Across studies addressing KQ1 and KQ2, there was significant heterogeneity in sample sizes (*ie*, 40 to 102,055 Veterans or SMs with history of mTBI), target populations (*eg*, Veterans, SMs, or both; era of service; combat exposure history; geographic region; comorbid physical or mental health conditions; and healthcare use), time since mTBI, and length of follow-up, as well as the methods used to identify, define, and operationalize both mTBI and chronic pain. In the studies addressing KQ3, all 3 interventions targeted the treatment of chronic headaches following mTBI – none examined other pain locations or compared efficacy of chronic pain treatments between those with and without mTBI history.

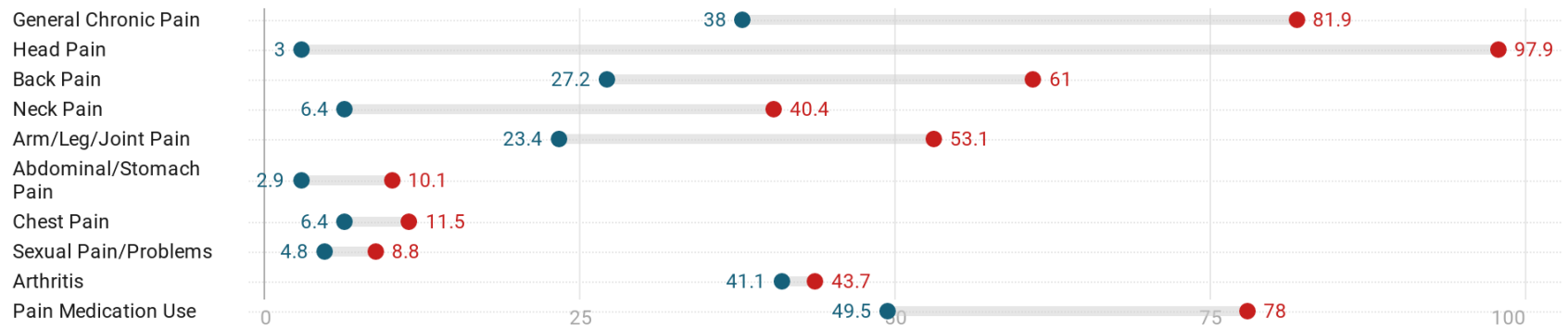
Figure 8. Number of studies reporting prevalence of chronic pain in Veterans and Servicemembers with mTBI by pain type



Note. Some studies reported multiple pain types.

Across these studies, the prevalence of chronic pain among Veterans and SMs varied widely but, overall, was high. In studies providing comparisons, pain prevalence estimates were consistently higher among those with, versus without, mTBI history, and for those with comorbid mTBI and PTSD compared to those with mTBI but no PTSD. While more recent literature distinguishes between chronic pain and “high impact chronic pain,”⁶² the studies meeting our inclusion criteria were generally published prior to when this distinction was more commonly used, and therefore type and impact of chronic pain were often unclear. As expected in this population, prevalence estimates of head pain and those of chronic pain generally were higher than estimates of other specific chronic pain conditions (*eg*, chest pain, abdominal/stomach pain). However, across studies, there were wide ranges of prevalence estimates for each pain type, likely due to the varying study designs, target populations or samples, pain definitions, operationalization of key variables, and pain ascertainment periods (see Figure 9). This heterogeneity across studies limits the conclusions that can be drawn about the frequency of pain or the most common pain types among Veterans and SMs who experience mTBI.

Figure 9. Range of chronic pain prevalence estimates by pain type across studies



For general chronic pain among Veterans with a history of mTBI, a relatively robust prevalence estimate of 59% was identified in a large study of Post-9/11 Veterans who use VA healthcare and completed the Comprehensive TBI Evaluation (CTBIE).⁴ This estimate was derived from a population-level database and, thus, represents a relatively large target population. However, Veterans who complete the CTBIE are generally seeking treatment for a variety of post-deployment health symptoms that may or may not be related to mTBI, or pain. The CTBIE is a standardized and templated clinical assessment completed by a specialty provider and includes standardized assessments of pain; however, patients who complete the CTBIE may not need pain-related care (*ie*, are not bothered by pain). When CTBIE data or pain diagnosis codes are used to estimate chronic pain, as in the case of this study, the true prevalence of chronic pain may be over- or underestimated.^{3,5} Most other studies examining general chronic pain included fewer than 500 participants, and varied in their methods used to identify and define chronic pain. The only other large study utilized EHR data and reported prevalence estimates of 82% for Veterans with a history of mTBI and comorbid PTSD, and 71% with no PTSD.³⁹ This study identified chronic pain by the presence of a single pain-related ICD diagnosis code, and may over- (or under-) estimate pain prevalence due to this approach.^{3,5} Studies of pain disability/interference (defined as moderate-to-severe interference in daily functioning) due to chronic pain provided relatively consistent estimates of 70-75%.^{4,44} Studies of pain severity, based on self-report using Likert-like scales, indicated that roughly half of Veterans and SMs with a history of mTBI reported moderate to extreme/very severe pain,^{41,53} and studies that examined pain frequency reported that about one-third to one-half of SMs and Veterans with a history of mTBI experience pain more than 15 days per month.^{42,46,50,54}

Head pain such as headaches and migraines were the most-studied chronic pain type among Veterans and SMs with mTBI history; prevalence estimates varied widely from 3% to 98%. Relatively robust, but still widely varied, estimates were derived from 5 large studies, all of which used either CTBIE data and thus, for the reasons indicated above, may not represent the true prevalence of head pain across the population of Veterans or SMs with mTBI history.^{7,39,45,52,53} Prevalence estimates of headache or migraines from 4 studies of Post-9/11 Veterans with a history of mTBI ranged from 20% to 94% (this latter study reported data from a CTBIE item assessing the presence of any headaches), and 1 study of SMs reported a prevalence of 15%. Prevalence estimates appear to vary substantially by target population (*eg*, Veteran versus Servicemember; healthcare utilization), time since mTBI, length of follow-up, method for identifying and classifying chronic pain (and possibly mTBI), and data source.

Prevalence estimates for back pain were largely consistent, falling between 32% and 44% for SMs in 3 studies using the PHQ-15,^{15,59,60} and 13%-15% for upper back pain, and 53%-58% for lower back pain among Veterans who completed the CTBIE.^{52,53} The 3 studies that used the PHQ-15^{15,59,60} also used similar methods overall, including a focus on very similar SM populations. We were unable to determine whether there was overlap between individual participants in these studies – a possibility given the database utilized. Therefore, we retained all 3 studies and report findings for all pain measures presented (which were remarkably consistent across studies).

There was wide variation in the prevalence estimate of neck pain in Veterans with a history of mTBI. The 2 largest studies reported prevalence estimates of 6% (VA EHR data) and 23%

(CTBIE).^{7,40} With the exception of arthritis (41% to 44%),^{40,57} the prevalence levels of other pain types were relatively low.

Four articles reported data on pain medication use, which we abstracted as a proxy measure for chronic pain. Of these, 2 relatively small studies^{40,42} specifically looked at opioid use. Estimates were disparate at 12% and 49% of Veterans with a history of mTBI, but these studies differed substantially in data source, population, and timing of follow-up. None of these studies measured the chronicity of opioid or other pain medication use; as such, it was unclear if these medications were used for chronic pain or for more intermittent pain. Future studies that examine the prescription of pain medications to Veterans and SMs with mTBI should specify the duration of medication use.

Three studies compared the prevalence of chronic pain in Veterans and SMs with a history of mTBI by etiology of the mTBI (all 3 compared blast versus non-blast etiologies). None of these studies provided compelling evidence that prevalence differed by etiology. However, 1 study presented data on headache prevalence among Veterans who experienced LOC after their mTBI, versus those who only experienced AOC, and by blast versus non-blast etiology. This study reported a statistically significant difference in headache prevalence among those whose mTBI resulted in LOC and was associated with blasts versus those whose mTBI resulted in LOC but was not associated with blasts (40% versus 23%, respectively).⁶⁰ There were no differences by blast/non-blast etiologies among those whose mTBI resulted only in AOC. None of the other pain types assessed in this study differed by mTBI etiology. Notably, none of the studies examined or compared pain prevalence by location of mTBI, location of co-occurring injuries, or timing of pain onset relative to the mTBI, which may all have important implications for onset and chronicity of pain conditions.

Although we did not find strong evidence suggesting that pain prevalence varied by mTBI etiology, it was clear across studies that, when examined, pain prevalence levels were substantially higher among those with comorbid PTSD. Although the assessment of pain prevalence by comorbid PTSD was not a specified focus of KQ1, the consistency of this finding across studies is noteworthy, particularly given the high prevalence of diagnosed PTSD among those with a history of mTBI. This finding lends further evidence to prior discourse about the “polytrauma clinical triad”²⁵ and has implications for the ongoing clinical management of Veterans and SMs with mTBI. Notably, we did not find parallel comparisons in pain prevalence by other mental health comorbidities. This is an evident gap in the literature as other mental and behavioral health conditions are also highly prevalent among those with mTBI (*eg*, depression, substance use disorders) and it is likely that pain conditions may also vary by the presence of these comorbidities. Such data may also have clinical implications for treatment of pain conditions among those with mTBI history. Importantly, Veterans with mTBI have considerably higher VA healthcare utilization and care costs than those without mTBI history, a large proportion of which is associated with pain and mental health care utilization.^{63,64} Research that helps forecast ongoing healthcare needs and that, ultimately, can lead to improved functioning and quality of life outcomes for this complex patient population is critical.

In contrast to large differences between those with and without comorbid PTSD, the studies that reported pain prevalence by “severity” of mTBI (*ie*, mTBI events associated with LOC versus those only associated with AOC) reported only small differences, with slightly higher pain

prevalence among those who experienced more severe mTBI.^{15,44,46,49,59,60} However, slightly larger differences in prevalence by mTBI severity were observed in the studies examining head pain.^{15,59,60}

As evident, there was relatively little consistency in the design or outcomes of the studies used to address KQ1 and KQ2. Although the wide variation in estimates is not surprising given the heterogeneity in methods across studies, these findings, or rather the *lack* of concrete findings, highlight a need to establish and implement consistent methods to assess pain conditions that are prevalent in US Veteran and SM populations. Studies are needed to assess the prevalence of chronic pain among *all* US Veterans and SMs with a history of mTBI (rather than, for example, treatment-seeking Veterans specifically) and to compare the prevalence levels of pain types by important Veteran and SM characteristics, including service history, physical and mental health comorbidities, and healthcare utilization patterns. Additionally, despite being beyond the scope of this review, we noted that few studies compared pain prevalence between those with *and without* mTBI and, thus, it remains unclear how pain conditions are associated with mTBI (*ie*, whether they tend to be more commonly diagnosed among treatment-seeking samples, whether they are a result of the mTBI itself, or whether they are a result of the same characteristics and exposures that led to mTBI). To answer these questions and to maximize usefulness of the evidence, studies that randomly sample Veterans and SMs, follow them over time, and use established and consistent definitions and operationalizations of mTBI and pain are needed.

Similarly, although we found well-conducted studies of treatment-seeking samples of Veterans and SMs that reported on chronic pain among those with mTBI, these studies by nature relied on selective (*ie*, non-random) samples and/or proxy measures of mTBI and pain such as ICD diagnosis codes. In some studies, ICD diagnoses were used to identify potential pain conditions even if the specific diagnoses are not associated with pain in all cases. For example, osteoarthritis diagnoses are used as a proxy for chronic pain in some studies, but recent research suggests that individuals diagnosed with osteoarthritis are not necessarily experiencing chronic pain.⁶⁵ To better understand the prevalence of chronic pain conditions and, in particular, to anticipate treatment needs among Veterans and SMs who utilize the VA or Military Health System, random or otherwise representative samples of individuals with (and, for comparison, *without*) mTBI should be assessed using established and consistent chronic pain definitions and measures.

It is notable that a large number of studies focusing on chronic pain among Veterans with a history of mTBI were excluded from this review because they did not report prevalence levels but, rather, outcomes of pain measures on a continuous scale (*ie*, means and medians). This precluded our ability to synthesize these studies in the current review, but it stands to reason that additional information on pain severity, frequency, and interference, as well as differences in these measures by pain etiology or assessment methods, may be gleaned from this body of literature. Our review used a relatively flexible definition of “chronic pain” so as not to exclude potentially useful data. Although this approach increased the variance across studies in terms of pain outcomes, we felt this was an acceptable trade-off in attempt to include as many published studies as possible. As described above, our review did not examine the potential impacts of comorbid mental health conditions on prevalence estimates or outcomes of chronic pain, and this limitation could be addressed in future systematic reviews of this body of literature.

A secondary purpose of this review was to describe strategies researchers use to assess chronic pain as part of clinical trials. While all 3 intervention studies used the BPI – a common and well-validated measure of pain intensity and function – the small number of studies examining interventions for chronic pain in this population precludes most generalizations about measures used to assess pain. Future trials should rely on validated, commonly used measures to facilitate comparisons across studies. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has developed recommended measures and outcomes that should be assessed in chronic pain clinical trials, including the domains of pain intensity, physical functioning, emotional functioning, improvement and satisfaction with treatment, adverse events, and treatment adherence.^{66,67} These recommendations were promoted by a recent VA workgroup on developing core outcome measures in chronic pain research, which also recommended including changes in sleep as a study outcome.⁶⁸ Future chronic pain research in Veterans and SMs with mTBI history would benefit from the continued use of these strategies for assessing pain and its associated consequences.

Results for KQ1c examining pain assessment methods suggest that different types of pain assessment methods were associated with higher or lower pain prevalence estimates. In addition to pain assessment methods, other aspects of study design likely influenced prevalence estimates. For example, studies of specialized clinics designed to treat a particular condition would be expected to have higher rates of that condition (such as in the study by Ruff et al,⁶ of a small sample seen in a polytrauma clinic) than studies examining the prevalence in a broad, full, or “all-comers” population (such as in studies examining all post-deployment SMs or identifying pain diagnoses in the EHR).

For this review, we included studies of chronic pain even if the study did not include a rigorous assessment to determine the chronicity or severity of symptoms. For example, we included studies where pain symptoms were assessed only for the past month. While this methodology could result in over-estimation of the prevalence of *chronic* pain, we opted to include these studies in order to generate a fuller picture of the problem of pain among patients with a history of mTBI. Future research that aims to understand chronic pain in a sample of all Veterans/SMs with mTBI history, or of specified treatment-seeking Veterans/SMs with mTBI history, would benefit from the assessment of pain chronicity (at least 3-6 months) and severity (moderate or higher). There are also recommended strategies for assessing chronic pain using administrative data, such as ICD diagnosis codes, that can improve the accuracy and comparability of prevalence estimates in these types of studies of chronic pain.³

We found only a single study examining suicide-related outcomes in US Veterans and SMs with both chronic pain and a history of mTBI.⁷ This study used VA EHR data and categorized Veterans with and without a history of mTBI into trajectory groups based on an algorithm using ICD diagnosis codes. As compared to those with relatively low rates of mental health, pain, and other sensory diagnoses during the trajectory development period, Veterans with high mental health, post-concussive symptoms, and pain comorbidities were significantly more likely to have been diagnosed with suicidal ideation or attempt during the follow-up period. This study compared the prevalence of suicide-related behaviors between those with and without a history of mTBI (eg, 6.6% versus 2.4%, respectively) but did not likewise directly compare suicide-related behaviors between those with mTBI with and without comorbid pain. However, considering the persistently higher rates of suicide in Veteran populations, and evidence

suggesting increased risk among Veterans with mTBI,^{10,11,29,30} more research of this particularly vulnerable population is urgently needed.^{8,9}

Although chronic pain is well established as a common comorbidity among Veterans and SMs with a history of mTBI, we found very few trials of interventions to treat chronic pain in this population, even when searching for studies from any country. The 3 studies that met inclusion criteria were small and provide insufficient strength evidence supporting the interventions studied (rTMS in 2 RCTs and FNS, a type of neurotherapy, in 1 small pre-post trial).¹²⁻¹⁴ All 3 studies targeted chronic headaches, and none assessed nor treated other types of chronic pain. Also of note is that no studies compared the efficacy of chronic pain treatments among those with, versus without, mTBI. This review was limited to chronic pain treatment trials of Veterans and SMs from any country with a history of mTBI because of the unique military-related circumstances (eg, blast exposure) that can contribute to pain in this population. However, due to the very small number of trials specific to this population, future efforts should consider results from pain interventions among broader populations (eg, adult civilians) or Veterans and SMs without a history of mTBI when making treatment, policy, or research scoping decisions. Future research could compare responses to chronic pain interventions for participants with and without mTBI history to determine mTBI results in a greater or lesser likelihood of benefit. Without such information, screening for presence and intensity of pain are likely warranted for Veterans and SMs with a history of mTBI so that they can be offered evidence-based treatment for chronic pain if needed.

Due to the prevalence of mTBI, and the prevalence and debilitating nature of chronic pain, in the population of Veterans and SMs, it is clear that more research targeting the treatment of chronic pain amongst those with mTBI history is warranted. Specifically, studies of interventions established to be effective for treating chronic pain in other patient populations, particularly Veterans and SMs without mTBI, should be prioritized for testing in those with mTBI history. Additionally, because rTMS has been studied in 2 small, pilot RCTs with a strong sham comparator and has shown positive preliminary findings,^{12,13} additional, larger RCTs of rTMS for chronic pain in Veterans and SMs with mTBI history are likely warranted.

CONCLUSION

Chronic pain, particularly head and back pain, is common among US Veterans and Servicemembers with a history of mTBI, as is the use of pain-related medications, including opioids. Although pain is prevalent among Veterans and SMs in general, the results of this review suggest that those with mTBI history – and especially those with comorbid mTBI and PTSD – experience pain at higher prevalence levels than those without a history of mTBI. Based on the existing research, precise estimates of the prevalence of pain conditions, locations, disability/interference, and severity are hampered by heterogeneity in study populations/samples, timing of pain ascertainment relative to individuals' mTBI history, duration of study follow-up, and methods used to identify, define, and operationalize both mTBI and chronic pain. Additionally, only a single study examined the risk of suicide, and only 3 studies tested interventions to mitigate pain in this complex population. Thus, the prevalence of chronic pain in the general population of US Veterans and SMs, the impact of comorbid pain and mTBI on suicide risk in this potentially high-risk population, and the efficacy of pain therapies among those with comorbid mTBI and chronic pain remain largely unknown. Research studies,

specifically designed with the intent of filling these knowledge gaps, are needed to inform current and future service needs for this population. Given the high prevalence of mTBI in Veterans and Servicemembers, and the importance of meeting the social and clinical needs of this large population, this research is urgent and essential.

REFERENCES

1. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 2019;160(1):19-27.
2. Department of Veterans Affairs/Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury*. Washington, DC2016.
3. Abel EA, Brandt CA, Czapinski R, Goulet JL. Pain research using Veterans Health Administration electronic and administrative data sources. *J Rehabil Res Dev*. 2016;53(1):1-12.
4. Seal KH, Bertenthal D, Barnes DE, et al. Association of Traumatic Brain Injury With Chronic Pain in Iraq and Afghanistan Veterans: Effect of Comorbid Mental Health Conditions. *Arch Phys Med Rehabil*. 2017;98(8):1636-1645.
5. Carlson KF, Barnes JE, Hagel EM, Taylor BC, Cifu DX, Sayer NA. Sensitivity and specificity of traumatic brain injury diagnosis codes in United States Department of Veterans Affairs administrative data. *Brain Inj*. 2013;27(6):640-650.
6. Ruff RL, Ruff SS, Wang XF. Headaches among Operation Iraqi Freedom/Operation Enduring Freedom veterans with mild traumatic brain injury associated with exposures to explosions. *J Rehabil Res Dev*. 2008;45(7):941-952.
7. Pugh MJ, Swan AA, Amuan ME, et al. Deployment, suicide, and overdose among comorbidity phenotypes following mild traumatic brain injury: A retrospective cohort study from the Chronic Effects of Neurotrauma Consortium. *PLoS ONE*. 2019;14(9):e0222674.
8. VHA Office of Mental Health and Suicide Prevention. *VA National Suicide Data Report 2005–2016*. September 2018.
9. VHA Office of Mental Health and Suicide Prevention. *National Strategy for Preventing Veteran Suicide 2018-2028*. 2018.
10. Byers AL, Li Y, Barnes DE, Seal KH, Boscardin WJ, Yaffe K. A national study of TBI and risk of suicide and unintended death by overdose and firearms. *Brain Inj*. 2020;34(3):328-334.
11. Madsen T, Erlangsen A, Orlovska S, Mofaddy R, Nordentoft M, Benros ME. Association Between Traumatic Brain Injury and Risk of Suicide. *Jama*. 2018;320(6):580-588.
12. Leung A, Shukla S, Fallah A, et al. Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. *Neuromodulation*. 2016;19(2):133-141.
13. Leung A, Metzger-Smith V, He Y, et al. Left Dorsolateral Prefrontal Cortex rTMS in Alleviating MTBI Related Headaches and Depressive Symptoms. *Neuromodulation*. 2018;21(4):390-401.
14. Nelson DV, Esty ML. Neurotherapy for chronic headache following traumatic brain injury. *Mil*. 2015;2:22.
15. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-463.
16. Defense and Veterans Brain Injury Center. DoD Worldwide Numbers for TBI. (2000-2019 Q3) Web site. <https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>. Published 2019. Accessed January 28, 2020.

17. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil.* 2014;95(3 Suppl):S152-173.
18. O'Neil ME, Carlson KF, Storzbach D, et al. Factors Associated with Mild Traumatic Brain Injury in Veterans and Military Personnel: A Systematic Review. *J Int Neuropsychol Soc.* 2014:1-13.
19. Ruff R. Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil.* 2005;20(1):5-18.
20. Department of Veterans Affairs. Polytrauma System of Care. In: Veterans Health Administration, ed. Vol VHA Directive 1172.01. Washington, DC2019.
21. Hendricks AM, Amara J, Baker E, et al. Screening for mild traumatic brain injury in OEF-OIF deployed US military: an empirical assessment of VHA's experience. *Brain Inj.* 2013;27(2):125-134.
22. Vanderploeg RD, Belanger HG. Screening for a remote history of mild traumatic brain injury: when a good idea is bad. *J Head Trauma Rehabil.* 2013;28(3):211-218.
23. Hoge CW, Goldberg HM, Castro CA. Care of war veterans with mild traumatic brain injury--flawed perspectives. *N Engl J Med.* 2009;360(16):1588-1591.
24. Vasterling JJ, Aslan M, Lee LO, et al. Longitudinal Associations among Posttraumatic Stress Disorder Symptoms, Traumatic Brain Injury, and Neurocognitive Functioning in Army Soldiers Deployed to the Iraq War. *J Int Neuropsychol Soc.* 2018;24(4):311-323.
25. Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. *J Rehabil Res Dev.* 2009;46(6):697-702.
26. Pagulayan KF, O'Neil M, Williams RM, et al. Mental Health Does Not Moderate Compensatory Cognitive Training Efficacy for Veterans With a History of Mild Traumatic Brain Injury. *Arch Phys Med Rehabil.* 2017;98(9):1893-1896.e1892.
27. Irvine KA, Clark JD. Chronic Pain After Traumatic Brain Injury: Pathophysiology and Pain Mechanisms. *Pain Med.* 2018;19(7):1315-1333.
28. Prevention VOoMHaS. *2019 National Veteran Suicide Prevention Annual Report.* 2019.
29. Finley EP, Bollinger M, Noel PH, et al. A national cohort study of the association between the polytrauma clinical triad and suicide-related behavior among US Veterans who served in Iraq and Afghanistan. *Am J Public Health.* 2015;105(2):380-387.
30. Hostetter TA, Hoffmire CA, Forster JE, Adams RS, Stearns-Yoder KA, Brenner LA. Suicide and Traumatic Brain Injury Among Individuals Seeking Veterans Health Administration Services Between Fiscal Years 2006 and 2015. *J Head Trauma Rehabil.* 2019;34(5):E1-e9.
31. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-46.
32. Treadwell JR, Singh S, Talati R, McPheeters ML, Reston JT. A framework for best evidence approaches can improve the transparency of systematic reviews. *J Clin Epidemiol.* 2012;65(11):1159-1162.
33. Higgins J, Savovic J, Page MJ, Sterne JA. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>. 2019.

34. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. 2016;355:i4919.
35. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 1/31/2020.
36. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *International journal of health policy and management*. 2014;3(3):123-128.
37. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;68(11):1312-1324.
38. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1198-1207.
39. Kulas JF, Rosenheck RA. A Comparison of Veterans with Post-traumatic Stress Disorder, with Mild Traumatic Brain Injury and with Both Disorders: Understanding Multimorbidity. *Mil Med*. 2018;183(3-4):e114-e122.
40. King PR, Wade MJ, Beehler GP. Health service and medication use among veterans with persistent postconcussive symptoms. *J Nerv Ment Dis*. 2014;202(3):231-238.
41. Hoot MR, Levin HS, Smith AN, et al. Pain and chronic mild traumatic brain injury in the US military population: a Chronic Effects of Neurotrauma Consortium study. *Brain Inj*. 2018;32(10):1169-1177.
42. Brickell TA, Lange RT, French LM. Health-related quality of life within the first 5 years following military-related concurrent mild traumatic brain injury and polytrauma. *Mil Med*. 2014;179(8):827-838.
43. Powell MA, Corbo V, Fonda JR, Otis JD, Milberg WP, McGlinchey RE. Sleep Quality and Reexperiencing Symptoms of PTSD Are Associated With Current Pain in U.S. OEF/OIF/OND Veterans With and Without mTBIs. *J Trauma Stress*. 2015;28(4):322-329.
44. Romesser J, Booth J, Bengtson J, Pastorek N, Helmer D. Mild traumatic brain injury and pain in Operation Iraqi Freedom/Operation Enduring Freedom veterans. *J Rehabil Res Dev*. 2012;49(7):1127-1136.
45. Beswick-Escanlar VP, Lee T, Hu Z, Clark LL. Increasing severity of traumatic brain injury is associated with an increased risk of subsequent headache or migraine: a retrospective cohort study of U.S. active duty service members, 2006-2015. *Msmr*. 2016;23(7):2-8.
46. Couch JR, Stewart KE. Headache Prevalence at 4-11 Years After Deployment-Related Traumatic Brain Injury in Veterans of Iraq and Afghanistan Wars and Comparison to Controls: A Matched Case-Controlled Study. *Headache*. 2016;56(6):1004-1021.
47. Farrell-Carnahan L, Barnett S, Lambert G, et al. Insomnia symptoms and behavioural health symptoms in veterans 1 year after traumatic brain injury. *Brain Inj*. 2015:1-9.
48. Jackson CE, Green JD, Bovin MJ, et al. Mild Traumatic Brain Injury, PTSD, and Psychosocial Functioning Among Male and Female U.S. OEF/OIF Veterans. *J Trauma Stress*. 2016;29(4):309-316.

49. MacGregor AJ, Dougherty AL, Tang JJ, Galarneau MR. Postconcussive symptom reporting among US combat veterans with mild traumatic brain injury from Operation Iraqi Freedom. *J Head Trauma Rehabil.* 2013;28(1):59-67.
50. Patil VK, St Andre JR, Crisan E, et al. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. *Headache.* 2011;51(7):1112-1121.
51. Schwab K, Terrio HP, Brenner LA, et al. Epidemiology and prognosis of mild traumatic brain injury in returning soldiers: A cohort study. *Neurology.* 2017;88(16):1571-1579.
52. Suri P, Stolzmann K, Williams R, Pogoda TK. Deployment-Related Traumatic Brain Injury and Risk of New Episodes of Care for Back Pain in Veterans. *J Pain.* 2019;20(1):97-107.
53. Suri P, Stolzmann K, Iverson KM, et al. Associations Between Traumatic Brain Injury History and Future Headache Severity in Veterans: A Longitudinal Study. *Arch Phys Med Rehabil.* 2017;98(11):2118-2125.e2111.
54. Theeler BJ, Flynn FG, Erickson JC. Chronic daily headache in U.S. soldiers after concussion. *Headache.* 2012;52(5):732-738.
55. Tsao JW, Stentz LA, Rouhanian M, et al. Effect of concussion and blast exposure on symptoms after military deployment. *Neurology.* 2017;89(19):2010-2016.
56. Vanderploeg RD, Belanger HG, Curtiss G. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. *Arch Phys Med Rehabil.* 2009;90(7):1084-1093.
57. Walker WC, Hirsch S, Carne W, et al. Chronic Effects of Neurotrauma Consortium (CENC) multicentre study interim analysis: Differences between participants with positive versus negative mild TBI histories. *Brain Inj.* 2018;32(9):1079-1089.
58. Webb TS, Whitehead CR, Wells TS, Gore RK, Otte CN. Neurologically-related sequelae associated with mild traumatic brain injury. *Brain Inj.* 2015;29(4):430-437.
59. Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW. Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments: association with postdeployment symptoms. *Psychosom Med.* 2012;74(3):249-257.
60. Wilk JE, Thomas JL, McGurk DM, Riviere LA, Castro CA, Hoge CW. Mild traumatic brain injury (concussion) during combat: lack of association of blast mechanism with persistent postconcussive symptoms. *J Head Trauma Rehabil.* 2010;25(1):9-14.
61. Walker WC, Nowak KJ, Kenney K, et al. Is balance performance reduced after mild traumatic brain injury?: Interim analysis from chronic effects of neurotrauma consortium (CENC) multi-centre study. *Brain Inj.* 2018;32(10):1156-1168.
62. NIH study broadens understanding of High Impact Chronic Pain in the U.S. [press release]. September 5 2018.
63. Dismuke-Greer C, Hirsch S, Carlson K, et al. Health Services Utilization, Health Care Costs, and Diagnoses by Mild Traumatic Brain Injury Exposure: A Chronic Effects of Neurotrauma Consortium Study. *Archives of Physical Medicine and Rehabilitation.* 2020.
64. Taylor BC, Hagel EM, Carlson KF, et al. Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran V.A. users. *Med Care.* 2012;50(4):342-346.
65. Goulet JL, Kerns RD, Bair M, et al. The musculoskeletal diagnosis cohort: examining pain and pain care among veterans. *Pain.* 2016;157(8):1696-1703.

66. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1).
67. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106(3):337-345.
68. Kroenke K, Krebs EE, Turk D, et al. Core Outcome Measures for Chronic Musculoskeletal Pain Research: Recommendations from a Veterans Health Administration Work Group. *Pain Med*. 2019;20(8):1500-1508.