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

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PREFACE

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

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

The program is comprised of 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.

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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.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked

areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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

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ABSTRACT

Aim: We conducted a systematic review on the prevalence of chronic pain in Veterans and Servicemembers (SMs) with a history of mild traumatic brain injury (mTBI), the risk of suicide, and the benefits and harms of interventions to treat chronic pain in this population.

Methods: We searched electronic databases, clinical trial registries, and reference lists through February 2020. For intervention studies, we included only randomized and non-randomized controlled trials. We abstracted study design, sample size, setting, population characteristics, inclusion and exclusion criteria, operationalizations of key variables, and results. Independent dual assessment of study's full text and quality ratings were agreed upon by consensus using pre-specified criteria.

Results: 27 articles (26 studies) reported chronic pain prevalence estimates, 1 study examined suicide outcomes, and 3 studies examined interventions for the treatment of chronic pain in Veterans and SMs with a history of mTBI. Across studies, the prevalence of chronic pain among this population varied widely but, overall, was high. Head pain (*ie*, headaches or migraines; 23 studies) was the most common, followed by back (10), and arm, leg, and/or joint pain (9). Four articles reported the use of pain medication as an indicator of chronic pain. The 1 study examining suicide outcomes found that compared to those with relatively low rates of pain and other sensory diagnoses, Veterans with high post-concussive symptoms, and mental health and pain comorbidities were more likely to have been diagnosed with suicidal ideation or attempt. The 3 intervention studies were small and provide insufficient evidence for rTMS (2 RCTs) and Flexyx Neurotherapy System, a type of neurotherapy.

Conclusion: Chronic pain in Veterans and SMs with a history of mTBI is common. Precise prevalence estimates are hampered by heterogeneity. There is very little current research of suicide-related outcomes in, and interventions for, this population. More research is needed.

EXECUTIVE SUMMARY

AIM

We conducted a systematic review to synthesize the existing literature on the prevalence of chronic pain in Veterans and Servicemembers (SMs) with a history of mild traumatic brain injury (mTBI), the risk of suicide in this population, and the benefits and harms of interventions to treat chronic pain in this population.

METHODS

We searched electronic databases (Ovid Medline; Ovid EBM Reviews: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews; Ovid PsycINFO; CINAHL; Scopus; Google Scholar; and Epistemonikos), clinical trial registries, and reference lists from database inception through February 7, 2020 for studies providing prevalence estimates of chronic pain in US Veterans or SMs with a history of mTBI, reporting estimates of suicide risk among US Veterans or SMs with a history of mTBI and chronic pain, or examining treatment interventions for chronic pain in Veterans or SMs with a history of mTBI from any country. For intervention studies, we included only randomized and non-randomized controlled trials.

Chronic pain is commonly defined as pain lasting or recurring for more than 3 months,[1] though definitions vary across published studies. In order to provide a comprehensive overview of this body of literature, we considered any pain measure that was not clearly described as measuring acute pain to be chronic pain (*eg*, pain over past 30 days, headaches, *etc*), along with proxies for measures of 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 US Veteran or SM study population that was explicitly defined as having a history of mTBI, distinct from TBI of greater severity. Mild TBI was defined as an external force to the head followed by ≤30 minutes of loss of consciousness, 0-1 days of posttraumatic amnesia, or up to 24 hours of altered mental status, along with normal structural imaging if completed.[2] We excluded studies that reported results for populations with mixed TBI severity (*eg*, mild plus moderate and/or severe TBI). 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.

For all studies we abstracted study design, sample size, setting, population characteristics, participant inclusion and exclusion criteria, definitions/operationalizations of key variables, and results. If data were presented for non-mTBI comparison groups, these 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. Two reviewers independently assessed the methodological quality of each study using established methods for each study design. Strength of evidence for intervention studies was determined by consensus.

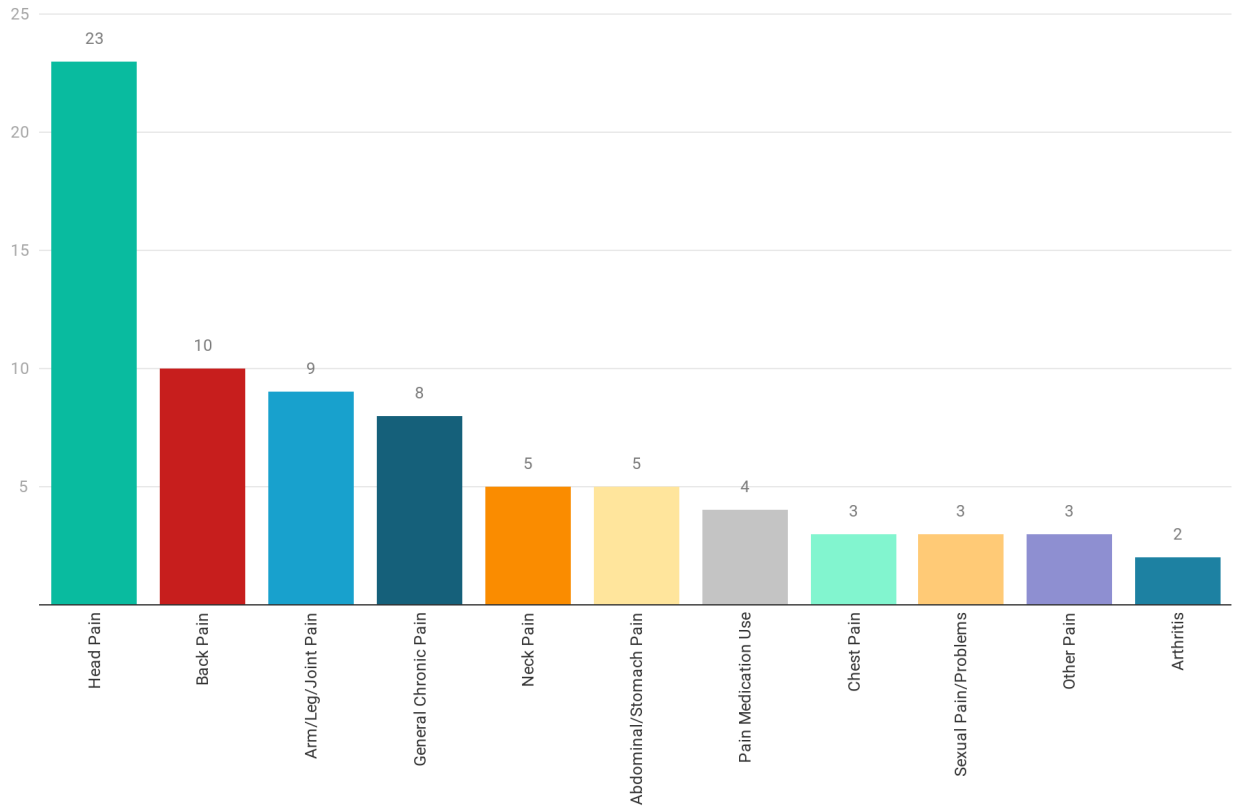
RESULTS

We identified 27 articles (representing 26 studies) reporting chronic pain prevalence estimates in US Veterans and SMs with a history of mTBI, 1 study examining suicide outcomes in US Veterans and SMs with a history of mTBI, and 3 studies examining interventions for the treatment of chronic pain in Veterans and SMs with a history of mTBI from any country.

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

Included prevalence studies describe a wide range of chronic pain types, with the most common being head pain (*ie*, headaches or migraines, 23 studies), followed by back pain (10 studies), and arm, leg, and/or joint pain (9 studies). Four articles reported the use of pain medication (*eg*, analgesics including opioids) as an indicator of chronic pain (see Figure i). Across studies there was substantial heterogeneity in sample size (*ie*, 40 to 102,055 Veterans or SMs with history of mTBI), population (*eg*, Veterans, SMs, or both; era of service; geographic region; comorbid conditions; and combat exposure), time since mTBI, and length of follow-up, as well as the methods used to identify, define, and operationalize both mTBI and chronic pain.

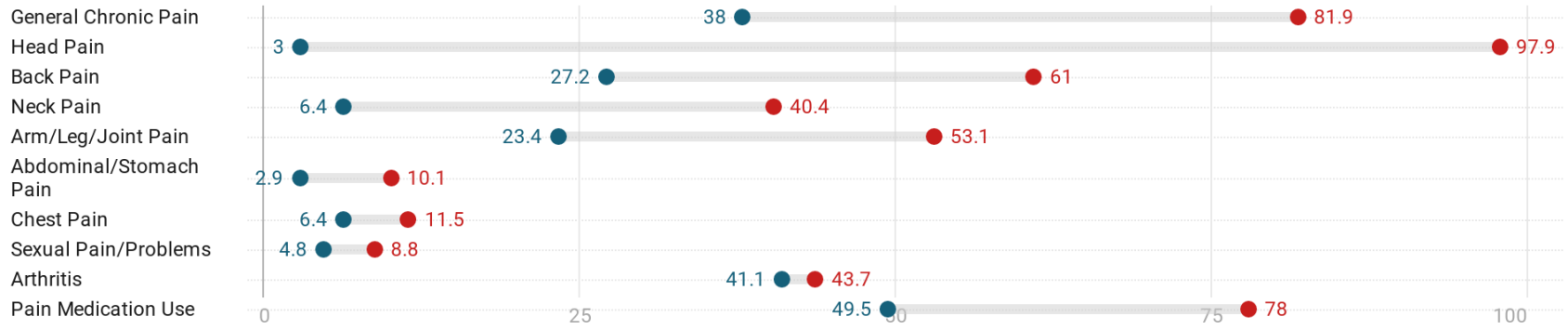
Figure i. Number of studies reporting prevalence of chronic pain in Veterans/Servicemembers with histoy of mTBI, by pain type



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. As expected in this population, prevalence estimates of head pain and 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 ii). 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 have experienced mTBI. However, when studies presented pain prevalence data for comparison groups *without* mTBI, they were consistently lower across all pain types.

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



Although the wide variation in estimates is not surprising given the heterogeneity 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 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 International Classification of Diseases (ICD) diagnosis codes. 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.

For this review, we chose to include studies of chronic pain even if the study did not include a rigorous assessment to determine the chronicity or severity of pain 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 Veterans and SMs 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]

For general chronic pain among Veterans with a history of mTBI, we identified a relatively robust prevalence estimate of 59% from Seal et al.[4] This estimate was derived from a large database of Post-9/11 Veterans who completed a Comprehensive TBI Evaluation (CTBIE) in the VA healthcare system 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. Most other studies examining general chronic pain included fewer than 500 participants and used varied methods to identify chronic pain. The only other large study utilized VA electronic health record (EHR) data and reported pain diagnoses in 82% of Veterans with diagnosed mTBI and comorbid posttraumatic stress disorder (PTSD), and 71% among those with mTBI but no PTSD diagnosis. This study identified mTBI and chronic pain by the presence of ICD diagnosis codes in EHR data and may over- (or even under-) estimate their 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 were fairly consistent, with estimates of 70-75%. 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 severe pain, and studies that examined pain frequency reported that about one-third to one-half experience pain more than 15 days per month.

Head pain such as headaches and migraines was the most studied chronic pain type (23 studies), with prevalence estimates ranging widely from 3% to 98%. Relatively robust (but still widely varied) estimates come from 5 large studies, all of which used EHR or CTBIE data and thus may not represent the true prevalence of head pain across the population of Veterans or SMs with mTBI history. Among these 5 studies, 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 headache prevalence estimate of 15.2%. Prevalence estimates appear to vary by target population (Veteran versus SM; healthcare utilization), time since mTBI, length of follow-up, method of identifying and classifying chronic pain (and mTBI), and data source. Many of the studies examined EHR data that include all Veterans or SMs with mTBI and chronic pain-related ICD codes. Other studies, including those of the large cohort of Veterans who completed the CTBIE, were of treatment-seeking populations, which would be expected to have higher pain prevalence. This difference alone may account for much of the variance between studies. The prevalence estimates of moderate to severe pain, and frequent pain, also varied widely.

Prevalence estimates for back pain were largely consistent, falling between 32% and 44% for SMs in 3 studies using the 15-item Patient Health Questionnaire (PHQ-15), and 13%-15% for upper back and 53%-58% for lower back pain among Veterans who completed the CTBIE. There was wide variation in the prevalence estimates 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). With the exception of arthritis (41.1% to 51%), the prevalence estimates of other pain types were relatively low.

Four articles reported on pain medication use which we abstracted as a proxy measure for chronic pain. Of these, 2 relatively small studies specifically looked at opioid medication use for pain. Estimates of prevalence of opioid use among Veterans with a history of mTBI from these studies were 12% and 49%; these differences were likely due to the different data sources, populations, and timing of measurements used in these studies.

Three studies compared the prevalence of chronic pain in Veterans and SMs with a history of mTBI by mTBI etiology. These studies compared chronic pain prevalence among individuals who experienced mTBI from blast versus non-blast sources; no studies were identified that compared pain prevalence levels by other etiologies. Overall, in the 3 studies identified, blast-

related mTBI did not appear to be associated with more frequent and more severe pain. However, 1 study reported that, among Veterans who experienced loss of consciousness (LOC) after their mTBI, those with blast-related mTBI had a significantly higher prevalence of head pain than those with non-blast-related mTBI (40% versus 23%). None of the other pain types assessed in this study differed by mTBI etiology. 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.

Results of studies examining pain assessment methods suggest that different types of pain measures were associated with higher or lower pain prevalence estimates. In addition to pain assessment methods, other aspects of study design likely influenced prevalence estimates as well. 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 Veterans/SMs or identifying pain diagnoses in the EHR).

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

We found only a single study examining suicide-related outcomes in US Veterans and SMs with both chronic pain and a history of mTBI. The 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.[7] 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 high rates of suicide in Veteran populations,[8,9] and higher rates of suicide and other causes of mortality among Veterans with a history of mTBI compared to those without,[10,11] more research of this particularly vulnerable population is needed.

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

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 (repetitive Transcranial Magnetic Stimulation [rTMS] in 2 RCTs and Flexyx Neurotherapy System [FNS], a type of neurotherapy, in 1 small pre-post trial). All 3 studies targeted chronic headaches, and none assessed nor treated other types of chronic pain.[12-14] Also notable 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 with a history of mTBI from any country 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.

CONCLUSION

Chronic pain, particularly head and back pain, is common among US Veterans and SMs with a history of mTBI, as is the use of medications indicative of pain conditions, such as prescription opioids. In studies providing comparisons, pain prevalence estimates are 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. 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 trials of interventions to treat chronic pain in this complex population were identified. 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 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 history in Veterans and SMs, and the importance of meeting the social and clinical needs of this large population, this research is urgent and essential.

ABBREVIATIONS TABLE

Abbreviation	Definition
AA	African-American
AE	Adverse Event
ANOVA	Analysis of Variance
AOC	Alteration of Consciousness
CA	California
CDC	Centers for Disease Control and Prevention
CDH	Chronic Daily Headaches
CDP-SOT	Computerized Dynamic Posturography Sensory Organization Test
CDSR	Cochrane Database of Systematic Reviews
CENC	Chronic Effects of Neurotrauma Consortium
CI	Confidence Interval
CO	Colorado
CoE	Center of Excellence
CP	Chronic pain
CTBIE	Comprehensive TBI Evaluation
DMDC	Defense Manpower Data Center
DMSS	Defense Medical Surveillance System
DoD	Department of Defense
DVBIC	Defense and Veterans Brain Injury Center
EBM	Evidence-Based Medicine
EEG	Electroencephalogram
EHR	Electronic Health Record
EM	Electromagnetic Energy
ESP	Evidence Synthesis Program
EQ-5D-5L	EuroQol Group 5-Dimension 5-Level version
FH	Frequent Headaches
FL	Florida
FNS	Flexyx Neurotherapy System
FY	Fiscal year
GCS	Glasgow Coma Scale
HI	Hawaii
HIT-6	6-item Headache Impact Test
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICDH-2	International Classification of Headache Disorders 2nd edition
ICDH-3	International Classification of Headache Disorders 3rd edition
ISS	Injury Severity Scale
KQ	Key Question
LOC	Loss of Consciousness
MA	Meta-Analysis

Abbreviation	Definition
MD	Mean Difference
mTBI	Mild Traumatic Brain Injury
MINI	Mini-International Neuropsychiatric Interview
M-VAS	Mechanical Visual Analog Scale
NA	Native American
NC	North Carolina
NR	Not Reported
NRCT	Non-Randomized controlled trial
NRS	Numerical Rating Scale
NS	Not Significant
NSI	Neurobehavioral Symptom Inventory
OEF	Operation Enduring Freedom
OH	Ohio
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
P	P-value
PCE	Potential Concussive Event
PCL-17	17-item Posttraumatic Stress Disorder Checklist
PDHA	Post-Deployment Health Assessment
PDHRA	Post-Deployment Health Re-Assessment
PHQ-15	15-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PICOTS	Population, Interventions, Comparators, Outcomes, Timing, Setting, and Study Design
PNS	Polytrauma Network Site
PPCS	Persistent Post-Concussive Symptoms
PTA	Posttraumatic Amnesia
pts	Participants
PTSD	Posttraumatic Stress Disorder
QOL	Quality of Life
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RR	Relative Risk
rTMS	Repetitive Transcranial Magnetic Stimulation
Rx	Prescription Medication
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SM	Servicemember
SMD	Standard Mean Difference
SOE	Strength of Evidence
SR	Systematic Review

Abbreviation	Definition
SRB	Suicide Related Behavior
TBI	Traumatic Brain Injury
TBIMS	Traumatic Brain Injury Model Systems
TEP	Technical Expert Panel
TMS	Transcranial Magnetic Stimulation
TRACTS	Translational Research Center for TBI and Stress Related Disorders
TX	Texas
US	United States
VA	Veterans Affairs; or Virginia
VALOR	Veterans' After-discharge Longitudinal Registry
VAMC	Veterans Affairs Medical Center
VCU-rCDI	Virginia Commonwealth University retrospective Concussion Diagnostic Interview
VHA	Veterans Health Administration
WRAMC	Walter Reed Army Medical Center

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, 2017[26]), there

is very limited research on interventions specifically targeting chronic pain among individuals with a history of mTBI (*eg*, Irvine, 2018[27]) 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?

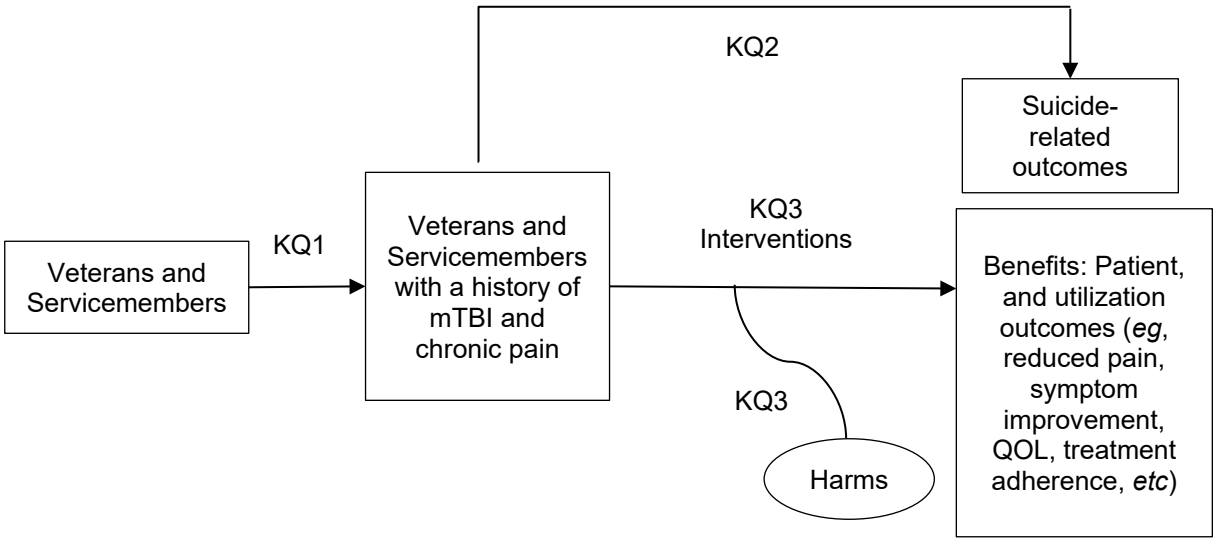
KQ2: What is the risk of suicide in US Veterans or Servicemembers with chronic pain and a history of mTBI?

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

Key Questions:	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?
Population	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		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
Intervention	NA		Pharmacologic, nonpharmacologic, and complementary and integrative health interventions
Comparator	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		Placebo, active comparator, usual care, wait-list control, pre-post
Outcome	Prevalence, demographics, chronic pain types	Suicide-related outcomes (including suicide, suicidal ideation/intent/plan, and suicidal self-directed harm)	Benefits: Intermediate and patient outcomes, utilization (*eg*, reduced pain, mental health diagnosis/symptoms,

			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 criteria[33] 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 Scale[35] supplemented with another critical appraisal tool for prevalence studies[36] 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.

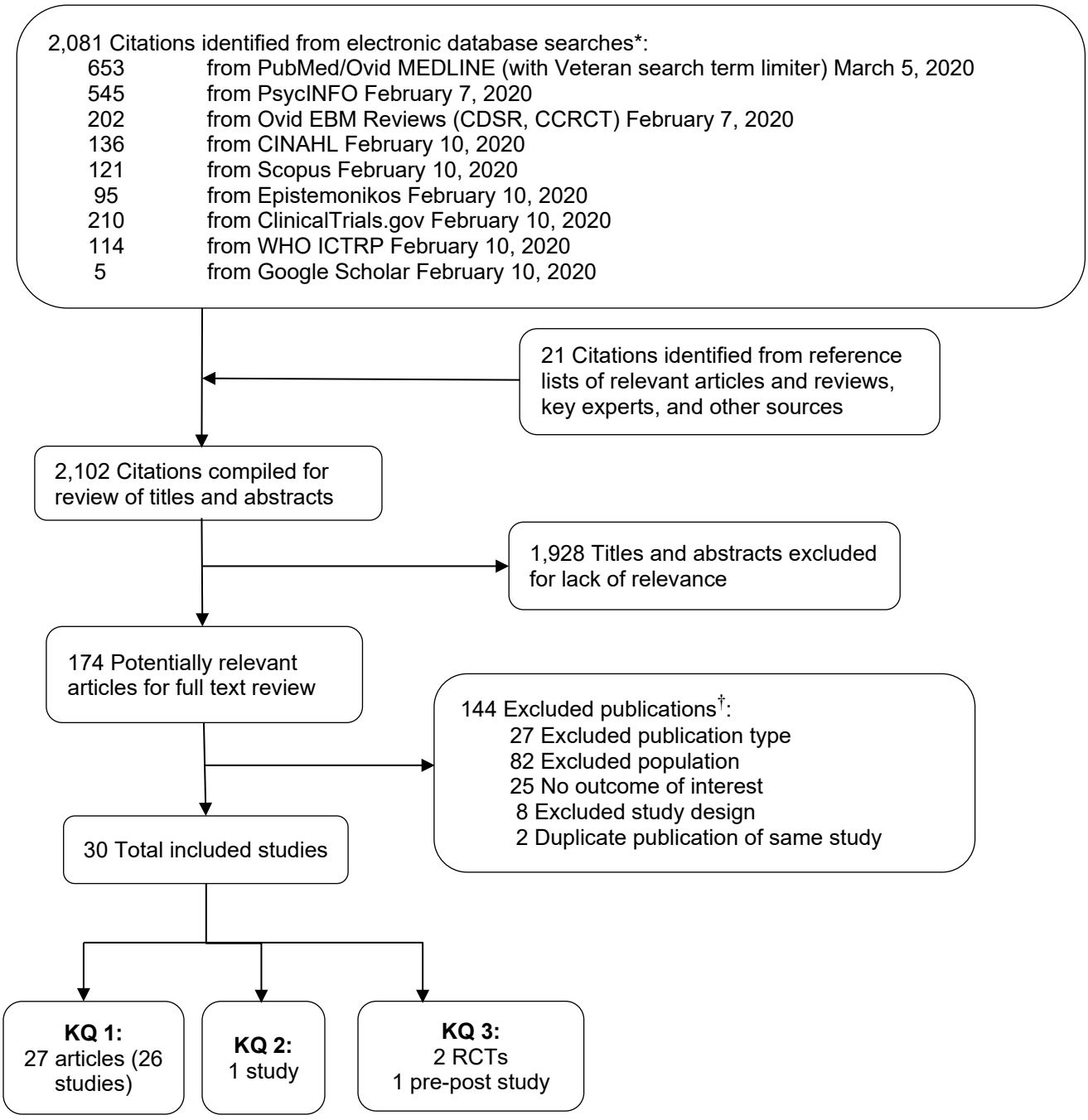
- Low: Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true 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 40[47] to 102,055[45] 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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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 Study Design Data Collection	mTBI *N pts with history of mTBI* *mTBI assessment and definition*	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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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 Muti-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) EHR (based on ICD diagnosis codes) during fiscal year 2012.	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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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 exageration.	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*** **Setting** **Dates** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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*** **Setting** **Dates** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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**
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. Exluded: 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** **Study Design** **Data Collection**	**mTBI** *N pts with history of mTBI* *mTBI assessment and definition*	**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 Study Design Data Collection	mTBI *N pts with history of mTBI* *mTBI assessment and definition*	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 al[4] 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 study[4] 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 Rosenheck[39] 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 al[43] 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 al[41] 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 (*ie*, 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. *[Note that we considered "No or slight pain or discomfort" = no chronic pain, while "Moderate, Severe, or Extreme pain or discomfort" = chronic pain.]*	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, 2012[59] 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 al[59] 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 Veterans [40] 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, 414[57] 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, 2012[59] 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 al[41] 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 al[42] 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 2012[59] 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%)
		Upper back pain (yes/no)	3,162/23,703 (13.3%)
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 (*ie*, 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.	Total mTBI: 216/354 (61.0%) LOC: 90/144 (62.5%) No LOC: 126/210 (60.0%)
		Upper back pain presence (yes/no): Same as above.	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 (*ie*, 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.	5,799/23,703 (24.5%)
		Other joint pain (legs, arms, hands, feet, or "other" location) presence (yes/no): Indicate whether experienced in last 30 days.	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.	30.0%
		Other joint pain (legs, arms, hands, feet, or "other" location) presence (yes/no): Indicate whether experienced in last 30 days.	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 (*ie*, 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 (*ie*, 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-steriodal anti-inflamatory 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 (*ie*, 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 mTBI[15] 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 2010[60] 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 al[41] 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

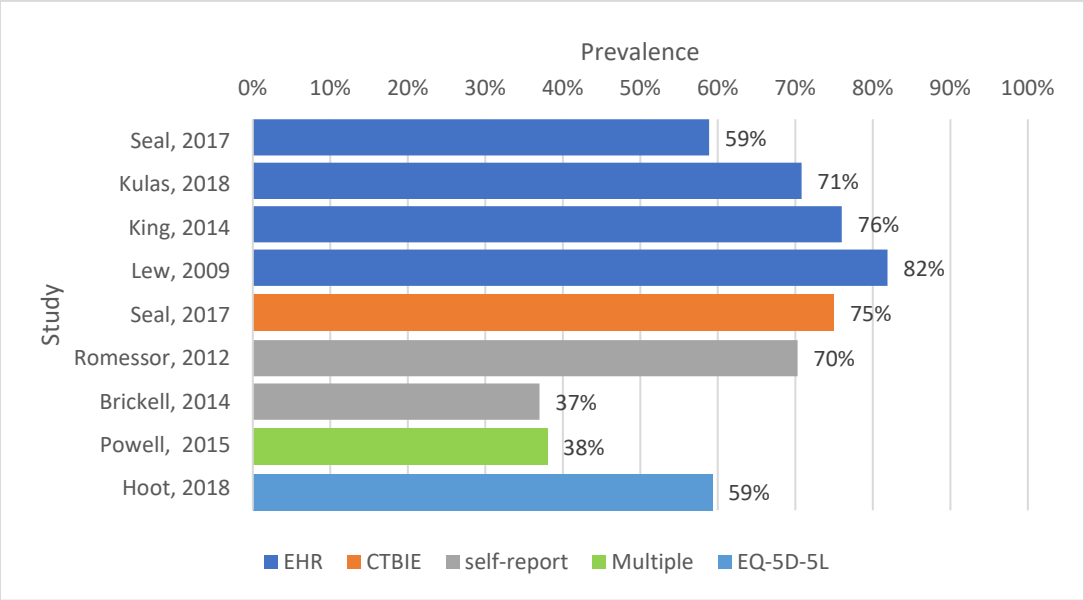
KQ1c. How do estimates of the prevalence of chronic pain and mTBI in US Veterans or Servicemembers differ according to pain measurement methods or definitions?

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 al[4] and Kulas and Rosenheck[39] 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).

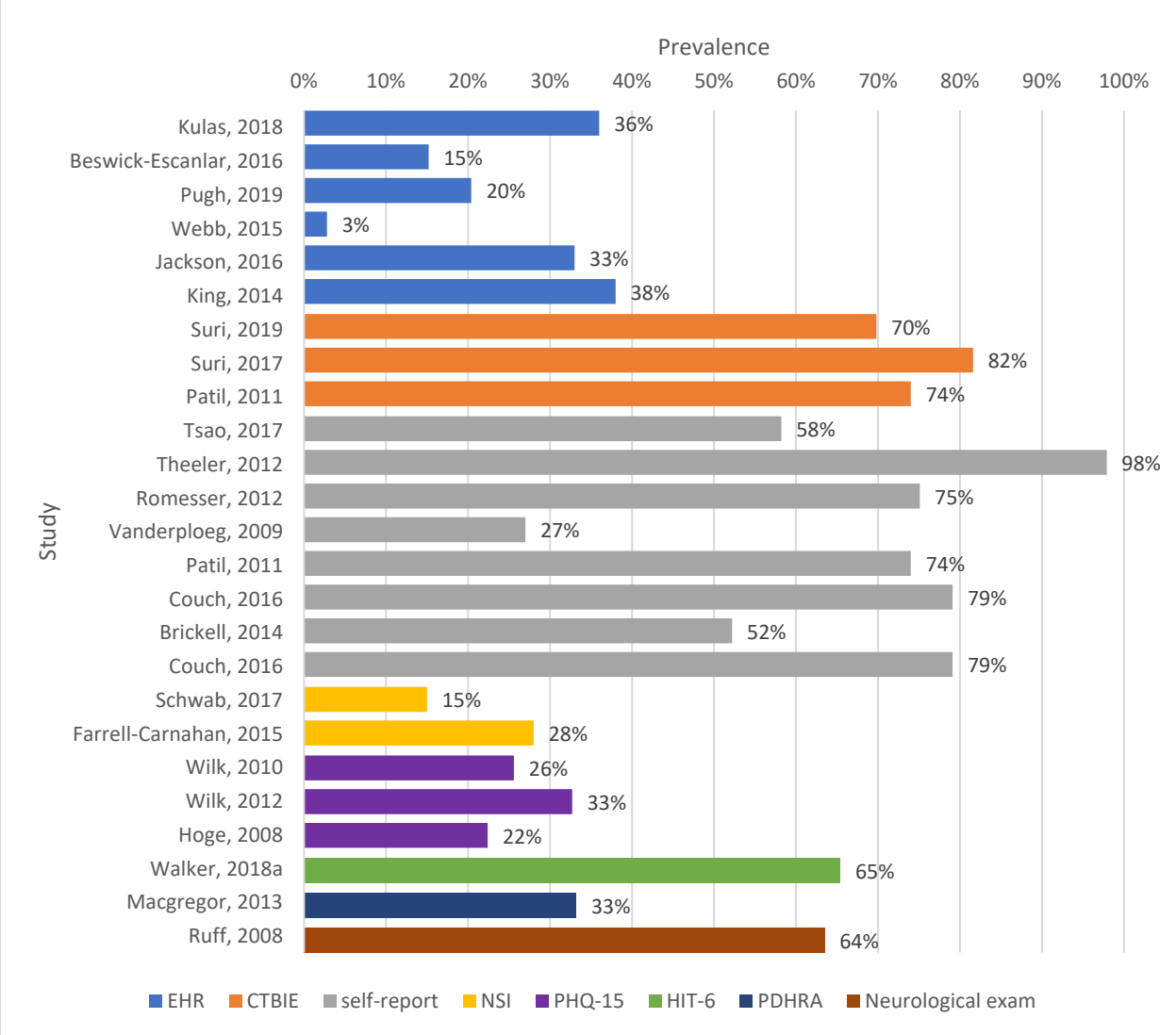
Figures 3-7 portray the range of prevalence estimates by study and tool for some of the most common types of chronic pain. Where severity or frequency data were available, the estimates in these figures reflect more severe pain (in some cases moderate or higher, in others severe to very severe pain), 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



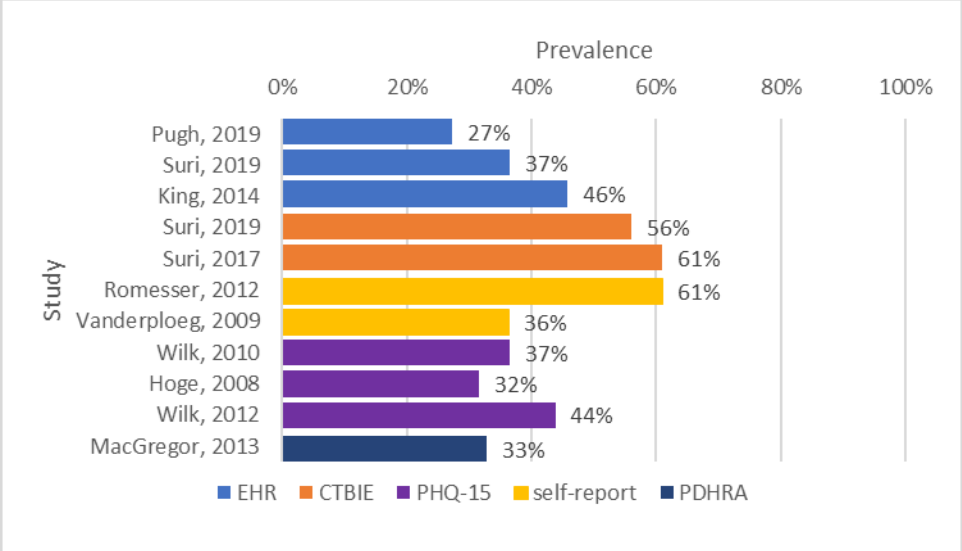
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; EQ-5D-5L=EuroQol Group 5-Dimension 5-Level version

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



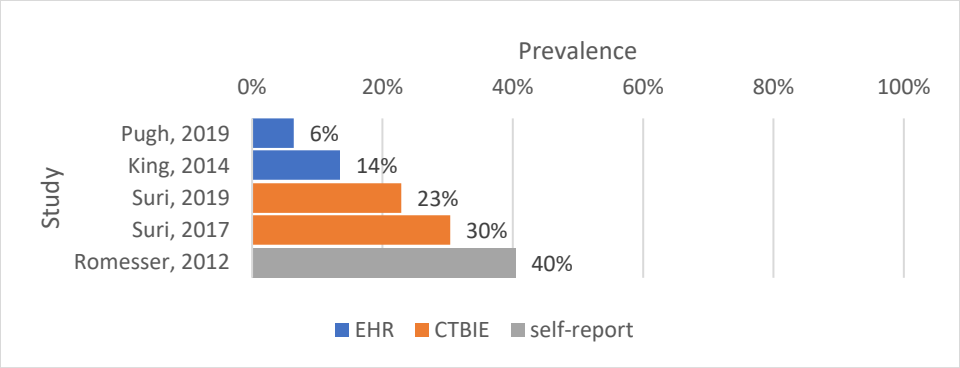
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; HIT-6=6-Item Headache Impact Test; NSI=Neurobehavioral Symptom Inventory; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire

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



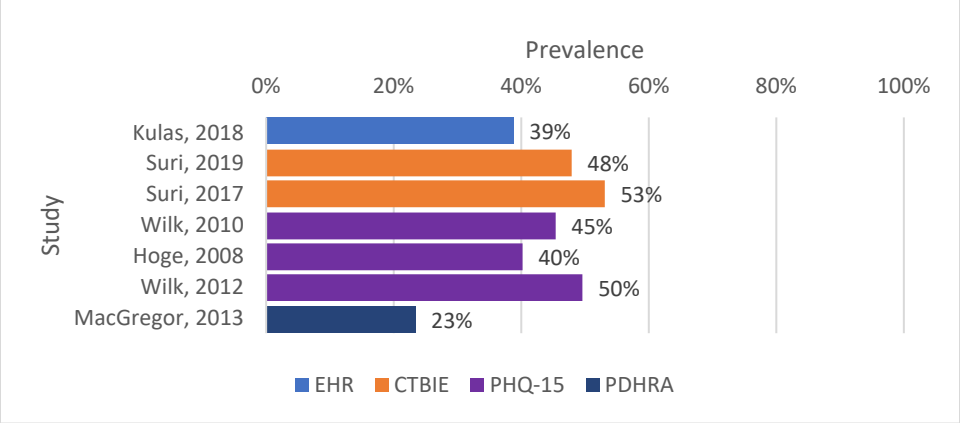
Abbreviations: CTBIE=Comprehensive TBI Evaluation; EHR=Electronic Health Record; PDHRA=Post-Deployment Health Re-Assessment; PHQ-15=15-item Patient Health Questionnaire

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 study[7] 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 studies[12-14] 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 criteria[33] 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 colleagues[14] 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 1st treatment: 6-103 months (median=46). Taking ≥1 Rx: 7/9 (range=1–7; median=2).

Study design Intervention Total N	Selection criteria	mTBI definition and participant characteristics	Intervention	Comparator	Demographics
		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 Headache pain	Findings Harms	Risk of Bias
Leung, 2016[12] RCT rTMS vs sham 12 vs 12	**Persistent headaches:** Between-visit persistent headache severity averaged (sum of headache rating score/number of days) from daily headache diary. **Debilitating headache exacerbation:** composite score generated by multiplying average duration (hours/episode) of headache exacerbation by average frequency (episodes/day) and average intensity (NRS) **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.	**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. **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. **Global Pain Intensity:** Visit and treatment interaction for global pain intensity was nonsignificant.	One participant had mild scalp discomfort, no other AEs reported.	High
Leung, 2018[13] RCT rTMS vs sham 14 vs 15	**Persistent headaches:** Between-visit persistent headache severity=averaged (sum of headache NRS score/number of days) from daily headache diary. **Debilitating headache exacerbation:** Composite score generated by multiplying average duration (hours/episode) of headache exacerbation by average frequency (episodes/day) and average intensity (NRS)	**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). **Debilitating Headache:** Non-significant difference for debilitating headache composite scores (F=3.71, p=0.062). rTMS group decreased 55.1% (SD=29%)	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	High

Study design T vs C N (T vs C)	Headache definition	Findings Headache pain	Findings Harms	Risk of Bias
	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

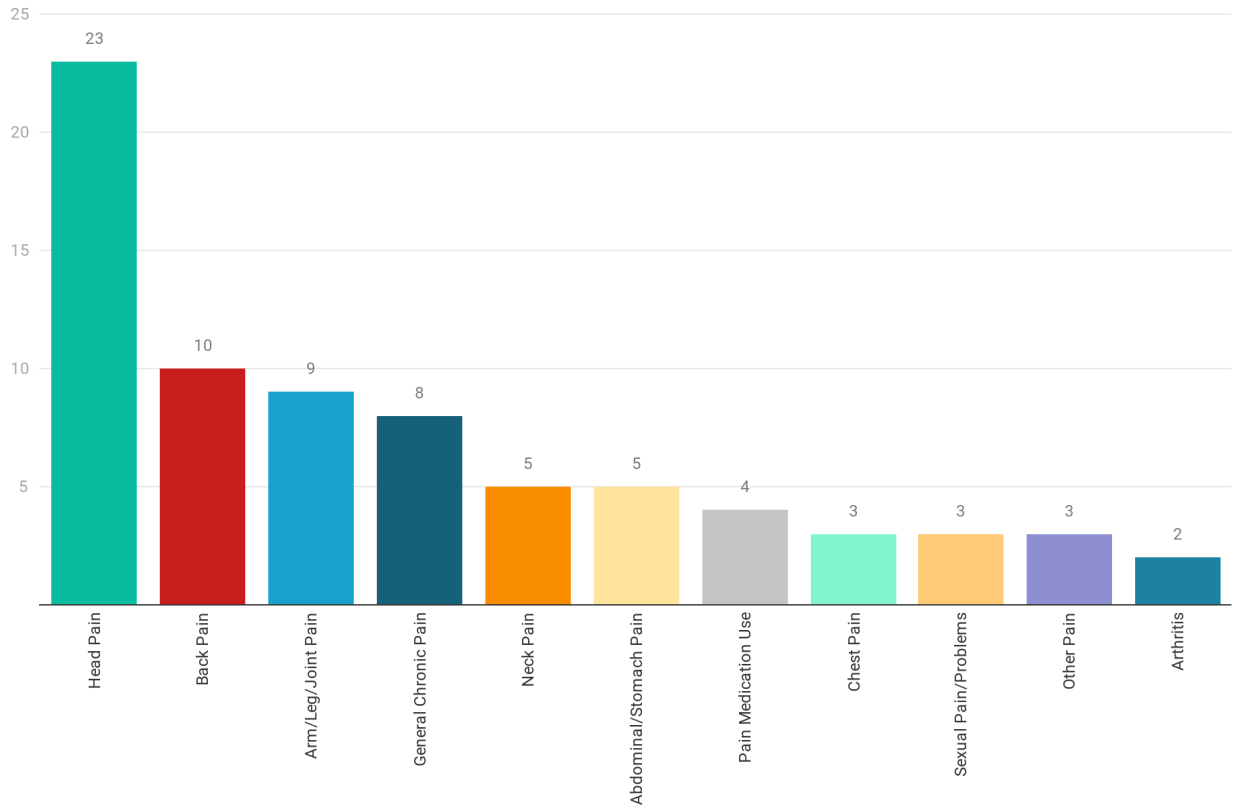
Study	Intervention vs comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias	Comment
Leung, 2016[12]	rTMS vs Sham rTMS	High	Some concerns	High	Some concerns	Low	High	Little information about 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.

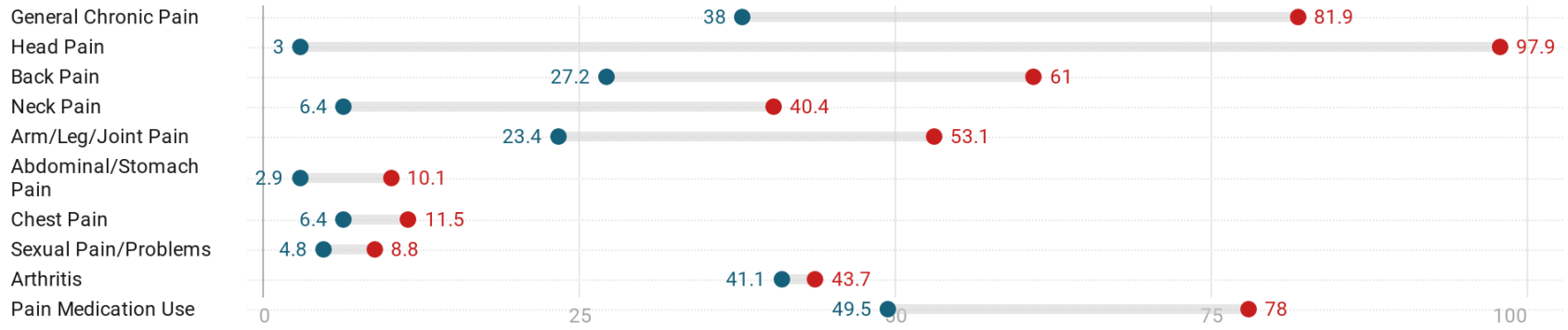
Figure 8. Number of studies reporting prevalence of chronic pain in Veterans and Servicemembers with mTBI by pain type



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 her or 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, Czlapinski 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, Benge 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, Lamberty 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.

APPENDIX A. SEARCH STRATEGIES

Ovid MEDLINE(R) ALL 1946 to March 04, 2020
Date searched: March 5, 2020

1	Brain Concussion/ or Brain Contusion/ or Brain Hemorrhage, Traumatic/ or Brain Injuries, Traumatic/ or Brain Stem Hemorrhage, Traumatic/ or Cerebral Hemorrhage, Traumatic/ or Chronic Traumatic Encephalopathy/ or Contrecoup Injury/ or Craniocerebral Trauma/ or Head Injuries, Closed/ or Intracranial Hemorrhage, Traumatic/ or Post-concussion Syndrome/ or Blast Injuries/
2	(TBI or mTBI or bTBI or ((trauma or traumas or traumatic or posttraumatic or post-traumatic) adj2 (brain or crania* or cranio* or cerebr* or cortex or cortical or head*)) or concussion or concussions or concussive or contrecoup or coup-contrecoup or "minor brain" or "minor head" or postconcussion or postconcussive or post-concussion or post-concussive).ti,ab,kf.
3	or/1-2
4	Arthritis/ or Arthritis, Psoriatic/ or exp Arthritis, Rheumatoid/ or Back Pain/ or Chronic Pain/ or exp Chondrocalcinosis/ or Complex Regional Pain Syndromes/ or exp Facial Neuralgia/ or Fatigue Syndrome, Chronic/ or Femoral Neuropathy/ or Fibromyalgia/ or exp Gout/ or Headache/ or Headache Disorders/ or Headache Disorders, Primary/ or Headache Disorders, Secondary/ or Low Back Pain/ or exp Migraine Disorders/ or Musculoskeletal Pain/ or Myalgia/ or Myofascial Pain Syndromes/ or Neck Pain/ or exp Neuralgia/ or exp Osteoarthritis/ or Pain, Intractable/ or Phantom Limb/ or Post-Traumatic Headache/ or Radial Neuropathy/ or exp Spondylosis/ or Tension-type Headache/ or exp Trigeminal Autonomic Cephalalgias/ or Vascular Headaches/
5	(exp Pain/ or pain.hw.) and (arthrit* or "complex regional pain" or CRPS or fibromyalgia or gout or headache* or "low back" or migrain* or myalgia or neuralgia or neuropath* or nocicept* or osteoarthrit* or osteo-arthrit* or "phantom limb" or "reflex sympathetic dystrophy" or spondylosis or (central* adj2 (pain* or sensit*))).ti,ab,kf.
6	(arthrit* or "chronic fatigue" or "complex regional pain" or CRPS or fibromyalgia or gout or headache* or migrain* or myalgia or neuralgia or neuropath* or nocicept* or osteoarthrit* or osteo-arthrit* or "phantom limb" or “polytrauma clinical triad” or "reflex sympathetic dystrophy" or spondylosis or (central* adj2 (pain* or sensit*)) or pain).ti,ab,kf.
7	or/4-6
8	and/3,7
9	8 not ((exp Animals/ not Humans/) or ("animal model*" or cat or cats or dog or dogs or mice or mouse or rat or rats or rodent).ti.)
10	9 not (((Adolescent/ or exp Child/ or exp Infant/) not exp Adult/) or (adolescent or adolescents or adolescence or child or children or childhood or juvenile or pediatric or paediatric or preschool or pre-school or school-age or teen or teens or teenager or teenagers or youth or youths).ti.)
11	10 not case reports.pt.

12 limit 11 to english language

Veteran/ Servicemember filter terms used:

13 exp Veterans/ or exp "United States Department of Veterans Affairs"/ or exp Veterans Disability Claims/ or exp Veterans Health/ or Veterans Health Services/ or exp Hospitals, Veterans/ or Aerospace Medicine/ or Armed Conflicts/ or Hospitals, Military/ or Military Health/ or Military Personnel/ or Military Medicine/ or Military Nursing/ or Military Psychiatry/ or exp Naval Medicine/ or Psychology, Military/ or Gulf War/ or Vietnam Conflict/ or World War ii/ or Afghan Campaign 2001-/ or Iraq War, 2003-2011/ or War/ or exp "Warfare and Armed Conflicts"/ or War-Related Injuries/ or War Exposure/ or Warfare/ or Biological Warfare/ or Chemical Warfare/ or Nuclear Warfare/ or Psychological Warfare/

14 ("active duty" or "armed forces" or "armed service*" or "coast guard*" or military or "air force" or army or "defense force*" or "marine corps" or marines or "national guard*" or (navy not bean) or naval or "security force*" or air-men or air-man or airmen or airman or corpsman or corpsmen or guardsman or guardsmen or infantry* or medic or medics or reservist* or sailor* or soldier* or servicemember* or service-member* or "special forces" or submariner* or troops or battle* or combat or deployed or deployment* or post-deployment* or postdeployment* or veteran* or VAMC or Veterans Administration Medical Center* or VHA or Veterans* Health Administration or war or wars or warfare or war-fighter* or warfighter* or war-related).tw,kf.

15 (((VA or Veteran Affairs or Veterans' Affairs or Veterans Affairs or Veterans Administration) adj4 (health care system or healthcare system or medical center or hospital)) or VAMC or Veteran Affairs or Veterans' Affairs or Veterans Affairs or Veterans Administration Medical Center or Veterans' Affairs Medical Center or Veterans Affairs Medical Center or Veterans Health Administration or QUERI or "Mental Health Quality Enhancement Research Initiative" or HSR&D or "Center of Innovation for Veteran-Centered Value-Driven Care" or "Evidence-based Synthesis Program" or ((Veteran* or VA) adj5 (Office of Research and Development)) or "Center for Health Equity Research and Promotion" or "Women's Health Research Network" or "Cooperative Studies Program" or "Million Veteran Program").in.

16 (military or army or soldier* or navy* or veteran or veterans).jw.

17 or/13-16

18 and/12,17

CINAHL Plus with Full Text (EBSCOHost)

Date searched: February 10, 2020

S1 MH Brain Concussion OR Brain Contusions OR Brain Injuries OR Chronic Traumatic Encephalopathy OR Head Injuries (32,064)

S2 TI (TBI OR mTBI OR bTBI OR ((trauma OR traumas OR traumatic OR posttraumatic OR post-traumatic) N2 (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*)) OR concussion OR concussions OR concussive OR contrecoup OR coup-contrecoup OR "minor brain" OR "minor head" OR postconcussion OR postconcussive OR post-concussion OR post-concussive) OR AB (TBI OR mTBI OR bTBI OR ((trauma OR traumas OR traumatic OR

posttraumatic OR post-traumatic) N2 (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*)) OR concussion OR concussions OR concussive OR contrecoup OR coup-contrecoup OR "minor brain" OR "minor head" OR postconcussion OR postconcussive OR post-concussion OR post-concussive) (22,788)
S3 S1 OR S2 (38,328)
S4 MH Arthritis OR Arthritis, Psoriatic OR Arthritis, Rheumatoid OR Back Pain OR Chondrocalcinosis OR Chronic Pain OR Cluster Headache OR Complex Regional Pain Syndromes OR Facial Pain OR Fatigue Syndrome, Chronic OR Gout OR Headache OR Headache, Primary OR Headache, Secondary OR Low Back Pain OR Migraine OR Muscle Pain OR Myofascial Pain Syndromes OR Neck Pain OR Neuralgia OR Osteoarthritis OR Phantom Limb OR Phantom Pain OR Spondylosis OR Tension Headache OR Trigeminal Autonomic Cephalalgias OR Vascular Headache (127,543)
S5 TI (arthrit* OR chondrocalcinosis OR "chronic fatigue" OR "complex regional pain" OR CRPS OR fibromyalgia OR gout OR headache* OR "low back" OR migrain* OR musculoskeletal OR musculo-skeletal OR myalgia OR neuralgia OR neuropath* OR nocicept* OR osteoarthrit* OR osteo-arthrit* OR "phantom limb" OR "reflex sympathetic dystrophy" OR spondylosis OR (central* N2 (pain* OR sensit*)) OR ((chronic OR intractable OR long-term OR longer-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persistent* OR refractory) N3 pain)) OR AB (arthrit* OR chondrocalcinosis OR "chronic fatigue" OR "complex regional pain" OR CRPS OR fibromyalgia OR gout OR headache* OR "low back" OR migrain* OR musculoskeletal OR musculo-skeletal OR myalgia OR neuralgia OR neuropath* OR nocicept* OR osteoarthrit* OR osteo-arthrit* OR "phantom limb" OR "reflex sympathetic dystrophy" OR spondylosis OR (central* N2 (pain* OR sensit*)) OR ((chronic OR intractable OR long-term OR longer-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persistent* OR refractory) N3 pain)) (198,244)
S6 S4 OR S5 (239,755)
S7 S3 AND S6 Limiters - English Language; Human; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over, All Adult (435)

PsycINFO (Ovid) 1806 to February Week 1 2020
Date searched: February 7, 2020
1 Traumatic Brain Injury/ or Brain Concussion/ (19109)
2 (TBI or mTBI or bTBI or ((trauma or traumas or traumatic or posttraumatic or post-traumatic) adj2 (brain or crania* or cranio* or cerebr* or cortex or cortical or head*)) or concussion or concussions or concussive or contrecoup or coup-contrecoup or "minor brain" or "minor head" or postconcussion or postconcussive or post-concussion or post-concussive).ti,ab. (21754)
3 or/1-2 (25224)
4 Arthritis/ or Rheumatoid Arthritis/ or Back Pain/ or Chronic Pain/ or "Complex Regional Pain Syndrome (Type I)"/ or Chronic Fatigue Syndrome/ or Fibromyalgia/ or Headache/ or Migraine Headache/ or Myofascial Pain/ or Muscle Contraction Headache/ or Neuropathy/ or Neuropathic Pain/ or Phantom Limbs/ or Trigeminal Neuralgia/ (43617)
5 (arthrit* or chondrocalcinosis or "chronic fatigue" or "complex regional pain" or CRPS or fibromyalgia or gout or headache* or "low back" or migrain* or musculoskeletal or musculo-skeletal or myalgia or neuralgia or neuropath* or nocicept* or osteoarthrit* or osteo-arthrit* or "phantom limb" or "reflex sympathetic dystrophy" or spondylosis or (central* adj2 (pain* or

sensit*)) or ((chronic or intractable or long-term or longer-term or noncancer or non-cancer or nonmalignant or non-malignant or persist?nt* or refractory) adj3 pain)).ti,ab. (86759)
6 or/4-5 (89596)
7 and/3,6 (1680)
8 limit 7 to animal (246)
9 7 not 8 (1434)
10 limit 9 to ("300 adulthood<age 18 yrs and older>" or 320 young adulthood<age 18 to 29 yrs>or 340 thirties<age 30 to 39 yrs>or 360 middle age<age 40 to 64 yrs>or "380 aged<age 65 yrs and older>" or "390 very old<age 85 yrs and older>") (711)
11 9 not (adolescent or adolescents or adolescence or child or children or childhood or juvenile or pediatric or paediatric or preschool or pre-school or school-age or teen or teens or teenager or teenagers or youth or youths).ti. (1327)
12 or/10-11 (1355)
13 limit 12 to ("0200 clinical case study" or 1400 nonclinical case study) (127)
14 12 not 13 (1228)
15 limit 14 to english language (1180)

EBM Reviews (Ovid) - Cochrane Central Register of Controlled Trials (December 2019) and Cochrane Database of Systematic Reviews (2005 to February 4, 2020)
Date searched: February 7, 2020
1 (TBI or mTBI or bTBI or ((trauma or traumas or traumatic or posttraumatic or post-traumatic) adj2 (brain or crania* or cranio* or cerebr* or cortex or cortical or head*)) or concussion or concussions or concussive or contrecoup or coup-contrecoup or "minor brain" or "minor head" or postconcussion or postconcussive or post-concussion or post-concussive).ti,ab. (5149)
2 (arthrit* or "chronic fatigue" or "complex regional pain" or CRPS or fibromyalgia or gout or headache* or "low back" or migrain* or myalgia or neuralgia or neuropath* or nocicept* or osteoarthrit* or osteo-arthrit* or "phantom limb" or "reflex sympathetic dystrophy" or spondylosis or (central* adj2 (pain* or sensit*)) or ((chronic or intractable or long-term or longer-term or noncancer or non-cancer or nonmalignant or non-malignant or persist?nt* or refractory) adj3 pain)).ti,ab. (87910)
3 and/1-2 (297)
4 3 not ("animal model*" or cat or cats or dog or dogs or mice or mouse or rat or rats or rodent).ti. (297)
5 4 not (adolescent or adolescents or adolescence or child or children or childhood or juvenile or pediatric or paediatric or preschool or pre-school or school-age or teen or teens or teenager or teenagers or youth or youths).ti. (273)

Scopus
Date searched: February 10, 2020
(TITLE-ABS-KEY (tbi OR mtbi OR btbi OR ((trauma* OR posttraumatic OR post-traumatic) W/2 (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*)) OR concussion* OR concussive OR contrecoup OR coup-contrecoup OR "minor brain" OR "minor head" OR postconcuss*)) AND ((TITLE-ABS-KEY (arthrit* OR "chronic fatigue" OR "complex regional pain" OR crps OR fibromyalgia OR gout OR headache* OR migrain* OR myalgia OR neuralgia OR neuropath* OR nocicept* OR osteoarthrit* OR osteo-arthrit* OR "phantom limb") OR TITLE-ABS-KEY ("reflex sympathetic dystrophy" OR spondylosis OR (

central* W/2 (pain* OR sensit*)) OR ((chronic OR intractable OR long-term OR longer-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persist?nt* OR refractory) W/3 pain)))) AND (LIMIT-TO (DOCTYPE , "cp")) AND (LIMIT-TO (LANGUAGE , "English")) (155)

Epistemonikos
Date searched: February 10, 2020
advanced_title_en:(TBI OR mTBI OR bTBI OR (trauma OR traumatic OR posttraumatic OR post-traumatic) AND (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*) OR concussion* OR concussive OR "minor brain" OR "minor head" OR postconcuss*) AND advanced_title_en:(arthritis OR chronic OR "complex regional" OR crps OR fibromyalgia OR gout OR headache OR migraine OR myalgia OR neuralgia OR neuropathy OR nociceptive OR osteoarthritis OR osteo-arthritis OR phantom limb OR spondylosis OR centralized pain OR central sensitization OR intractable OR long-term OR longer-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persistent OR refractory) NOT advanced_title_en:(adolescent OR adolescents OR adolescence OR child OR children OR childhood OR juvenile OR pediatric OR paediatric OR preschool OR pre-school OR school-age OR teen OR teens OR teenager OR teenagers OR youth OR youths) [Filters: classification=systematic-review, protocol=no, cochrane=missing, pmc=without] (109)

ClinicalTrials.gov
Date searched: February 10, 2020
(arthritis OR chronic fatigue OR complex regional pain OR crps OR fibromyalgia OR gout OR headache OR migraine OR myalgia OR neuralgia OR neuropathy OR nociceptive OR osteoarthrits OR osteo-arthritis OR phantom limb OR post-traumatic headache OR reflex sympathetic dystrophy OR spondylosis OR central pain OR centralized pain OR centralized sensitivity OR chronic pain OR intractable pain OR long-term pain OR longer-term pain OR noncancer pain OR non-cancer pain OR nonmalignant pain OR non-malignant pain OR persistent pain OR refractory pain) | TBI OR mTBI OR bTBI OR (trauma* OR posttraumatic OR post-traumatic) AND (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*) OR concussion* OR concussive OR contrecoup OR coup-contrecoup OR EXPAND[Concept] "minor brain" OR EXPAND[Concept] "minor head" OR postconcuss* | Adult, Older Adult (210)

WHO ICTRP
Date searched: February 10, 2020
Title=TBI OR mTBI OR bTBI OR (trauma OR traumatic OR posttraumatic OR post-traumatic) AND (brain OR crania* OR cranio* OR cerebr* OR cortex OR cortical OR head*) OR concussion* OR concussive OR "minor brain" OR "minor head" OR postconcuss*
Condition=arthritis OR chronic OR "complex regional" OR crps OR fibromyalgia OR gout OR headache OR migraine OR myalgia OR neuralgia OR neuropathy OR nociceptive OR osteoarthritis OR osteo-arthritis OR phantom limb OR reflex sympathetic dystrophy OR spondylosis OR centralized pain OR central sensitization OR intractable OR long-term OR longer-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persistent OR refractory (without synonyms checked)
Recruitment status=ALL (140)

Google Scholar
Date searched: February 10, 2020
2 separate searches were conducted, reviewed first 10 pages of results for each
(TBI OR mTBI OR "traumatic brain" OR concussion OR "minor brain" OR "minor head" OR postconcuss*) AND (pain OR central sensitization OR intractable OR long-term OR noncancer OR non-cancer OR nonmalignant OR non-malignant OR persistent OR refractory)
(TBI OR mTBI OR "traumatic brain" OR concussion OR "minor brain" OR "minor head" OR postconcussion) AND (chronic OR intractable OR long-term OR persistent OR refractory) AND (treatment OR management OR intervention)
(10)

APPENDIX B. STUDY SELECTION

Inclusion/Exclusion Criteria for Full Text Review

VA-ESP Chronic Pain in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury

1. **Language**: Is the full text of the article in English?
   Yes → Proceed to #2
   No → Code **X1**. STOP

2. **Publication type:** Is this a published study (exclude: dissertations, conference abstracts, protocols, unpublished results, letters, reviews, *etc*)?
   Yes → Proceed to #3
   No → Code **X2**. Add code **B** (example: X2 – B) if retaining for background/discussion. STOP

3. **Population**: Does the study include adult Veterans or Servicemembers with chronic pain and a history of mTBI?
   Definitions: ***Pain****: Include headaches/migraines. Chronic>3 months. Assume chronic unless explicitly says acute.* ***mTBI****: If mixed TBI population (eg mild, mod, and or severe), only include if mTBI results are reported separately. Include concussion. "Post-concussive symptoms" okay only if there's confirmation of mTBI or concussion that caused the symptoms (eg, a sample of recently returned Vets who complete the NSI and score 20 or higher does NOT qualify unless the study specifies that they all had a concussion or mTBI).*

   Yes → Proceed to #4
   No → **Code X3**. Add code **B** if retaining for background/discussion. STOP

4. **Population**: Is this a U.S. population?
   Yes → Proceed to #5
   No, they're international → Does it appear to address benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI (KQ3)?
   Yes → Proceed to #5
   No → **Code X3.** STOP

5. **Intervention:** Is the study examining pharmacologic, nonpharmacologic, or complementary and integrative health interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI (KQ3)?
   Yes → Proceed to **#8**
   No, not a treatment/intervention study → Proceed to **#6**.
   No, not treating chronic pain → **Code X5**

6. **Study design**: Does the study report prevalence of chronic pain in the population of interest?
   Yes, reports prevalence → Proceed to #7
   No → Code **X6**

7. **KQ2**: Does this study report the prevalence of suicide-related outcomes (including suicide, suicidal ideation/intent/plan, and suicidal self-directed harm) in Veterans or Servicemembers with chronic pain and a history of mTBI?
   Yes → **Code 1 for KQ2**. Proceed to #8
   No → Proceed to #8

8. **Study design**: Is this an RCT, NRCT, cohort, prospective, or retrospective study (Exclude: Case studies/reports, cross-sectional, modeling studies)?
   Yes → Proceed to #9
   No → but it does have at least 1 KQ coded. STOP.
   No → and it has no previous code. **Code X6**

9. **Comparators**: Is the comparator population 1 of the following: Placebo, active comparator, usual care, wait-list control, pre-post? *Note: KQ1 and 1c do not require comparator, proceed to #11.*
   Yes → Proceed to #10
   No → **Code X4**

10. **Outcomes**: does the study report benefits (*eg* reduced pain, mental health diagnosis/symptoms, opioid use; better QOL, functioning, treatment adherence) or harms (*eg* AEs, SAEs, withdrawals due to AEs) outcomes for chronic pain in Veterans/Servicemembers with history of mTBI measured by a validated tool?
    Yes → **Code 1 for KQ3**. STOP
    No → **Code X5**. STOP

Codes Key:
X1: Not English-language
X2: Excluded publication type
X3: Excluded population
X4: Excluded comparator
X5: No outcomes of interest
X6: Excluded study design

APPENDIX C. QUALITY ASSESSMENT

Table 10. Criteria used in quality assessment of randomized controlled trials

Cochrane RoB 2.0:[33] Five domains through which bias may be introduced	
1. Risk of bias arising from the randomization process: 1.1. Was the allocation sequence random? 1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions? 1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	
2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): 2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? 2.5. If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? 2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention? 2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	
3. Risk of bias due to missing outcome data: 3.1. Were data for this outcome available for all, or nearly all, participants randomized? 3.2. If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data? 3.3. If N/PN to 3.2: Could missingness in the outcome depend on its true value? 3.4. If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	
4. Risk of bias in measurement of the outcome: 4.1. Was the method of measuring the outcome inappropriate? 4.2. Could measurement or ascertainment of the outcome have differed between intervention groups? 4.3. If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ? 4.4. If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? 4.5. If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	
5. Risk of bias in selection of the reported result: 5.1. 5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from... 5.2. ...multiple outcome measurements (*eg* scales, definitions, time points) within the outcome domain? 5.3. ...multiple analyses of the data?	
Overall risk-of-bias judgement	
Low ROB	The study is judged to be at **low risk of bias for all domains** for this result.
Some Concerns	The study is judged to raise **some concerns** in at least 1 domain for this result, but not to be at high risk of bias for any domain.
High ROB	The study is judged to be at **high risk of bias** in at least 1 domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

Abbreviations: NI=not indicated; N=no; PN=probably not; PY=probably yes; ROB=risk of bias; Y=yes

Table 11. Quality ratings for studies reporting prevalence of chronic pain in Veterans/Servicemembers with history of mild traumatic brain injury

Study *Author, year*	#1	#2	#3	#4	Overall study quality/Quality concerns	Applicability
Beswick-Escanlar, 2016[45]	1	NA	0	0	Entire population of SMs and focused on incident mTBI with incident headache or migraine pain (no diagnosis codes prior to study start date) during 1-year follow-up period. Both mTBI and pain were defined as ≥1 diagnosis code.	Post-9/11 SMs receiving military health care between 2006 and 2015.
Brickell, 2014[42]	1	0	0	0	Small sample size, and different patients at each follow-up. High attrition; no report of non-responder characteristics. mTBI definition inconsistent with VA-DoD common definition (required LOC<15 minutes and allowed intracranial abnormality). Non-standard pain measure (based on open-ended telephone interview questions).	Post-9/11 SMs with mTBI and polytrauma.
Couch, 2016[46]	0	0	1	0	Small sample size; highly selective patient group treated in 1 reintegration clinic. mTBI assessed clinically according to VA/DoD common definition. Headache or migraine pain self-reported based on clinical assessment questionnaire.	Male, Post-9/11 Veterans at 1 site, between ages of 20 and 60, enrolled in reintegration clinic.
Farrell-Carnahan, 2015[47]	1	0	1	1	Small study of Post-9/11 Veterans admitted to inpatient rehabilitation at 1 of 4 VA polytrauma rehabilitation centers and enrolled in TBI Model Systems. mTBI assessed using TBI Model Systems form. Headache intensity assessed using single item from NSI. Differences between participants (80% of those recruited) and non-participants (20% of recruited) are unclear.	Post-9/11 Veterans requiring inpatient rehabilitation for TBI and who enroll in VA TBI Model Systems.
Hoge, 2008[15]	1	0	0	1	Survey with 59% response rate, no information on non-respondents. mTBI assessed using screening questions; mTBI group included n=4 with LOC>30 mins. Pain measures assessed using validated instrument.	Post-9/11 Army SMs shortly after return from combat deployment.
Hoot, 2018[41†]	1	0	1	1	Fairly selective study sample from 4 sites (no information on Veterans/SMs who were recruited but did not enroll). Standardized and validated measures of mTBI and pain were used.	Post-9/11 Veterans/SMs with combat exposure enrolled in a comprehensive longitudinal study.
Jackson, 2016[48]	1	0	1	0	Veterans sampled nationally. mTBI assessed using VA 4-item screen plus	Post-9/11 Veterans who received mental health

Study *Author, year*	#1	#2	#3	#4	Overall study quality/Quality concerns	Applicability
					clinical interview. Headache pain assessed using post-concussive symptom indicators on VA 4-item screen.	evaluation in VA; oversampled females and Veterans with PTSD.
King, 2014[40]	1	NA	0	0	Entire population of VA users across region. mTBI defined using ≥1 ICD diagnosis code for post-concussion syndrome. Pain conditions also based on ICD diagnosis codes.	Post-9/11 Veterans who used VA primary care in VISN 2.
Kulas, 2016[39]	1	NA	0	0	Large study that included full population of patients from VA for 1 year. Both mTBI and pain conditions based on presence of ≥1 ICD diagnosis code during study period.	Post-9/11 Veterans receiving VA care in fiscal year 2012.
Lew, 2009[25]*	0	NA	1	1	Single site; chart review of all patients assessed for 22 months. No demographics provided. mTBI and general chronic pain defined as clinician documentation in CTBIE chart note but making assumption that post-concussive symptoms associated only with mTBI and not TBI of greater severity.	Post-9/11 Veterans treated at single Level 2 polytrauma clinic.
MacGregor, 2013[49]	1	NA	0	0	Fairly small multi-site sample but representative of population described. mTBI measurement based on ICD codes and include 1 that would be categorized as 'moderate' using VA/DoD common definition. Pain assessment not validated but standard.	Post-9/11 SMs that incur minor-to-moderate deployment injuries as recorded in deployment healthcare database and complete both PDHA and PDHRA within 1-year post-deployment.
Patil, 2011[50]*	0	NA	1	0	Consecutive patients from a single VA polytrauma site. mTBI assessed using CTBIE. Headache pain assessed using question on CTBIE and referral/follow-up at Neurology clinic.	Post-9/11 Veterans receiving care in a single VA (polytrauma network site).
Powell, 2015[43]	1	0	1	0	Fairly selective study sample from 1 site (no information on Veterans/SMs who were recruited but did not enroll). mTBI based on clinical interview and consensus among PhD-level psychologists. General pain assessment non-standard.	Post-9/11 Veterans receiving VA care in Boston that would enroll in TRACTS longitudinal study.
Pugh, 2019[7]	1	NA	1	0	Entire population of VA users. mTBI defined using complex algorithm taking many data sources into account. Pain conditions based on ICD diagnosis codes.	Post-9/11 Veterans who enrolled in and used VA healthcare.
Romesser, 2012[44]	0	NA	1	0	Fairly selective study sample from 2 polytrauma sites. mTBI and pain assessed from patient self-reported	Post-9/11 Veterans assessed in 2 VA polytrauma clinics.

Study *Author, year*	#1	#2	#3	#4	Overall study quality/Quality concerns	Applicability
					clinical questionnaire; unclear if standardized or validated.	
Ruff, 2008[6]	1	NA	1	0	Fairly small sample of consecutive patients at VA polytrauma clinic. mTBI assessed clinically and defined using VA-DoD standard definition. Headache pain measures were self-reported; focused on deployment-related headaches.	Post-9/11 Veterans seeking care for TBI at VA with blast-related mTBI.
Schwab, 2017[51]	1	1	1	1	Sampled from among SMs with positive mTBI screen at 2 sites; used structured interview to confirm mTBI history. Headache intensity assessed using NSI. Excluded participants with potential symptom exaggeration. Loss to follow-up of 34%; compared responders to non-responders and reported few differences.	Post-9/11 Army soldiers with Iraq/Afghanistan deployment history from 2 military sites.
Seal, 2017[4]*	1	NA	1	1	Large study of entire patient population; mTBI assessed using CTBIE; General chronic pain assessed using ICD diagnosis codes, but pain interference assessed using standardized measure from CTBIE.	Post-9/11 Veterans who use VA and completed CTBIE.
Suri, 2017[53]*	1	0	1	1	Large multi-site sample of VA users that completed CTBIE, considered gold standard assessment for mTBI. Pain measures standard and/or validated (pain interference question from NSI).	Post-9/11 Veterans who use VA and completed CTBIE.
Suri, 2019[52]*	1	NA	1	0	Large multi-site population of VA users that completed CTBIE, considered gold standard assessment for mTBI; pain assessed using “pain location” measure on CTBIE. Large proportion of Veterans excluded because of missing data.	Post-9/11 Veterans who use VA and completed CTBIE.
Theeler, 2012[54]	0	0	1	0	Participants from 1 site; enrolled based on positive mTBI screen but presumed confirmed in TBI clinic. Demographics not reported. Unknown if pain measure was standardized or validated.	Post-9/11 SMs who had a deployment-related concussion in Iraq or Afghanistan.
Tsao, 2017[55]	1	0	0	0	Sample of post-deployment SMs from 3 sites; unclear what proportion of recruited SMs participated and how responders differed from non-responders. mTBI assessed using screening questions (VA-DoD common definition). Headache pain assessed using non-	Post-9/11 male Marines returning from Iraq/Afghanistan deployments at 1 of 3 sites in the US.

Study *Author, year*	#1	#2	#3	#4	Overall study quality/Quality concerns	Applicability
					standardized/validated item(s) on questionnaire.	
Vanderploeg, 2009[56]	1	0	0	0	Random-sample and in-person assessments. No description of non-respondents. Non-standard measures of mTBI and pain.	Male Vietnam-era Army Veterans.
Walker, 2018[57†]	1	0	1	1	Fairly selective study sample from 4 sites (no information on Veterans/SMs who were recruited but did not enroll). Standardized and validated measures of mTBI and pain were used.	Post-9/11 Veterans/SMs with combat exposure enrolled in a comprehensive longitudinal study.
Webb, 2015[58]	1	NA	0	0	Entire population of Military Health System users across multiple sites. mTBI defined using CDC-recommended series of ICD diagnosis codes. Headache and migraine pain based on ICD diagnosis codes.	Post-9/11 Air Force SMs who used Military Health System between 2001 and 2008.
Wilk, 2010[60]	1	0	0	1	Survey from single-site with 57% response rate, no information on non-respondents. mTBI assessed using screening questions. Pain measures assessed using validated instrument (PHQ-15). Bivariable analyses only in blast/non-blast comparisons.	Post-9/11 Army SMs shortly after return from high-combat deployment.
Wilk, 2012[59]	1	0	0	1	Survey from single site with 73% response rate, no information on non-respondents. mTBI assessed using screening questions. Pain measures assessed using validated instrument (PHQ-15).	Post-9/11 Army SMs shortly after return from combat deployment.

*Study based on VA Comprehensive TBI Evaluation (CTBIE) data. †Chronic Effects of Neurotrauma Consortium (CENC) longitudinal cohort study.
Abbreviations: CDC=Centers for Disease Control and Prevention; CTBIE=Clinical TBI Evaluation; DoD=Department of Defense; ICD=International Classification of Diseases; mTBI=Mild Traumatic Brain Injury; SMs=Servicemembers; VA=Veterans Affairs; VISN=Veterans Integrated Services Network; PTSD=Posttraumatic stress disorder; NA=Not applicable

Quality Assessment Criteria

1. **Representativeness of the sample:**
   1=Truly representative of the target population
   1=Somewhat representative of the target population
   0=Selected subset of Veterans/SMs
   0=No
2. **Non-respondents/non-enrolled:**
   Enter 0 or 1:
   1=Comparability between respondent and non-respondent characteristics is established; response rate is satisfactory
   0=Comparability between respondents and non-respondents is unsatisfactory; response

rate is unsatisfactory
0=No description of the characteristics of the responders versus non-responders; no description of response rate
NA=EHR studies (patient does not opt in versus opt out)

3. **Were objective, standard criteria used for measurement of mTBI?**
   Enter 0 or 1:
   1=Validated measures (*eg* any that uses VA/DoD common definition with clinical interview)
   0=Administrative codes
   0=Non-validated (*eg*, reported concussion, self-report, initial screen)
4. **Were standard, validated criteria used for measurement of chronic pain?**
   Enter 0 or 1:
   a) All measures standard and/or validated? (if some are validated and some are not, note which get 1 or 0)
   1=yes
   0=no, self-report measure; not validated for chronic pain measurement
   0=no, proxy measure used (*eg*, opioid medication use)

APPENDIX D. STUDIES EXCLUDED AT FULL TEXT LEVEL

Excluded publication type

Barrett RS. Post-traumatic headache. Combat soldiers are suffering. Adv NPs PAs. 2012;3(1):33-34.

Bell KR, Brockway JA, Fann JR, et al. Concussion treatment after combat trauma: development of a telephone based, problem solving intervention for service members. Contemp Clin Trials. 2015;40:54-62.

Daggett V. Feasibility and satisfaction with the VETeranS Compensate, Adapt, REintegrate (VETS-CARE) intervention. Brain Inj. 2014;28(5-6):554.

DePalma RG. Combat TBI: History, Epidemiology, and Injury Modes. CRC Press/Taylor & Francis. 2015;2.

Eskridge SL. Combat-related blast injuries: Injury types and outcomes. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2012;72(7-B):3929.

Finkel A. Headaches in soldiers with mild traumatic brain injury--additional data. Headache. 2012;52(8):1320.

Gelinas C. Validation of a revised pain assessment tool for brain-injured ICU patients. Critical care medicine Conference: 46th critical care congress of the society of critical care medicine, SCCM. 2016;44(12 Supplement 1):269.

Hoffer ME, Donaldson C, Gottshall KR, Balaban C, Balough BJ. Blunt and blast head trauma: different entities. Int Tinnitus J. 2009;15(2):115-118.

Hoffman JM, Ehde DM, Dikmen S, et al. Telephone-delivered cognitive behavioral therapy for veterans with chronic pain following traumatic brain injury: Rationale and study protocol for a randomized controlled trial study. Contemp Clin Trials. 2019;76:112-119.

Khoury S, Benavides R. Pain with traumatic brain injury and psychological disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87(Pt B):224-233.

Kjeldgaard D, Forchhammer H, Jensen R. Cognitive, emotional and somatic symptoms among patients with chronic posttraumatic headache. A controlled study...The European Headache and Migraine Trust International Congress, London, UK. 20-23 September 2012. J Headache Pain. 2013;14:1-1.

Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain, behavior, and immunity. 2012;26(8):1191-1201.

Malozzi SL. Predicting clinical outcomes in OEF/OIF/OND veterans with the polytrauma clinical triad. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2019;80(2-B(E)):No-Specified.

Mehalick ML, Glueck AC. Examining the relationship and clinical management between traumatic brain injury and pain in military and civilian populations. Brain Inj. 2018;32(11):1307-1314.

Metti A. Post-traumatic vs non-traumatic headaches: a phenotypic analysis. Neurology. 2018;90(15).

Nassif TH. Examining the effectiveness of mindfulness meditation for chronic pain management in combat Veterans with traumatic brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2014;75(3-B(E)):No-Specified.

NCT00862095. Medical Therapies for Chronic Post-Traumatic Headaches. A Randomized Controlled Trial of Medical Therapies for Chronic Post-Traumatic Headaches. 2009.

NCT01306968. Hyperbaric Oxygen Therapy (HBO2) for Persistent Post-concussive Symptoms After Mild Traumatic Brain Injury (mTBI). In. Research USAM, Materiel Command Y, trans2011.

NCT01611194. mTBI Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms. In. Research USAM, Materiel Command Y, trans2012.

O'Connor KL. Concussion among military service academy members: Identifying risk factors, recovery trajectories, and the role of mental health. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;79(12-B(E)):No-Specified.

Ruff RL, Riechers RG, Ruff SS. Relationships between mild traumatic brain injury sustained in combat and post-traumatic stress disorder. F1000 Med Rep. 2010;2:64.

Saper RB, Lemaster CM, Elwy AR, et al. Yoga versus education for Veterans with chronic low back pain: study protocol for a randomized controlled trial. Trials. 2016;17(1):224.

Tang V, Warden J, Cullen N, Rutledge E. Topiramate in traumatic brain injury: Adverse effects on cognitive function. The Journal of Head Trauma Rehabilitation. 2007;22(6):409-410.

Tepper D. Post-traumatic headache in veterans. Headache. 2013;53(5):875-876.

Theeler B, Lucas S, Riechers RG, 2nd, Ruff RL. Post-traumatic headaches in civilians and military personnel: a comparative, clinical review. Headache. 2013;53(6):881-900.

Wortman K. Personality and executive functioning in male veterans with mild traumatic brain injury. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;79(1-B(E)):No-Specified.

Zhang K, Jiang W, Ma T, Wu H. Comparison of early and late decompressive craniectomy on the long-term outcome in patients with moderate and severe traumatic brain injury: A meta-analysis. Br J Neurosurg. 2016;30(2):251-257.

Excluded population

Adams RS, Larson MJ, Meerwijk EL, Williams TV, Harris AHS. Postdeployment Polytrauma Diagnoses Among Soldiers and Veterans Using the Veterans Health Affairs Polytrauma System of Care and Receipt of Opioids, Nonpharmacologic, and Mental Health Treatments. J Head Trauma Rehabil. 2019;34(3):167-175.

Afari N, Pittman J, Floto E, et al. Differential impact of combat on postdeployment symptoms in female and male veterans of Iraq and Afghanistan. Mil Med. 2015;180(3):296-303.

Arbisi PA, Polusny MA, Erbes CR, Thuras P, Reddy MK. The Minnesota Multiphasic Personality Inventory-2 Restructured Form in National Guard soldiers screening positive for posttraumatic stress disorder and mild traumatic brain injury. Psychol Assess. 2011;23(1):203-214.

Avallone KM, Smith ER, Ma S, et al. PTSD as a Mediator in the Relationship Between Post-Concussive Symptoms and Pain Among OEF/OIF/OND Veterans. Mil Med. 2019;184(1-2):e118-e123.

Balba NM, Elliott JE, Weymann KB, et al. Increased Sleep Disturbances and Pain in Veterans with Comorbid Traumatic Brain Injury and Posttraumatic Stress Disorder. J Clin Sleep Med. 2018;14(11):1865-1878.

Bertenthal D, Yaffe K, Barnes DE, et al. Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain? Brain Inj. 2018;32(10):1188-1196.

Blakey SM, Wagner HR, Naylor J, et al. Chronic Pain, TBI, and PTSD in Military Veterans: A Link to Suicidal Ideation and Violent Impulses? J Pain. 2018;19(7):797-806.

Bomyea J, Lang AJ, Delano-Wood L, et al. Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans. Headache. 2016;56(4):699-710.

Bryan CJ, Hernandez AM. Predictors of post-traumatic headache severity among deployed military personnel. Headache. 2011;51(6):945-953.

Bushnik T, Englander J, Wright J. The experience of fatigue in the first 2 years after moderate-to-severe traumatic brain injury: a preliminary report. J Head Trauma Rehabil. 2008;23(1):17-24.

Carlozzi NE, Kisala PA, Boulton AJ, et al. Measuring Pain in TBI: Development of the TBI-QOL Pain Interference Item Bank and Short Form. Arch Phys Med Rehabil. 2020;101(1):11-19.

Carlson KF, Taylor BC, Hagel EM, Cutting A, Kerns R, Sayer NA. Headache diagnoses among Iraq and Afghanistan war veterans enrolled in VA: a gender comparison. Headache. 2013;53(10):1573-1582.

Cifu DX, Taylor BC, Carne WF, et al. Traumatic brain injury, posttraumatic stress disorder, and pain diagnoses in OIF/OEF/OND Veterans. J Rehabil Res Dev. 2013;50(9):1169-1176.

Cohen SP, Plunkett AR, Wilkinson I, et al. Headaches during war: analysis of presentation, treatment, and factors associated with outcome. Cephalalgia. 2012;32(2):94-108.

Combs MA, Critchfield EA, Soble JR. Relax while you rehabilitate: A pilot study integrating a novel, yoga-based mindfulness group intervention into a residential military brain injury rehabilitation program. Rehabil Psychol. 2018;63(2):182-193.

Copeland LA, Finley EP, Bollinger MJ, Amuan ME, Pugh MJ. Comorbidity Correlates of Death Among New Veterans of Iraq and Afghanistan Deployment. Med Care. 2016;54(12):1078-1081.

Davis L, Hanson B, Gilliam S. Pilot study of the effects of mixed light touch manual therapies on active duty soldiers with chronic post-traumatic stress disorder and injury to the head. J Bodywork Mov Ther. 2016;20(1):42-51.

Denby E, Murphy D, Busuttil W, Sakel M, Wilkinson D. Neuropsychiatric Outcomes in UK Military Veterans with Mild Traumatic Brain Injury and Vestibular Dysfunction. J Head Trauma Rehabil. 2020;35(1):57-65.

Detweiler MB, Arif S, Candelario J, et al. Salem VAMC-U.S. Army Fort Bragg Warrior Transition Clinic telepsychiatry collaboration: 12-month operation clinical perspective. Telemed J E Health. 2012;18(2):81-86.

Eagle SR, Kontos AP, Mi QI, et al. Shared Neuromuscular Performance Traits in Military Personnel with Prior Concussion. Med Sci Sports Exerc. 2019;51(8):1619-1625.

Elbogen EB, Alsobrooks A, Battles S, et al. Mobile Neurofeedback for Pain Management in Veterans with TBI and PTSD. Pain Med. 2019;07:07.

Elnitsky CA, Blevins C, Findlow JW, Alverio T, Wiese D. Student Veterans Reintegrating from the Military to the University With Traumatic Injuries: How Does Service Use Relate to Health Status? Arch Phys Med Rehabil. 2018;99(2S):S58-S64.

Epstein EL, Martindale SL, Va Mid-Atlantic Mirecc W, Miskey HM. Posttraumatic stress disorder and traumatic brain Injury: Sex differences in veterans. Psychiatry Research. 2019;274:105-111.

Eskridge SL, Macera CA, Galarneau MR, et al. Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. J Neurotrauma. 2013;30(16):1391-1397.

Finkel AG, Yerry JA, Klaric JS, Ivins BJ, Scher A, Choi YS. Headache in military service members with a history of mild traumatic brain injury: A cohort study of diagnosis and classification. Cephalalgia. 2017;37(6):548-559.

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.

Fonda JR, Gradus JL, Brogly SB, McGlinchey RE, Milberg WP, Fredman L. Traumatic Brain Injury and Opioid Overdose Among Post-9/11 Veterans with Long-Term Opioid Treatment of Chronic Pain. J Head Trauma Rehabil. 2019;08:08.

Golub A, Bennett AS. Prescription opioid initiation, correlates, and consequences among a sample of OEF/OIF military personnel. Subst Use Misuse. 2013;48(10):811-820.

Harch PG, Andrews SR, Fogarty EF, Lucarini J, Van Meter KW. Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder. Medical Gas Research. 2017;7(3):156-174.

Hershaw JN, Hill-Pearson CA, Arango JI, Souvignier CAR, Pazdan CRM. Semi-Automated Neurofeedback Therapy for Persistent Postconcussive Symptoms in a Military Clinical Setting: A Feasibility Study. Mil Med. 2019;11:11.

Higgins DM, Kerns RD, Brandt CA, et al. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/operation New Dawn veterans. Pain Med. 2014;15(5):782-790.

Higgins DM. Internet-based Pain Self-management for Veterans: Feasibility and Preliminary Efficacy of the Pain EASE Program. In.

Hoffman SN, Herbert MS, Crocker LD, et al. The Role of Pain Catastrophizing in Cognitive Functioning Among Veterans with a History of Mild Traumatic Brain Injury. J Head Trauma Rehabil. 2019;34(4):E61-E66.

Howard L, Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Symptoms of Autonomic Dysfunction Among Those with Persistent Posttraumatic Headache Attributed to Mild Traumatic Brain Injury: A Comparison to Migraine and Healthy Controls. Headache. 2018;58(9):1397-1407.

Hudson TJ, Painter JT, Gressler LE, et al. Factors Associated with Opioid Initiation in OEF/OIF/OND Veterans with Traumatic Brain Injury. Pain Med. 2018;19(4):774-787.

Hudson TJ, Painter JT, Martin BC, et al. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. Pain. 2017;158(6):1039-1045.

Jaramillo CA, Cooper DB, Wang CP, et al. Subgroups of US IRAQ and Afghanistan veterans: associations with traumatic brain injury and mental health conditions. Brain Imaging Behav. 2015;9(3):445-455.

Jaramillo CA, Eapen BC, McGeary CA, et al. A cohort study examining headaches among veterans of Iraq and Afghanistan wars: Associations with traumatic brain injury, PTSD, and depression. Headache. 2016;56(3):528-539.

Johansson B, Wentzel AP, Andréll P, Mannheimer C, Rönnbäck L. Methylphenidate reduces mental fatigue and improves processing speed in persons suffered a traumatic brain injury. Brain Inj. 2015;29(6):758-765.

Johnson SS, Levesque DA, Broderick LE, Bailey DG, Kerns RD. Pain Self-Management for Veterans: Development and Pilot Test of a Stage-Based Mobile-Optimized Intervention. JMIR Med Inform. 2017;5(4):e40.

Jonas WB, Bellanti DM, Paat CF, et al. A Randomized Exploratory Study to Evaluate Two Acupuncture Methods for the Treatment of Headaches Associated with Traumatic Brain Injury. Med Acupunct. 2016;28(3):113-130.

Jouzdani SR, Ebrahimi A, Rezaee M, Shishegar M, Tavallaii A, Kaka G. Characteristics of posttraumatic headache following mild traumatic brain injury in military personnel in Iran. Environ. 2014;19(6):422-428.

King PR, Beehler GP, Wade MJ. Self-Reported Pain and Pain Management Strategies Among Veterans with Traumatic Brain Injury: A Pilot Study. Mil Med. 2015;180(8):863-868.

Kjeldgaard Nielsen D FHTTWJRH. EHMTI-0162. Cognitive behavioural treatment for the chronic posttraumatic headache patient: a randomised controlled trial. Journal of headache and pain. 2014;15.

Lang KP, Veazey-Morris K, Andrasik F. Exploring the role of insomnia in the relation between PTSD and pain in veterans with polytrauma injuries. J Head Trauma Rehabil. 2014;29(1):44-53.

Lee CJ, Felix ER, Levitt RC, et al. Traumatic brain injury, dry eye and comorbid pain diagnoses in US veterans. Br J Ophthalmol. 2018;102(5):667-673.

Losoi H, Silverberg ND, Waljas M, et al. Resilience Is Associated with Outcome from Mild Traumatic Brain Injury. J Neurotrauma. 2015;32(13):942-949.

Mahmood S, Al-Thani H, El-Menyar A, et al. Tramadol in traumatic brain injury: Should we continue to use it? Journal of Anaesthesiology Clinical Pharmacology. 2015;31(3):344-348.

Martindale SL, Epstein EL, Taber KH, Workgroup VAM-AM, Rowland JA. Behavioral and Health Outcomes Associated with Deployment and Nondeployment Acquisition of Traumatic Brain Injury in Iraq and Afghanistan Veterans. Arch Phys Med Rehabil. 2018;99(12):2485-2495.

Miller RS, Weaver LK, Bahraini N, et al. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. JAMA Intern Med. 2015;175(1):43-52.

Moeller DR, Duffey JM, Goolsby AM, Gallimore JT. Use of a Removable Mandibular Neuroprosthesis for the Reduction of Posttraumatic Stress Disorder (PTSD) and Mild Traumatic Brain Injury/PTSD/Associated Nightmares, Headaches, and Sleep Disturbances. J Spec Oper Med. 2014;14(3):64-73.

Moriarty H, Winter L, Robinson K, et al. Exploration of Individual and Family Factors Related to Community Reintegration in Veterans with Traumatic Brain Injury. Journal of the American Psychiatric Nurses Association. 2015;21(3):195-211.

Mortera MH, Kinirons SA, Simantov J, Klingbeil H. Long-Term Neurobehavioral Symptoms and Return to Productivity in Operation Enduring Freedom/Operation Iraqi Freedom Veterans with and Without Traumatic Brain Injury. Arch Phys Med Rehabil. 2018;99(2S):S50-S57.

Norris JN, Smith S, Harris E, Labrie DW, Ahlers ST. Characterization of acute stress reaction following an IED blast-related mild traumatic brain injury. Brain Inj. 2015;29(7-8):898-904.

Paltsev AI, Torgashov MN, Voronova YS, Bayandina EV, Lunyakina SB. Role of combat stress in the formation of chronic pain syndrome in combatants and its treatment with pantogam active. Neuroscience and Behavioral Physiology. 2011;41(8):878-882.

Phillips KM, Clark ME, Gironda RJ, et al. Pain and psychiatric comorbidities among two groups of Iraq and Afghanistan era Veterans. J Rehabil Res Dev. 2016;53(4):413-432.

Pugh MJ, Finley EP, Wang CP, et al. A retrospective cohort study of comorbidity trajectories associated with traumatic brain injury in veterans of the Iraq and Afghanistan wars. Brain Inj. 2016;30(12):1481-1490.

Ribeiro CJN, Araujo ACS, Brito SB, et al. Pain assessment of traumatic brain injury victims using the Brazilian version of the Behavioral Pain Scale. Revista Brasileira de Terapia Intensiva. 2018;30(1):42-49.

Rosenthal JF, Erickson JC. Post-traumatic stress disorder in U.S. soldiers with post-traumatic headache. Headache. 2013;53(10):1564-1572.

Sayer NA, Cifu DX, McNamee S, et al. Rehabilitation needs of combat-injured service members admitted to the VA Polytrauma Rehabilitation Centers: the role of PM&R in the care of wounded warriors. Pm R. 2009;1(1):23-28.

Scott BR, Uomoto JM, Barry ES. Impact of Pre-Existing Migraine and Other Co-Morbid or Co-Occurring Conditions on Presentation and Clinical Course Following Deployment-Related Concussion. Headache. 2020;03:03.

Seal KH, Bertenthal D, Barnes DE, et al. Traumatic Brain Injury and Receipt of Prescription Opioid Therapy for Chronic Pain in Iraq and Afghanistan Veterans: Do Clinical Practice Guidelines Matter? J Pain. 2018;19(8):931-941.

Shah A, Ayala M, Capra G, Fox D, Hoffer M. Otologic assessment of blast and nonblast injury in returning Middle East-deployed service members. Laryngoscope. 2014;124(1):272-277.

Shan K, Cao W, Yuan Y, et al. Use of the critical-care pain observation tool and the bispectral index for the detection of pain in brain-injured patients undergoing mechanical ventilation: A STROBE-compliant observational study. Medicine (Baltimore). 2018;97(22):e10985-e10985.

Sheng T, Fairchild JK, Kong JY, et al. The influence of physical and mental health symptoms on Veterans' functional health status. J Rehabil Res Dev. 2016;53(6):781-796.

Stilling Jm PEMLJGLSWMAFDSPMODCT. Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. J Neurotrauma. 2019.

Strigo IA, Spadoni AD, Inslicht SS, Simmons AN. Repeated Exposure to Experimental Pain Differentiates Combat Traumatic Brain Injury with and without Post-Traumatic Stress Disorder. J Neurotrauma. 2018;35(2):297-307.

Strigo IA, Spadoni AD, Lohr J, Simmons AN. Too hard to control: compromised pain anticipation and modulation in mild traumatic brain injury. Transl Psychiatry. 2014;4:e340.

Tan G, Fink B, Dao TK, et al. Associations among pain, PTSD, mTBI, and heart rate variability in veterans of Operation Enduring and Iraqi Freedom: a pilot study. Pain Med. 2009;10(7):1237-1245.

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.

Terrio H, Brenner LA, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. J Head Trauma Rehabil. 2009;24(1):14-23.

Theeler BJ, Erickson JC. Mild head trauma and chronic headaches in returning US soldiers. Headache. 2009;49(4):529-534.

Tschiffely AE, Haque A, Haran FJ, et al. Recovery from Mild Traumatic Brain Injury Following Uncomplicated Mounted and Dismounted Blast: A Natural History Approach. Mil Med. 2018;183(3-4):e140-e147.

Van Pelt KL, Allred D, Cameron KL, et al. A cohort study to identify and evaluate concussion risk factors across multiple injury settings: findings from the CARE Consortium. Inj Epidemiol. 2019;6(1):1.

Vanderploeg RD, Belanger HG, Horner RD, et al. Health outcomes associated with military deployment: mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. Arch Phys Med Rehabil. 2012;93(11):1887-1895.

Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. Arch Phys Med Rehabil. 2005;86(9):1793-1800.

Weaver LK, Wilson SH, Lindblad AS, et al. Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. Undersea Hyperb Med. 2018;45(2):129-156.

Williams KA, Lawson RM, Perurena OH, Coppin JD. Management of Chronic Migraine and Occipital Neuralgia in Post 9/11 Combat Veterans. Mil Med. 2019;184(7-8):e207-e211.

Winter L, Moriarty H, Robinson K. Employment Status Among U.S. Military Veterans with Traumatic Brain Injury: Mediation Analyses and the Goal of Tertiary Prevention. Front Neurol. 2019;10:190.

Winter L, Moriarty HJ, Robinson K, et al. Efficacy and acceptability of a home-based, family-inclusive intervention for veterans with TBI: A randomized controlled trial. Brain Inj. 2016;30(4):373-387.

Wojtowicz M, Silverberg ND, Bui E, Zafonte R, Simon N, Iverson GL. Psychiatric Comorbidity and Psychosocial Problems Among Treatment-Seeking Veterans with a History o

Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma. 2012;29(17):2606-2612.

No outcome of interest

Aase DM, Babione JM, Proescher E, et al. Impact of PTSD on post-concussive symptoms, neuropsychological functioning, and pain in post-9/11 veterans with mild traumatic brain injury. Psychiatry Research. 2018;268:460-466.

Armed Forces Health Surveillance C. Incident diagnoses of common symptoms ("sequelae") following traumatic brain injury, active component, U.S. Armed Forces, 2000-2012. MSMR. 2013;20(6):9-13.

Betthauser LM, Brenner LA, Cole W, Scher AI, Schwab K, Ivins BJ. A Clinical Evidence-Based Approach to Examine the Effects of mTBI and PTSD Symptoms on ANAM Performance in Recently Deployed Active Duty Soldiers: Results from the Warrior Strong Study. J Head Trauma Rehabil. 2018;33(2):91-100.

Cook AJ, Meyer EC, Evans LD, et al. Chronic pain acceptance incrementally predicts disability in polytrauma-exposed veterans at baseline and 1-year follow-up. Behav Res Ther. 2015;73:25-32.

Cooper DB, Chau PM, Armistead-Jehle P, et al. Relationship between mechanism of injury and neurocognitive functioning in OEF/OIF service members with mild traumatic brain injuries. Mil Med. 2012;177(10):1157-1160.

Finkel AG, Ivins BJ, Yerry JA, Klaric JS, Scher A, Sammy Choi Y. Which Matters More? A Retrospective Cohort Study of Headache Characteristics and Diagnosis Type in Soldiers with mTBI/Concussion. Headache. 2017;57(5):719-728.

Finkel AG, Klaric JS, Yerry JA, Choi YS. Staying in service with posttraumatic headache: A retrospective cohort study of patient outcome. Neurology. 2017;89(11):1186-1194.

Finkel AG, Yerry J, Scher A, Choi YS. Headaches in soldiers with mild traumatic brain injury: findings and phenomenologic descriptions. Headache. 2012;52(6):957-965.

Kanefsky R, Motamedi V, Mithani S, Mysliwiec V, Gill JM, Pattinson CL. Mild traumatic brain injuries with loss of consciousness are associated with increased inflammation and pain in military personnel. Psychiatry Research. 2019;279:34-39.

Klaric JS, Forbes LL, Finkel AG. Painful Craniofacial/Cervical Surface Area and Continuous Headache After Military Concussion: A Morphometric Retrospective Cohort Study. Headache. 2018;58(9):1457-1464.

Kozminski M. Combat-related posttraumatic headache: diagnosis, mechanisms of injury, and challenges to treatment. J Am Osteopath Assoc. 2010;110(9):514-519.

Lindquist LK, Love HC, Elbogen EB. Traumatic Brain Injury in Iraq and Afghanistan Veterans: New Results from a National Random Sample Study. J Neuropsychiatry Clin Neurosci. 2017;29(3):254-259.

Mac Donald CL, Johnson AM, Wierzechowski L, et al. Prospectively assessed clinical outcomes in concussive blast vs nonblast traumatic brain injury among evacuated US military personnel. JAMA Neurol. 2014;71(8):994-1002.

Merritt VC, Jurick SM, Crocker LD, et al. Associations Between Multiple Remote Mild TBIs and Objective Neuropsychological Functioning and Subjective Symptoms in Combat-Exposed Veterans. Arch Clin Neuropsychol. 2020;02:02.

Romesser J, Shen S, Reblin M, et al. A preliminary study of the effect of a diagnosis of concussion on PTSD symptoms and other psychiatric variables at the time of treatment seeking among veterans. Mil Med. 2011;176(3):246-252.

Seidl JN, Pastorek NJ, Lillie R, et al. Factors related to satisfaction with life in veterans with mild traumatic brain injury. Rehabil Psychol. 2015;60(4):335-343.

Song K, Wang CP, McGeary DD, et al. Five-year Pain Intensity and Treatment Trajectories of Post-9/11 Veterans with Mild Traumatic Brain Injury. J Pain. 2020;22:22.

Stewart-Willis JJ, Heyanka D, Proctor-Weber Z, England H, Bruhns M. Premorbid IQ Predicts Postconcussive Symptoms in OEF/OIF/OND Veterans with mTBI. Arch Clin Neuropsychol. 2018;33(2):206-215.

Stojanovic MP, Fonda J, Fortier CB, et al. Influence of Mild Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD) on Pain Intensity Levels in OEF/OIF/OND Veterans. Pain Med. 2016;17(11):2017-2025.

Stratton KJ, Hawn SE, Amstadter AB, Cifu DX, Walker WC. Correlates of pain symptoms among Iraq and Afghanistan military personnel following combat-related blast exposure. J Rehabil Res Dev. 2014;51(8):1189-1202.

Swan AA, Amuan ME, Morissette SB, et al. Long-term physical and mental health outcomes associated with traumatic brain injury severity in post-9/11 veterans: A retrospective cohort study. Brain Inj. 2018;32(13-14):1637-1650.

Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. Headache. 2010;50(8):1262-1272.

Walker WC, Franke LM, Sima AP, Cifu DX. Symptom Trajectories After Military Blast Exposure and the Influence of Mild Traumatic Brain Injury. J Head Trauma Rehabil. 2017;32(3):E16-E26.

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.

Wu E, Graham DP. Association of Chronic Pain and Community Integration of Returning Veterans with and Without Traumatic Brain Injury. J Head Trauma Rehabil. 2016;31(1):E1-12.

Excluded study design

Baker VB, Eliasen KM, Hack NK. Lifestyle modifications as therapy for medication refractory post-traumatic headache (PTHA) in the military population of Okinawa. J Headache Pain. 2018;19(1):113.

Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: an observational study. Headache. 2011;51(6):932-944.

Hoot MR, Khokhar B, Walker WC. Self-report Pain Scale Reliability in Veterans and Service Members with Traumatic Brain Injuries Undergoing Inpatient Rehabilitation. Mil Med. 2019;09:09.

Janak JC, Cooper DB, Bowles AO, et al. Completion of Multidisciplinary Treatment for Persistent Postconcussive Symptoms Is Associated with Reduced Symptom Burden. J Head Trauma Rehabil. 2017;32(1):1-15.

Leung A, Fallah A, Shukla S, et al. rTMS in Alleviating Mild TBI Related Headaches--A Case Series. Pain physician. 2016;19(2):E347-E354.

Ruff RL, Riechers RG, 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. J Rehabil Res Dev. 2012;49(9):1305-1320.

Ruff RL, Ruff SS, Wang XF. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. J Rehabil Res Dev. 2009;46(9):1071-1084.

Yerry JA, Kuehn D, Finkel AG. Onabotulinum Toxin A for the Treatment of Headache in Service Members with a History of Mild Traumatic Brain Injury: A Cohort Study. Headache: The Journal of Head & Face Pain. 2015;55(3):395-406.

Duplicate publication of included study

Ferdosi H, Schwab KA, Metti A, et al. Trajectory of Postconcussive Symptoms 12 Months After Deployment in Soldiers with and Without Mild Traumatic Brain Injury: Warrior Strong Study. Am J Epidemiol. 2019;188(1):77-86.

Lippa SM, Fonda JR, Fortier CB, et al. Deployment-related psychiatric and behavioral conditions and their association with functional disability in OEF/OIF/OND veterans. J Trauma Stress. 2015;28(1):25-33.

APPENDIX E. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Reviewer Number	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?		
1	Yes	
2	Yes	
3	Yes	
4	Yes	
5	Yes	
6	Yes	
7	Yes	
8	Yes	
9	Yes	
10	Yes	
Is there any indication of bias in our synthesis of the evidence?		
1	No	
2	No	
3	No	
4	No	
5	No	
6	No	
7	Yes - This review had tremendous amount rejection of articles. Would like to see a list of articles that were rejected by a third reviewer, as opposed to those that had 2 reviewers that agreed.	We understand this point. Our search terms were purposely broad to identify all possible papers with data on TBI and pain. This resulted in a large number of irrelevant studies that were excluded upon review of abstracts or full text for reasons such as focusing on moderate/severe rather than mild TBI, or being conducted in civilian samples (i.e., outside of the scope of this review). Inclusion/exclusion determinations were based on dual review and consensus. We now include a table of studies that were excluded after the full text review (Appendix D).
8	No	
9	No	
10	No	
Are there any published or unpublished studies that we may have overlooked?		
1	No	
2	No	
3	Yes - For awareness and potential mention- study of VHA cohort just published: Amy L. Byers, Yixia Li, Deborah E. Barnes, Karen H. Seal, W. John Boscardin & Kristine Yaffe (2020) A national study of TBI and risk of suicide and unintended death by overdose and	Thank you. We have cited this new publication in the Introduction and Discussion sections of the report.

	firearms, Brain Injury, 34:3, 328-334, DOI: 10.1080/02699052.2019.1701708	
4	No	
5	No	
6	No	
7	No	
8	No	
9	No	
10	No	
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report		
1	This is a well-conducted and well-described review. I have only a few minor suggestions.	We appreciate the feedback.
	Page 16: The authors have been appropriately inclusive in their selection criteria for studies of chronic pain and have not applied a strict definition of chronic pain; however, I think it would be helpful to provide a standard definition of chronic pain (e.g., IASP, National Pain Strategy) in the introduction.	Thank you for this suggestion. We have added a definition of chronic pain to the Introduction section of the report.
	Page 58, lines 23-34: I think it is misleading to describe use of ICD-9/10 codes as "comprehensive diagnostic assessment." ICD-9/10 do not include a systematic approach to chronic pain, so studies using these codes typically infer the presence of chronic pain from codes that indicate the presence of a symptom (e.g., low back pain), imaging finding (e.g., disc degeneration), or disease (e.g., osteoarthritis) that may or may not be associated with chronic pain. Perhaps the best way to think about most of these codes is as "diagnoses potentially related to chronic pain." Clinicians often do not code comprehensively, but typically chose codes for reasons related to billing. This could lead to under or over coding. In most cases when chronic pain is present, clinicians have little incentive to add codes for pain-related diagnoses because they add little to the overall complexity of the visit. In some cases, such as when patients have a service-connected condition potentially related to chronic pain, clinicians may code a pain-related diagnosis to spare a patient a copay, even if the condition was briefly discussed and determined not to be bothersome.	Thank you for this information. We agree that ICD diagnosis codes do not necessarily equate to chronic pain and there are circumstances when the use of these codes may increase false positive or false negative rates. We have edited the report to include this as a limitation to the conclusions drawn from studies using ICD codes. Additionally, we have reviewed and edited the report for use of appropriate language, including the suggested "diagnoses potentially related to chronic pain."
2	This reviewer appreciates the efforts put forth to produce this review. Methods are clearly articulated and implemented.	We appreciate this feedback.
	*May be helpful to clarify that the most robust study - Key Question 1 - CTBIE - findings - are for that specific cohort. The fact that those in this group also had the most comprehensive	We agree. We have added additional information about the CTBIE to the Results section, including potential caveats when interpreting findings from these studies.

	eval creates further challenges in terms of interpretation.	
	*The role of co-occurring MH sx could be further integrated throughout. If this is not possible - may be helpful to identify as a limitation.	Though this was outside the scope of Key Question 1, Key Question 2 examined suicide-related outcomes (evidence from 1 study). Key Question 3 examined whether benefits or harms of treatment differed by mental health comorbidities, though due to the small number of studies and participants relevant to this key question, we were unable to generalize about potential impacts of mental health comorbidities. We have noted this as a limitation of our review and recommended it as a future research area in the discussion. We have also included a discussion section highlighting differences in prevalence estimates for individuals with PTSD: “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 diagnoses 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.”
	*In addition, further discussion of multiple pain types and clinical implications would be useful.	We have included a description of pain definitions in the evidence tables to facilitate comparisons across different definitions of pain used in the included studies. Few studies reported the prevalence of participants with multiple pain types; however, where possible, we have added this information to the Results section as well as a description of the clinical implications in the Discussion section.
3	1. P4 (line 46) Consider reporting the higher rates of suicide in Veterans with history of mTBI (beyond non-TBI or all Veterans). Given that suicide is VA's clinician priority, it may be prudent to briefly summarize findings from published, peer-reviewed studies on the prevalence of suicide following TBI. This may serve to highlight it's importance for this	We have added text and references to the Executive Summary identifying the higher rates of mortality, and suicide mortality, among Veterans with a history of mTBI. In the full Introduction section, we have added a paragraph describing the findings from past peer-reviewed studies.

	population in light of the lack of studies that met the ESR's criteria.	
	2. The ESR on mTBI and pain could be stronger by mentioning the contributions of other factors, including prevalent medical/mental health comorbidities to pain/symptom chronicity. Along the same lines, the conclusion could be more compelling from a clinical, research and VHA policy perspective if there was brief mention of the impact of co-existing mTBI and pain on (for example) long-term healthcare utilization, functional outcomes and quality of life.	We agree with this recommendation and have added more information on the consideration of comorbidities in the included studies and the potential interplay of comorbidities with chronic pain among those with mTBI. Similarly, we have included a brief reference to likely healthcare utilization, functional outcomes, and quality of life in this patient population.
	Very interesting to read and informative ESR. Thank you.	We appreciate this feedback.
4	This is a very nice review and summary of the literature. I appreciate the authors grouping of the studies and the fact that the summary results were not overstated. I would like to recommend a paragraph in the executive summary that provides a high level overview of the noted gaps in the literature as this would be helpful for future grant applications to reference. There body of the report could include a short discussion of the gaps in the literature and challenges (lack of consistent use of similar outcome measures, impact of co-morbid MH diagnosis and pain prevalence which is already described on page 64, recommendations to include suicide risk assessment in future studies, and need for treatment studies). Overall very nicely done.	Thank you for this suggestion. We have added a paragraph to the executive summary identifying the gaps and challenges and have now better highlighted this throughout the report, including additional text in the Discussion section.
5	P 2 line 49 figure 2 Insert comment/analytics about the reasons for the wide range of reported prevalence's and how this affects report utility.	We have added text describing the likely reasons for heterogeneity in prevalence estimates as well as the effect on report utility.
6	As expected, this is a critical, comprehensive, unbiased, and important review of the scientific literature regarding co-occurring TBI and pain that identifies both the limited available high quality literature and the lack of clinically important associations. I have no significant recommended edits or additions.	Thank you. We agree this review highlights gaps in the current literature and important next-steps for addressing chronic pain among Veteran and military populations with a history of mTBI.
7	Would like a list of publications that required a tie-breaker vote.	We now include an appendix (Appendix D) with the list of studies excluded after full text review. We used dual review and team consensus to determine study eligibility.
8	This Evidence Synthesis Program review is both timely and significant in light of growing attention to chronic pain as a significant public health and clinical problem, particularly for Veterans and Military Service Members (SMs).	We appreciate this feedback.

	Overall, the report is very well done. Prespecified key questions were addressed appropriately via strong and well-supported review and thoughtful and comprehensive discussion of the findings. Although there are numerous concerns about the reliability and reproducibility of the findings, the authors have generally acknowledged serious limitations of the existing literature and the approach to answering the questions. The methods employed in the search process are state-of-the-art and encourage confidence that the literature relevant to addressing key questions was identified and considered. The description of individual studies identified in the search is a strength of the report. Tables are particularly valuable in capturing key features of individual studies. While the authors' efforts to draw conclusions based on a summary of these findings given the heterogeneity of the studies and their approaches is admirable, summary statements and conclusions based on this review are likely to be less than optimally useful in informing operational partner interests in identifying actionable recommendations for improving the care of Veterans and SMs with co-occurring mTBI and chronic pain.	
	Numerous concerns and recommendations for improving the quality of the report, most of which already acknowledged by the authors, can be cited. In the Executive Summary, care is taken to explicate how "chronic pain" was ascertained. However, the examples don't provide confidence since standard definitions of chronic pain abound, and none would consider pain lasting 30 days as "chronic." I think that inclusion of studies that explicitly including persons with pain for only the past month is a mistake. Surely, most people experiencing a significant TBI will experience acute head pain, and since TBI in this population commonly is associated with polytrauma, that is, injury to other sites, as well, acute pain may occur in sites other than the head and face, as well. Multiple other caveats should be noted, even in the Executive Summary. For example, arthritis can be painful, but for many who have a diagnoses of osteoarthritis, for example, pain may be rare (people with the disease can go long periods without any pain, and even then,	We agree that there are limitations related to broadly defining chronic pain in this manner. Though we include more studies, it is not as clear that all participants met a more conservative definition of chronic pain when the definitions are allowed to vary so greatly. We have attempted to mitigate this concern by providing definitions of chronic pain used in each of the primary studies in the evidence tables. We can also assume that in many cases, when a participant responds that they have had pain for at least 30 days, that the pain lasted longer than that period of time in many cases (i.e., many positive endorsements of this item likely indicate chronic pain, though some cases might possibly reference acute pain lasting just over 30 days). This is particularly likely because many pain assessments were reflective of routine follow-up assessment of pain, not assessments completed at the time of injury (i.e., one can assume that the pain lasted longer than 30 days). Other assumptions such as that a diagnosis of osteoarthritis is associated with chronic

most “flares” are short in duration) and it can certainly not be assumed that people with a diagnosis of arthritis experience chronic pain. Also, the currently accepted nomenclature increasing distinguishes “chronic pain” and “high impact chronic pain.” A note about this potentially important distinction would be helpful.	pain are well supported in the literature, though our description of the chronic pain measures and definitions in each included study enables readers to select and examine only those with a more narrow and specific definition if they so choose. Finally, we mention the distinction between chronic pain and high impact chronic pain in the revised discussion section, though note that most included studies were published prior to this terminology being commonly used.
Realizing that many studies reported on prevalence of headache or migraine as a single group, I’m not sure of the value of this approach given that migraine is understood to be a specific condition that is quite distinct from other headache conditions. In the context of mTBI, this difference may be particularly important.	We agree that these are distinct conditions and have now made edits throughout the report to help distinguish these two types of pain conditions. We have reported data for headache and migraine prevalence separately when the distinct data were reported separately in the primary studies. Of the 23 included studies for Key Question 1, only 1 combined headaches and migraines; 4 reported both outcomes separately, and the remaining 18 reported only headaches with no mention of migraines.
Also, as important is the definition used to define mTBI, so I think this should be added. This is not a minor point, since it could have been expected that an answer to key questions hinges on the operational definition of both mTBI and chronic pain that is applied in the search.	We agree and have added a standard definition of mTBI to the report. We chose to include studies with a range of approaches for operationalizing “mTBI” in order to include all available and relevant data for the Key Questions of interest. Though this means that some studies were included that may have used a broader definition of mTBI than that we cited, we have described these approaches in the evidence tables and considered the definitions and operationalizations in the data synthesis. Readers who are interested in a more specific definition or operationalization of “mTBI” can utilize the evidence tables to examine only the studies using definitions relevant to their questions of interest.
Bottom of page 1 (page 9/94) - Reference to “pain medication” includes “non-analgesics” as example; it is unclear what is meant by a non-analgesic pain medication. The authors probably intended to refer to “non-opioids” such as NSAIDS and/or “co-analgesics” such or anti-depressants or gabapentinoids.” This is not a minor point, since many medications have analgesic properties and are commonly used for purposes other than pain management (even NSAIDs).	We appreciate this point. The original publication provides no additional detail about this category of data and the two publications that reported data from the same parent study did not include a category with this label. We have therefore removed “non-analgesic pain medication” from the findings section of the report.

Be more careful in use of terms such as "directly related to mTBI." (Page 2) How is this term defined? For example, does it mean that the onset was at the same time? Or that there was evidence of trauma to the specific site? Although one might conclude that "headache" could be associated with TBI, that's not necessarily the case, since headache is known to be common in younger persons including an unknown proportion of SMs prior to their military service. And, of course, TBI is often associated with traumatic injury to other body sites, including painful traumatic injuries. Or pain may emerge in the context of prolonged bed rest and/or activity restrictions and other factors, even other treatments, in the context of acute treatment for TBI.	Thank you for bringing this to our attention. We have revised the language in the report to better represent the variety of circumstances in which individuals with mTBI may experience chronic pain (and, in most cases, our inability to distinguish between them).
I'm not sure how valuable Figure ii is. It seems likely that there are many factors that affect prevalence estimates of chronic pain across studies reporting on specific sites, so it doesn't seem helpful to know how estimates vary within pain site and to try to compare them across sites, as implied by presenting the estimates in a single figure.	We have included Figure ii to summarize findings from Key Question 1 and not necessarily to compare prevalence levels across pain conditions. We have retained this Figure because we believe it helps depict the state of the science on pain condition prevalence in Veterans and Servicemembers with mTBI.
The first sentence on page 3 should be referenced and information about the methodology, and a critique of the weaknesses of the study, should be provided. The CTBIE should be described. Is it a clinical exam or self-report measure?	Thank you. We have added a citation to this sentence and provided more context about the study, including the CTBIE.
I note that later in the Summary, a point is made that this measure is completed by treatment-seeking patients. Of course, this fact suggests that the estimates of prevalence of chronic pain in such samples will be highly inflated (if one is interested in true population level estimates). The following sentence about an observational study using VA health record data seems at least as relevant; I'm not sure why the estimates reported in this study are questioned whereas the estimates from the former "best" study are not.	We concur that estimates will be greatly influenced based on whether participants are seeking treatment or part of a general, non-treatment seeking sample. We have edited this section to provide better consistency in our evaluation of study samples. Additionally, we have included this consideration in our risk of bias assessment of the included studies and provided detailed information regarding the samples and inclusion criteria to transparently provide readers with information pertaining to potential sources of bias.
On page 3, the term "pain interference" is introduced and should be defined. How was 'moderate to severe pain" defined? Note that the concept of having pain on half the days in a specific time frame is an accepted way to operationalize "chronic pain" although a minimum three-month period (or six-month) is usually required.	Thank you. We have now defined "pain interference" as well as pain severity levels.
Again, headache and migraine should not be considered as a single "pain type." They are	As noted above, we have now been more careful to distinguish between these two

quite distinct and should not be considered together. Also, note that these diagnoses are known to be poorly identified by clinicians and particularly poorly captured in the electronic record.	distinct conditions in the report. We reported prevalence data for the conditions separately when the data were reported separately in the primary studies. Of the 23 included studies for Key Question 1, only one combined headaches and migraines; 4 reported both outcomes separately, and the remaining 18 reported only headaches with no mention of migraines.
The paragraph beginning with “Five studies” on page 3 is not useful without explication of how medication use was employed to define presence of chronic pain.	Thank you. We have clarified this paragraph and revised other locations in the report where pain medication use is used as a proxy measure for chronic pain.
With regard to KQ1b, etiology is apparently solely defined in terms of history of blast-injury and LOC. Another important factor studied in the literature is whether pain is at the site of traumatic injury, so since TBI often occurs in the context of multiple sites of injury, and since sites of pain other than the face or head are being examined, then whether the onset of pain co-occurred with the mTBI may also be important.	This is an interesting point and one that we would like to include in the report. However, the included studies do not report details on polytraumatic sites of injury or timing of pain onset. We have included this point as a potential limitation of the review findings and a gap in the current literature.
With regard to KQ1c, the issue of pain measurement is critical. As already noted, inferring the presence of chronic pain from ICD or medication use data is fraught with problems. In addition, the population from which study samples were derived is also a critical variable. Prevalence estimates from samples of treatment seeking persons will clearly result in inflated estimates. And although some ICD codes specifically include the word “chronic” in the name of the diagnosis, most potentially painful conditions do not. The report from Goulet et al., 2016 noted that a large proportion of Veterans with musculoskeletal diagnoses such as osteoarthritis reported no pain on the date of the diagnosis. Even more problematic is inferring the presence of chronic pain from health record data on medication fills. Greater clarity in the description of the approaches employed both in the studies and during the review is important to encourage confidence in the results of the review.	We agree with the reviewer on each of these assessments. Per our prior responses, we have added text to the report to clarify the pain assessment methods used in each of the studies and to acknowledge the limitations inherent to these methods. We have also now cited the Goulet et al. 2016 paper in the Discussion section of the report.
The bottom line is that the detailed reporting of the prevalence rates reported in the literature is not particularly relevant given all the apparent differences in the methods across studies from which these estimates were derived. It seems to me that it would be more important to summarize the variations and limitations of the literature rather than presenting estimates that are almost certainly unreliable and not	We understand this recommendation. In the revised report, we have taken care to specify the variations and limitations of the literature and to not make inferences based on disparate study types. Additionally, the referenced conclusion statement has now been moved to an earlier section of the Executive Summary to help highlight this point.

	meaningful. The conclusion in the paragraph on the top of page 4 should be moved to the front of the summary.	
	Although I was a member of the Technical Expert Panel that helped develop the key questions and approach, in retrospect, it seems that the review was likely misguided. Rates of chronic pain are known to be high among Veterans and SMs. A CDC MMWR published in 2017 reported that Veteran status was specifically and uniquely associated with the presence of chronic pain. Other data on Veterans and SMs also encourage similar conclusions. The key question is not whether prevalence rates are high among Veterans and SMs with histories of mTBI, it's whether the rates of chronic pain are higher in this subpopulation than among the general population of Veterans and SMs.	We agree with this sentiment. Although the Key Questions and approach remain the same, we have taken this opportunity to revise the results section for Key Question 1 so that, where available, prevalence estimates of chronic pain are included for those with, versus without, a history of mTBI. We have also added a summary of these findings to the Executive Summary and to the Discussion section.
	Similarly, KQ3 might have been more appropriately specified as whether there is evidence that Veterans and SMs with mTBI are less likely to accrue benefit from commonly delivered interventions for chronic pain. In the absence of answers to these questions, it seems that current policies for universal screening for the presence and intensity of pain, and for suicide risk assessment, should continue, and that Veterans and SMs with histories of mTBI should continue to be offered evidence-based treatments for chronic pain.	Thank you for this feedback. We have added additional information about this important consideration to the discussion of Key Question 3.
9	Line 17 P1: Helpful to include databases searched in the summary as described on P10 Search Strategy.	Thank you. This has been added to the summary.
	Huge variability in the incidence of headaches - 3 - 98%. What could this be attributed to?	We agree. The wide range is likely due to variation in study design, particularly in samples, pain definitions, and pain ascertainment periods. This has been added to the report.
	It is extremely interesting that the analysis started with >2000 pubs but only 31 made the "cut". Are your inclusion/exclusion criteria too stringent? Can you use some of the studies or parts of studies not meeting criteria? There is a paucity of studies in the area and most of these studies are of poor quality.	Our search terms were purposely broad to identify all possible papers with data on mTBI and pain. This resulted in a large number that were excluded upon review of abstracts or full text. Inclusion and exclusion determinations were based on dual review and consensus. We now include an appendix (Appendix D) table of studies that were excluded after the full text review.
10	Page 25 line 22-23 has an incomplete sentence.	Thank you. We have edited this sentence.
	Table 2: Reference 4 also provided prevalence of "other pain". This is other musculoskeletal pain including arthritis. If the mixed definition is	We agree and have added the data from this reference to the "other pain" section.

	the reason for exclusion of this, that makes sense. If the authors think this should be included it could be added to the other pain aspect of Table 5	
	For the study examining suicide, it may be worthwhile to also note that the phenotype that transitioned from relatively healthy to Polytrauma phenotype where chronic pain emerged between year 1 and 5 also had significantly higher odds of suicidal ideation/attempt after the phenotype development period.	Thank you. We have added the Moderately Healthy + Decline phenotype to these findings.