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.

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.

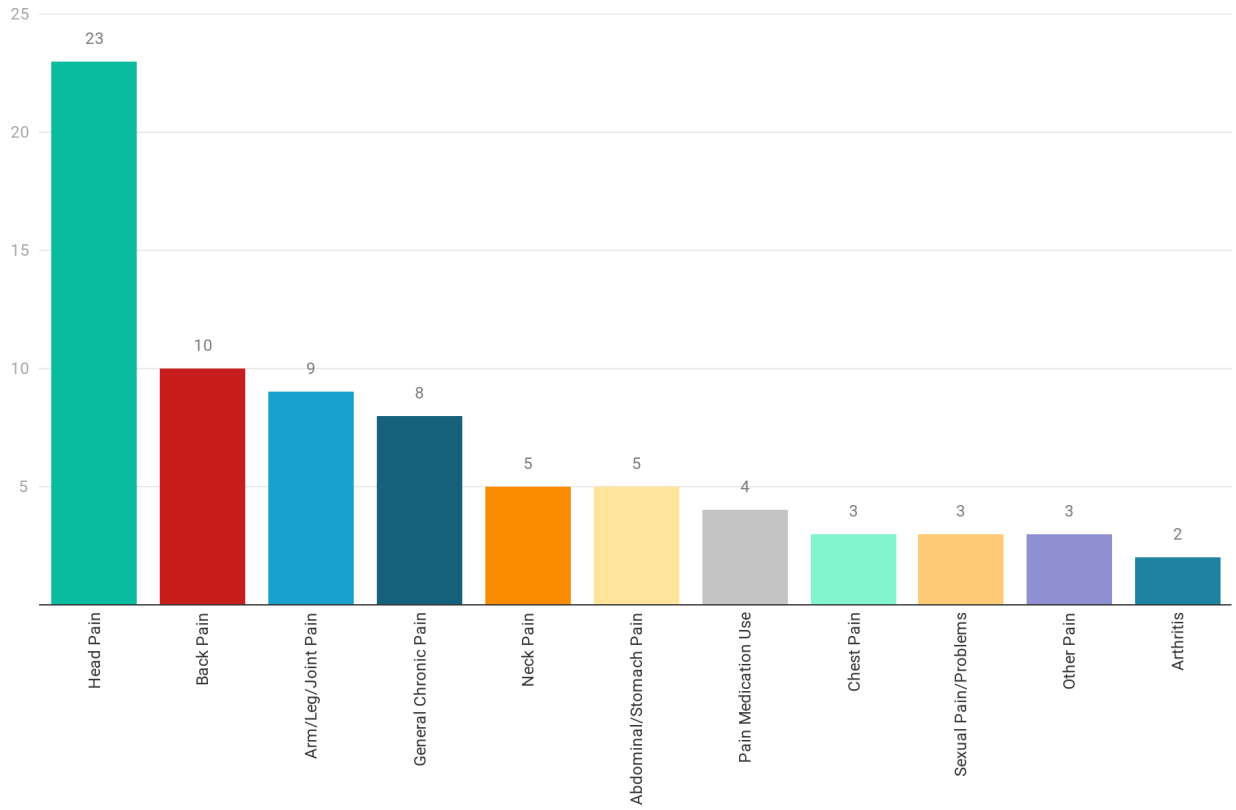
RESULTS

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.

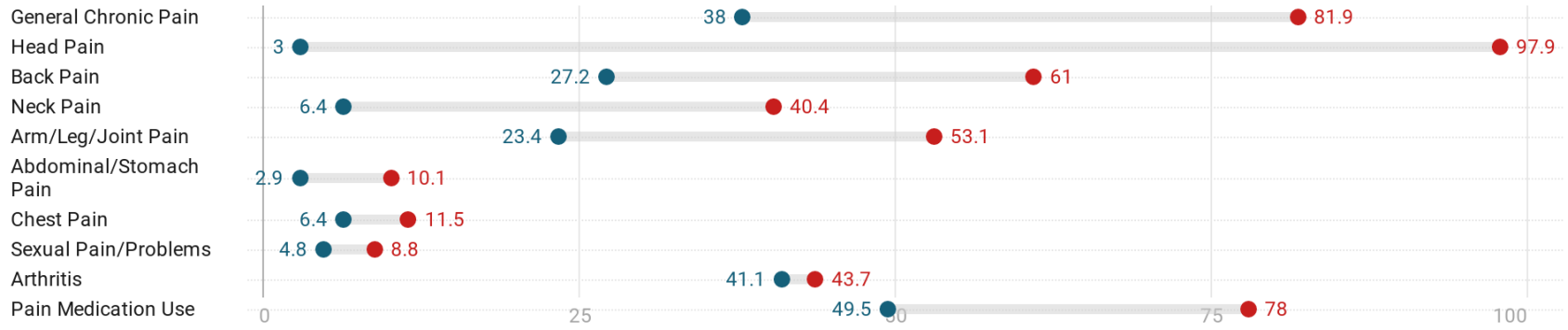
Figure i. Number of studies reporting prevalence of chronic pain in Veterans/Servicemembers with histoy of mTBI, by pain type



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