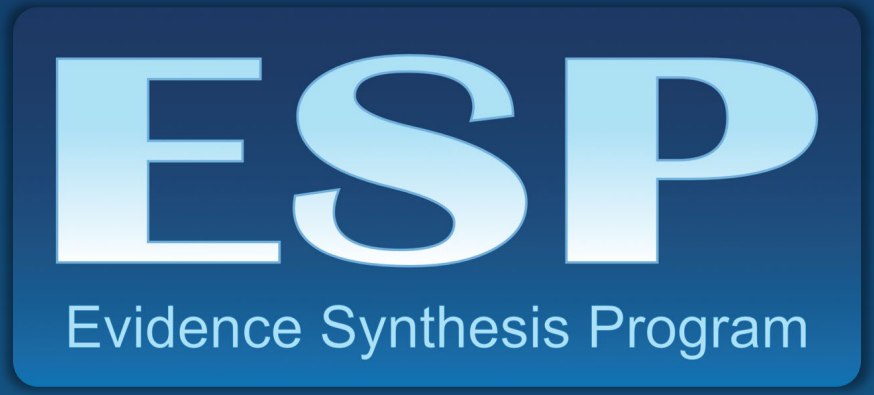

A Systematic Review of Chronic Pain Prevalence and Interventions in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury

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VA Portland Healthcare System

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Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend TEP members; 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 report dissemination.

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Disclosure

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VA Evidence Synthesis Program overview

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- Established in 2007
- Provides tailored, timely, and accurate evidence syntheses of VA-relevant, Veteran-focused healthcare topics. These reports help:
  - Develop clinical policies informed by evidence;
  - Implement effective services and support VA clinical practice guidelines and performance measures; and
  - Set the direction for future research to address gaps in clinical knowledge.
- Three ESP Centers across the US:
  - Directors are VA clinicians, recognized leaders in the field of evidence synthesis, and have close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration
- ESP Coordinating Center in Portland:
  - Manages national program operations and interfaces with stakeholders
  - Produces rapid products to inform more urgent policy and program decisions

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.

ESP Center locations

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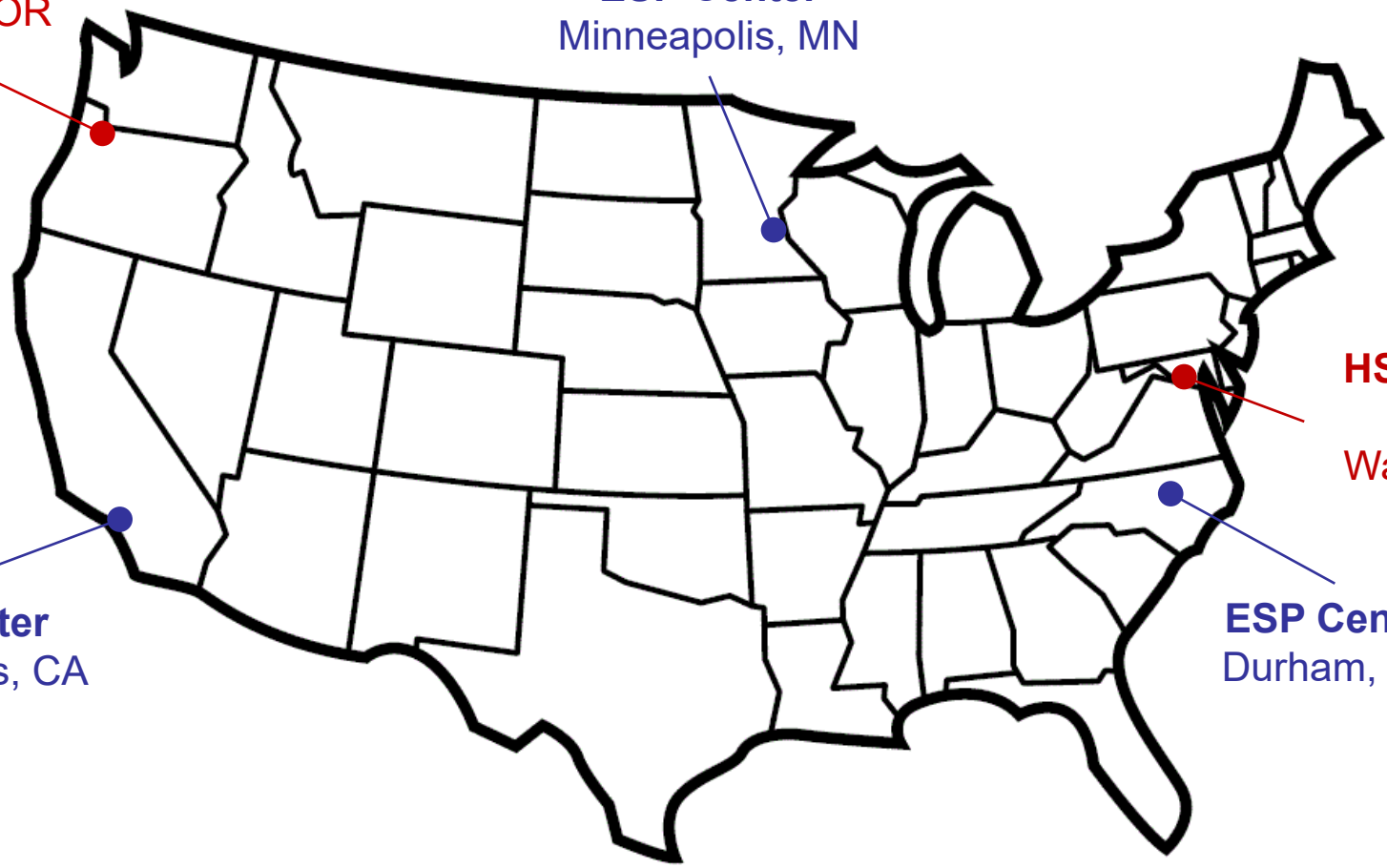

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Chronic Pain in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury: A Systematic Review

Maya E. O'Neil, Kathleen F. Carlson, Haley K. Holmer, Chelsea K. Ayers, Benjamin J. Morasco, Devan Kansagara, Karli Kondo

Full-length report available on ESP website:
http://www.hsrd.research.va.gov/publications/esp/reports.cfm

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Background

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- Approximately 413,000 servicemembers (SMs) have experienced a traumatic brain injury (TBI) since the year 2000
  - Over 80% of those were classified as mild in severity
- Many symptoms associated with mTBI resolve within a few months
  - Up to one-third of individuals who experience an mTBI have a longer and/or more severe symptom course
- Common sequelae and health conditions associated with mTBI include mental health concerns such as posttraumatic stress disorder (PTSD) and depression, cognitive problems, sensory sensitivity, and chronic pain
  - It is unclear whether symptoms attributed to mTBI are due to the mTBI itself or, rather, are health outcomes related to the same exposures (e.g., combat, accident) that led to the mTBI

Aim

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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.

Key questions

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- Key question 1
  - What is the prevalence of chronic pain in US Veterans or Servicemembers with a history of mTBI?
- Key question 2
  - What is the risk of suicide in US Veterans or Servicemembers with chronic pain and a history of mTBI?
- Key question 3
  - What are the benefits and harms of interventions to treat chronic pain in Veterans or Servicemembers with a history of mTBI?

Methods: Search

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- **Search:** Electronic databases including 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
- **Dates:** database inception through February 7, 2020
- **Types of included studies:** 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
  - **Intervention studies:** RCTs and nRCTs of interventions for chronic pain in Veterans or SMs with a history of mTBI from **any country**

Methods: PICOs

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Key Questions:	KQ1	KQ2	KQ3
Population	US Veterans or SMs 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 SMs 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
	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

Methods: Definitions

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- **Chronic Pain:** defined as pain lasting or recurring for more than 3 months
  - Definitions varied across studies
  - Pain not explicitly referred to as acute was considered to be chronic pain and included
  - Proxy definitions were included (e.g., health record diagnosis, analgesic medication use, and conditions associated with chronic pain such as arthritis)
- **Mild TBI:** 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
  - Definitions varied across studies
  - Proxy definitions were included (e.g., health record diagnosis, clinical intake forms) as long as authors reported a clear definition for mTBI differentiated from and excluded moderate/severe TBI

Methods: Data Abstraction

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- **Abstracted Variables: All dual reviewed**
  - Study design, sample size, setting, population characteristics, participant inclusion and exclusion criteria, definitions/operationalizations of key variables, and results
  - **Intervention Studies:** 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

Methods: Quality Assessment

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- **Quality Assessment:**
  - Two reviewers independently assessed the methodological quality of each study using established methods for each study design
  - Cochrane Risk-of-Bias 2.0 criteria for randomized controlled trials
  - Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) for non-randomized intervention studies
  - Adapted the Newcastle-Ottawa Scale for all other study designs

Methods: Strength of Evidence

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- **Strength of Evidence:**
  - Strength of evidence for intervention studies was determined by consensus
  - Used Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers methods
  - Considered study limitations, directness, consistency, precision, and reporting bias as well as supplemental observational study domains of dose-response association, plausible confounding that would decrease the observed effect and strength of association, and applicability
  - Ratings were based on High (very confident that the estimate of effect lies close to the true effect for this outcome), Moderate, Low, and Insufficient (No evidence, unable to estimate an effect, or no confidence in the estimate of effect for this outcome) criteria

Results: Literature Flow Chart

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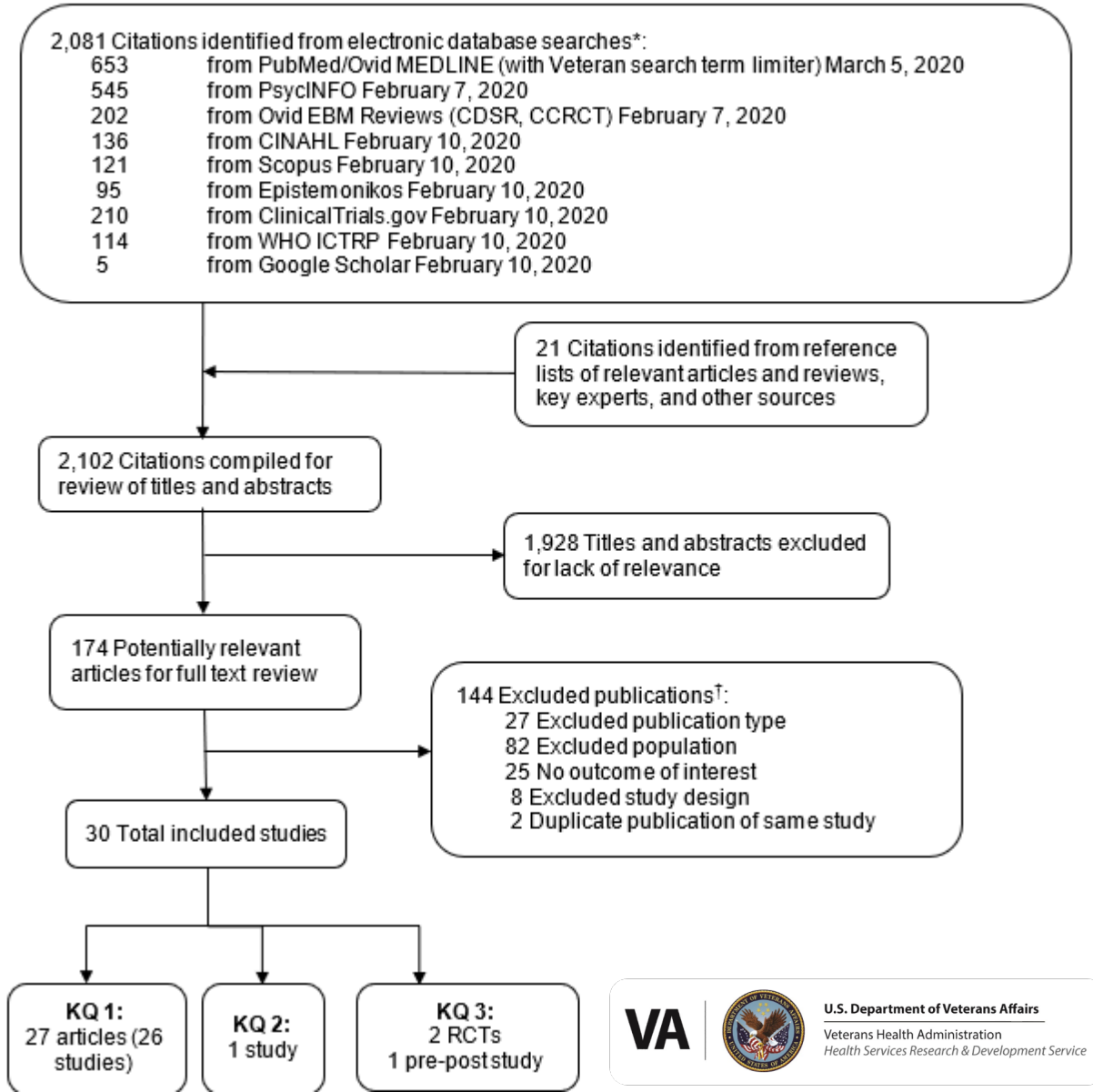
- 2,102 abstracts
- 174 full-text manuscripts
- 30 studies included



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Results: Prevalence of Chronic Pain

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Key Question 1:

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

- This question also addressed prevalence by pain type/location, mTBI etiology (e.g., blast versus other), and methods used to define or measure pain.
- Included any primary study – except case studies/reports – reporting prevalence of chronic pain in this population. (Non-systematic literature reviews and non-human subjects studies were excluded.)
- 27 articles (26 studies) presented chronic pain prevalence data.

Results: Pain Locations

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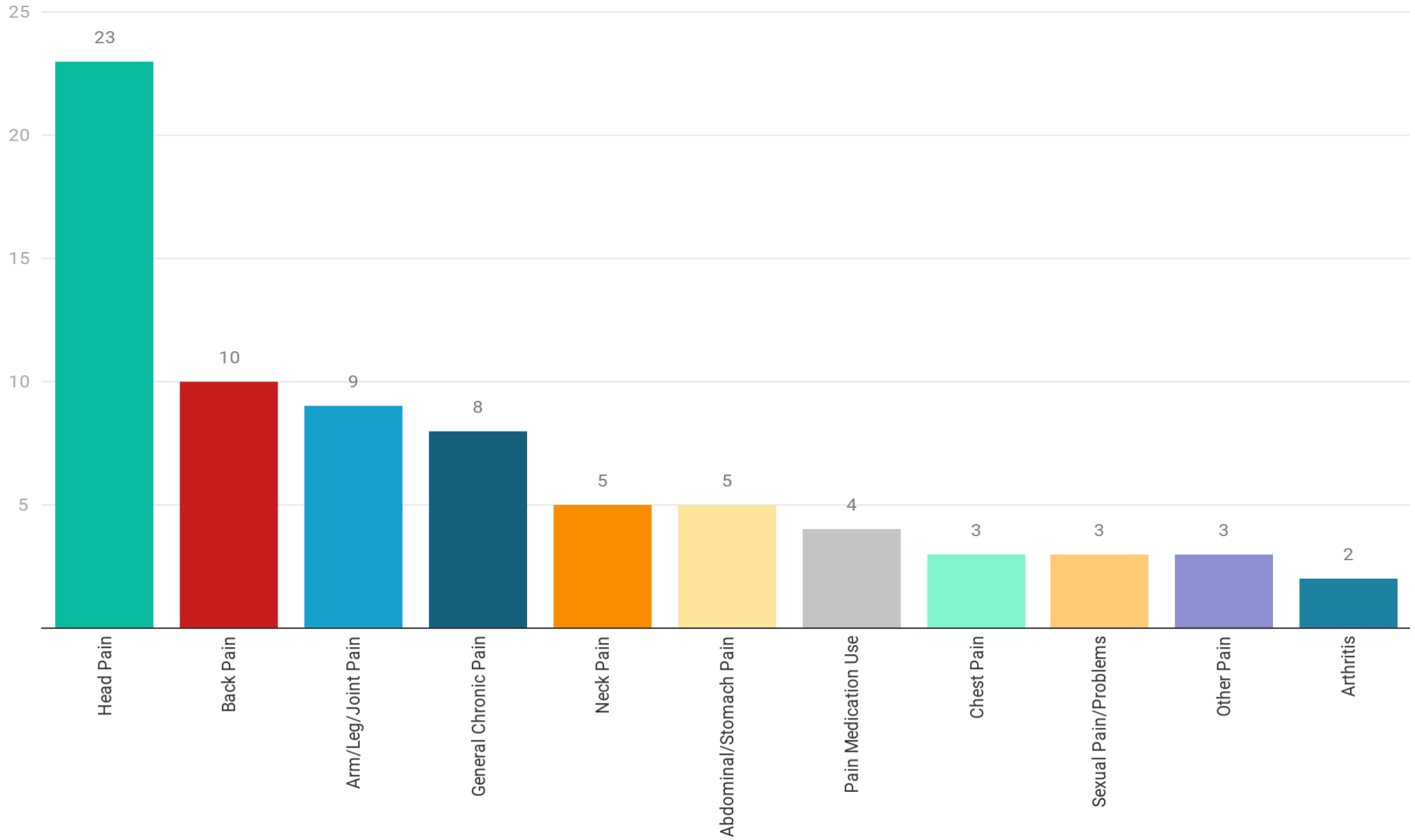
- Among 27 articles:



Results: Ranges of Pain Prevalence

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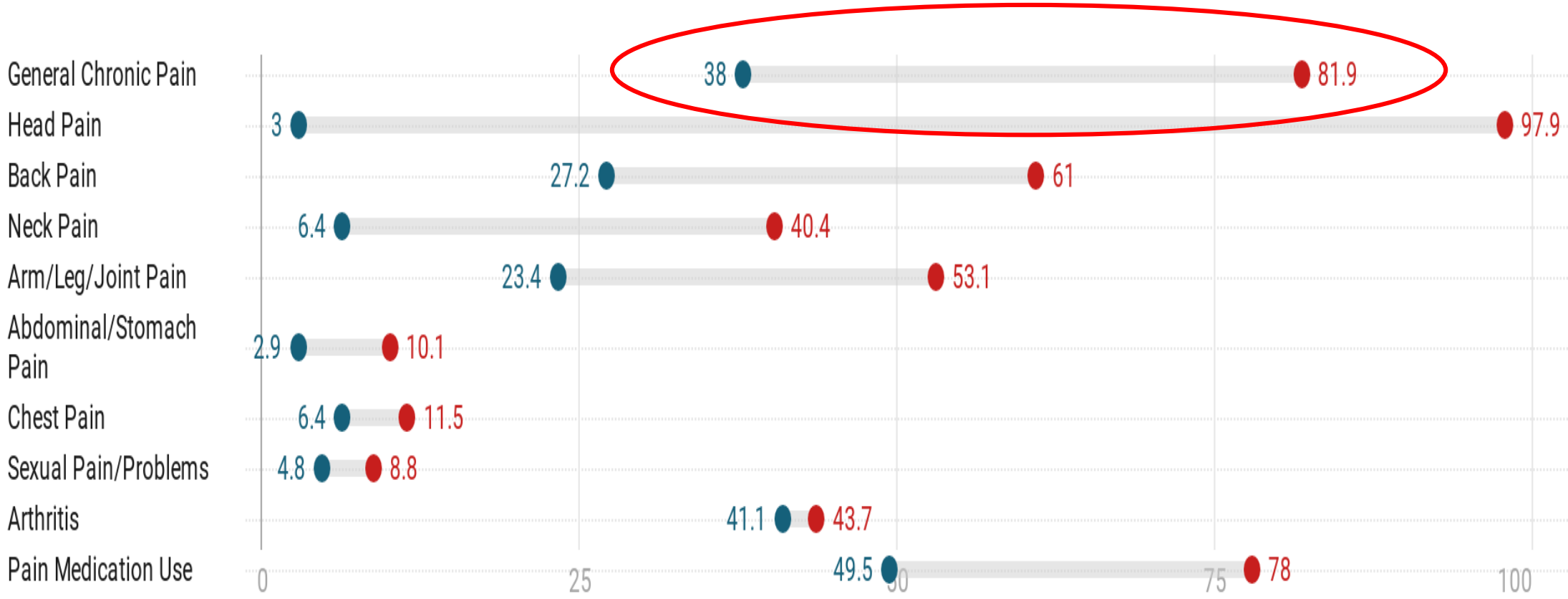

Results: Prevalence of General Chronic Pain

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Study N Design	Study Inclusion	Eligibility	Sample Description	Prevalence
Brickell, 2014 N=167 1 site: WRAMC Dates NR Cohort – prospective.	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.	Bodily pain (other than headache) past month: 6 mos: 78.3% 12 mos: 76.4% 24 mos: 88.9% 36 mos: 78.6% 48 mos: 66.7% 60 mos: 80.0%
Hoot, 2018 N=454 4 CENC sites. Cross-sectional.	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%.	Level of pain intensity or discomfort moderate-to-extreme: 224/378 (59.3%).
King, 2014 N=842 VA VISN 2, Oct 2001-Sept 2011. Cross-sectional.	≥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.	Presence of treated for conditions commonly associated with pain for ≥3 months: 320/421 (76.0%).

Results: Prevalence of General Chronic Pain

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Study N Design	Study Inclusion	Eligibility	Sample Description	Prevalence
Kulas, 2018 N=164,884 Muti-site: National data (VA EHR) Cohort – retrospective.	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: Age: 32.8 (8.3) yrs. Female: 5%. mTBI no PTSD: Age: 32.1 (8.6) yrs. Female: 8%.	Presence: Y/N of ICD diagnosis code for pain in EHR: mTBI+PTSD: 81.5% mTBI no PTSD: 70.8%
Lew, 2009 N=340 Single-site: VA level 2 polytrauma clinic. Cross-sectional.	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	Presence of chronic pain defined as persisting reports of pain in ≥1 body part for ≥3 months after onset: Total mTBI: 81.9%.
Powell, 2015 N=171 Boston VA Cross-sectional.	Clinical interview by doctoral-level psychologist (reviewed by 3+ doctoral-level psychologists for consensus diagnosis).	Post-9/11 Veterans.	Age: 33.3 (8.6) yrs. Female: 13.5%.	Presence of chronic pain: 65/171 (38.0%).

Results: Prevalence of General Chronic Pain

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Study N Design	Study Inclusion	Eligibility	Sample Description	Prevalence
Romesser, 2012 N=433 2 sites: VAMC polytrauma clinics. Cohort – retrospective. .	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%.	How much pain interfered with life in the past 30 days (moderately, severely, or extremely versus not at all or mild): Moderately to extremely = 70.3%.
Seal, 20174 N=116,913 Multi-site: VA CTBIE database. Cohort – retrospective. .	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%.	Presence ≥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%). Pain interference presence as ascertained during the CTBIE: 75%.

Results: Prevalence of General Chronic Pain

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- 8 studies reported prevalence of general/any chronic pain
  - All focused on post-9/11 Veterans
  - 3 retrospective cohort studies based on VA data
- Seal et al. (2017) reported that **59% of 65,675** Veterans with mTBI were diagnosed with pain
  - 75% reported moderate to very severe interference in daily functioning
- Kulas and Rosenheck (2018) reported that **82% of Veterans with mTBI+PTSD**, and **71% of Veterans with mTBI without PTSD**, were diagnosed with pain (62% of PTSD-only).
- King et al. (2014) reported that **76% of Veterans with mTBI** (versus 52% of those without mTBI) were diagnosed with pain.
- Hoot et al. (2018) reported that **59% of Veterans with mTBI** had moderate-extreme pain discomfort (versus 65% without mTBI).

Results: Prevalence of Head Pain

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- 23 studies reported prevalence of head pain/migraine
  - Assessment methods included 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).
  - Prevalence estimates ranged from 3% to 98%.
- Kulas and Rosenheck (2018) reported that **48% of Veterans with mTBI+PTSD**, and **36% of Veterans with mTBI without PTSD**, were diagnosed with headache.
- King et al. (2014) reported that **51% of Veterans with mTBI+PTSD**, and **38% of Veterans with mTBI without PTSD**, were diagnosed with headache.
- Pugh et al. (2019) reported that **20% of Veterans with mTBI** were diagnosed with pain in their first year of VA care.
- Beswick-Escanlar (2016) reported that **15% of Servicemembers with mTBI** were diagnosed with head pain within one year of mTBI.

Results: Prevalence of Back Pain

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- 10 studies reported prevalence of back pain
  - Wide variety of assessment methods; study sizes ranged from 260 to 93,003.
  - Prevalence estimates ranged from 27% to 61%.
- 3 studies used similar assessment methods (PHQ-15) and had similar results:
  - Wilk et al. (2012) reported that **44% of Veterans with mTBI** were "bothered a lot" by back pain.
  - Wilk et al. (2010) reported that **37% of Veterans with mTBI** were bothered a lot.
  - Hoge et al. (2008) reported that **32% of Veterans with mTBI** were bothered a lot.
  - Wilk et al. (2012) also reported that **56% of Veterans with mTBI+PTSD**, versus **37% of Veterans with mTBI without PTSD**, were "bothered a lot" by back pain.
- Suri et al. (2017) reported that **56% of Veterans with mTBI** had back pain in past 30 days.
- King et al. (2016) reported that **46% of Veterans with mTBI** were diagnosed with back pain (versus 23% of those without mTBI).
- Pugh et al. (2019) reported that **27% of Veterans with mTBI** were diagnosed with back pain in their first year of VA care (versus 18% among those without mTBI).

Results: Most Prevalent Pain Types

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- Across studies, **back pain, head pain, and arm/leg/joint pain** had the highest prevalence levels
  - Hoge et al. (2008) reported outcomes of PHQ-15 assessing multiple pain locations in 384 Servicemembers with mTBI: 40% “bothered a lot” by arm/leg/joint pain, 32% by back pain, 22% by head pain

Results: Prevalence by mTBI Etiology

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- 3 studies compared pain prevalence among Veterans with mTBI associated with blast versus those with mTBI from non-blast causes.
    - Wilk et al. (2010) reported headache in **40% of Veterans with blast-related mTBI with loss of consciousness**, versus **23% with non-blast mTBI with LOC**.
    - Hoot et al. (2018) reported small difference in pain prevalence (**63% versus 56%**) among those with blast versus non-blast mTBI.

- Overall, blast did not appear to be associated with greater prevalence of chronic pain.

Results: Prevalence by Pain Measure

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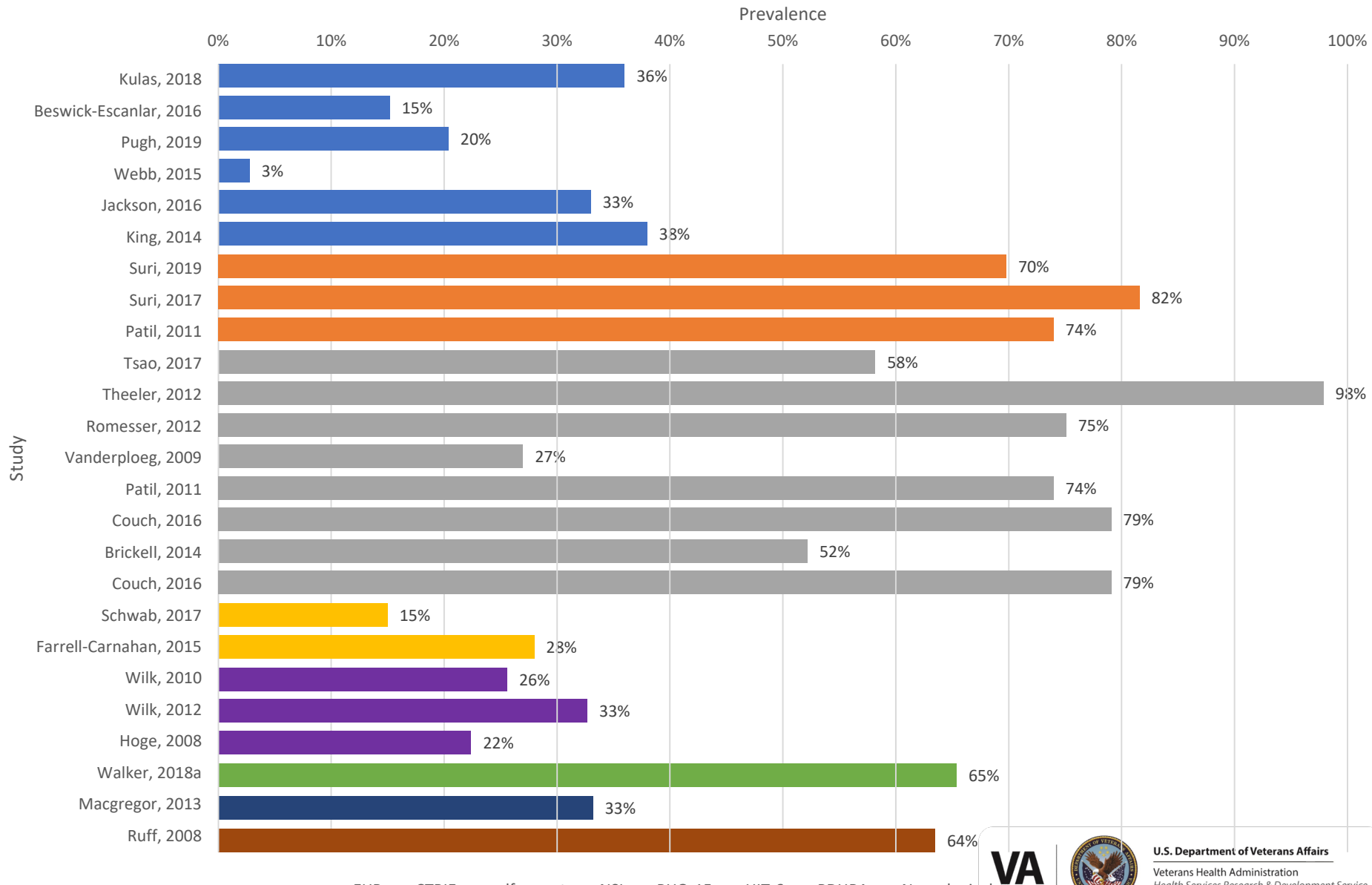
- In general, studies relying on more stringent pain definitions and comprehensive diagnostic measures reported lower levels of prevalence.



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Results: Suicide Risk

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

- One study addressed this question: Pugh et al., 2019
- This study examined all post-9/11 VA users and defined pain based on ICD diagnosis codes
- Suicide-related behaviors included suicidal ideation or attempt, identified based on ICD diagnosis codes
- Participants were grouped by phenotype
  - "Polytrauma" group with consistently high comorbidities of mental health disorders, post-concussive symptoms, and pain
  - "Moderately Healthy" comparison group comprised those with a history of mTBI who had low rates of these comorbidities
- Prevalence of suicide related behaviors:
  - Polytrauma phenotype (n=11,333) = 6.1%
  - Moderately Healthy phenotype (n=29,168) = 2.9%

Results: Chronic Pain Treatment

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Key Question 3:

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

- Included studies must have consisted of an intervention delivered in a research context. Studies examining outcomes from clinical care were not included.
- 2 randomized controlled trials and 1 pre-post study were included.

Description of Included Intervention Studies (RCTs)

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Study Design N	Study Inclusion	Intervention	Comparator	Sample description
Leung, 2016 RCT n=24 (but 5 dropped out prior to intervention and not included)	US Veterans, age 18-80, history of mTBI and posttraumatic headache, average chronic persistent daily headache intensity > 30 (on 0-100 VAS), and average pain intensity > 3/10 on NRS	Three neuronavigation-guided rTMS study treatments with intertreatment interval at least 24 hours or no more than 72 hours apart were administered within 1 week.	Sham rTMS	rTMS: Age: 41.2 (14.0) years Female: 2/12 (16.7%) Sham: Age: 41.4 (11.6) years Female: 1/12 (8.3%)
Leung, 2018 RCT N=29 (but 15 dropped out prior to intervention and not included in analyses)	US Veterans, age 18-65, history of mTBI, diagnosed with posttraumatic headache, average chronic persistent daily chronic persistent daily headache intensity > 30 (on 0-100 VAS), and average pain intensity > 3/10 on NRS	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.	Sham rTMS	Age: 34.1 (7.9) years Female: 6/29 (20.7%)

Description of Included Intervention Studies (pre-post)

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Study Design N	Study Inclusion	Intervention	Comparator	Sample description
Nelson, 2015 Pre-post N=9	US Veterans with wartime deployments in Afghanistan and/or Iraq; experienced service-connected TBI; have chronic daily headaches following service-related TBI; other criteria not reported	FNS: Brainwave-based biofeedback. Involves subtle minute pulses of electromagnetic energy stimulation, which is computer-adjusted based on EEG feedback. Total of 4 seconds of stimulation spaced over 4 minutes. 2-3 sessions/week until 20 sessions completed.	None	Age: 37.3 (12.6) years Time from end of deployment to first treatment = 6-103 months (median=46). 8/9 had comorbid PTSD. Taking ≥ 1 prescription: 7/9.

Study Results (RCTs)

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Study Design N	Headache Pain	Harms	Risk of Bias
Leung, 2016 RCT rTMS vs Sham (n=12 vs 12)	rTMS group had significantly higher percentage of persistent headache intensity reduction than the sham group at 1-week post-treatment (p=0.041). A significantly higher percentage of rTMS participants demonstrated at least 50% headache reduction than the Sham group participants (58.3% vs 16.6%, p=0.035). Debilitating headache exacerbation was significantly reduced in the rTMS group at 4-weeks compared with Sham group (p=0.017). No significant group differences in global pain intensity.	One participant had mild scalp discomfort. No other adverse events reported.	High
Leung, 2018 RCT rTMS vs Sham (n=14 vs 15)	rTMS group had significantly more improvement for average daily persistent headache intensity (p=0.002). At 4-weeks post-treatment, 57% of rTMS group no longer experienced persistent headaches compared to 20% of the Sham group (p=0.009). No significant difference between groups for debilitating headache composite scores (rTMS decreased by 58%, Sham decreased by 9.5%; p=0.062). Debilitating headache duration and frequency had improvements in rTMS vs Sham. No significant group differences on pain interference (measured by BPI).	No adverse events reported	High

Study Results (pre-post)

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Study Design N	Headache Pain	Harms	Risk of Bias
Nelson, 2015 Pre-post Flexyx Neurotherapy System (FNS) N = 9	• BPI-Headache worst pain in past week reduced from 7.3 (1.2) at baseline to 2.9 (2.6) at session 20 (p=0.001). • BPI-Headache average pain in past week reduced from 4.6 (1.6) at baseline to 1.4 (1.2) at session 20 (p<0.001). • PTSD Checklist total scores decreased from 48.6 (16.1) at baseline to 33.4 (15.9) at session 20 (p=0.009).	"…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

Summary: Chronic Pain Treatment Results

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Only 3 trials (2 RCTs) met inclusion criteria.

- Two studies examining rTMS identified significant reductions in persistent headache, relative to participants randomized to Sham rTMS.
- A small pre-post trial found a consistent decrease in mean headache pain scores over time after 20 neurotherapy (electricomagnetic stimulation) sessions.
- All reported trials were rated as having a high risk of bias.

While all 3 studies investigated the population of interest, high ROB in combination with the small number of studies and small sample sizes of included studies resulted in a strength of evidence rating of “insufficient” (according to AHRQ methods). Thus, we were unable to estimate an effect for this outcome.

Discussion

- Many chronic pain studies were excluded because they did not report prevalence levels but, rather, pain measures on a continuous scale (i.e., means and medians), precluding the ability to estimate prevalence
  - These studies may provide other important information on pain severity, frequency, and interference
- We used a relatively flexible definition of “chronic pain” so as not to exclude potentially useful data
  - We included studies even if chronicity or severity of chronic pain was unclear
  - This approach likely explains some of the wide variance in prevalence estimates obtained from the included studies

Conclusions: Pain Prevalence

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- Chronic pain, particularly head and back pain, is quite common in Veterans and SMs with a history of mTBI
  - 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
  - Pain prevalence may be higher among those with loss of consciousness versus those with alteration of consciousness after mTBI
  - Results regarding blast versus non-blast etiology were inconclusive
- Precise prevalence estimates are hampered by heterogeneity across studies

Conclusions: Risk of Suicide

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- There is very little current research that provides data on prevalence of suicide-related outcomes in US Veterans and SMs with chronic pain and a history of mTBI
  - Given the higher rates of suicide in Veterans, and evidence suggesting increased risk among Veterans with mTBI, more prevalence and treatment research is urgently needed for those who also experience chronic pain

Conclusions: Treatment of Chronic Pain

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- There is very little current research on interventions for chronic pain in Veterans and SMs from any country who have a history of mTBI
  - Studies of interventions effective in other patient populations, particularly Veterans and SMs without mTBI, should be prioritized
  - Due to the preliminary, positive findings of rTMS, larger rTMS trials in Veterans and SMs with chronic pain and mTBI history are warranted

Questions?

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If you have further questions, please feel free to contact:

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Full-length report and cyberseminar available on ESP website:

http://www.hsrd.research.va.gov/publications/esp/

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