Ralph DePalma: This presentation is a review of chronic pain prevalence and interventions in veterans with mTBI from the VA Portland Healthcare Core Center to improve veteran involvement in care.

The first speaker, Maya O'Neil, is a neuropsychologist and Associate Professor at Oregon Health & Science University; our second speaker, Kathleen Carlson, is a core investigator at the HSR&D Center to improve veterans’ involvement in care and prognosis and she's Associate Director at the Oregon Healthcare University. The third speaker, Ben Morasco, is also a psychologist and Systems Associate Director at the Portland Group. Thank you very much.

Maya O’Neil: Dr. DePalma, thank you so much for having all of us today. We're really excited to be here. This is Maya O'Neil; I’ll start out. And thanks to you all for joining us, for joining Kathleen, Ben, and me to talk about the recent systematic review that we completed with the Evidence Synthesis Program. So, let me get it onto our cover slides there for a sec.

So, there you go. You can see the information about Kathleen, and Ben, and I, and we'll go ahead and get started with the information about our review. Alright. So, in addition to the co-authors that I’m going to mention in a minute here and the folks at our ESP who supported the project, we also want to acknowledge our very engaged and helpful operational partners. They didn't only request this report, they also guided us in terms of our key questions and our technical expert selection; these folks ensured that the questions and report were relevant to veterans in the VA and they gave us feedback every step of the way down to really detailed written feedback on our initial drafts of this report. So, thank you to those folks--including Dr. DePalma, of course. We also want to acknowledge our technical expert panel, they also provided feedback along the way both in terms of relevance and providing clinical, and rehabilitation, and health services expertise related to TBI and pain.

We have our standard disclosures slide next and I’ll start by giving you a bit of background on the ESP before transitioning to background and methods for this specific report. So, as you can see here, established in 2007, there were four ESP centers including the coordinating center here in Portland, Oregon. In a nutshell, the ESP provides tailored, timely, accurate evidence synthesis of VA-relevant and veteran-focused healthcare topics, our reports are designed to ensure that clinical policies relevant to veterans are informed by evidence and that services the VA offers are effective.

The reports can also set the direction for future research by highlighting the gaps in evidence that could address key questions of importance to the VA, and you'll see that with our report today; we're definitely going to highlight some future research needs.

There you can see the locations of all the ESP centers. And then, as I said, we have a larger team of colleagues working with us on our report and we really appreciate their contributions, they're all listed here.

Alright. So, for some background. We'll start by covering some general information on the consequences of mild TBI. So, approximately 413,000 service members have experienced a traumatic brain injury since the year 2000 and over 80 percent of those were classified as mild; in the case of mild TBI, many symptoms resolve within a few months for most people as I’m sure many of you are familiar; however, up to one-third have a longer or more severe symptom course. Conditions associated with mild TBI include mental health concerns such as PTSD and depression, cognitive problems, sensory sensitivity, and chronic pain, that's what we're going to focus on today.

It's unclear whether symptoms attributed to mild TBI are due to the mild TBI itself or rather are health outcomes related to this same exposure? So, for example, the combat or the accident that led to the mild TBI. It's also important to consider some of the unique ways that mild TBI is related to military service. So, for example, while falls or other accidents may happen among civilians, service members can also experience exposure to blast which may or may not cause a TBI. So, our report is going to examine some of these comparisons related to TBI etiology as well and you'll hear about that shortly.

While more research has been done on symptoms and comorbidities such as PTSD and cognitive problems, there was less robust evidence synthesis of research on chronic pain in folks that have experienced mild TBI; and because of its relevance to service members and veterans, we conducted this review to focus on these groups and examine the prevalence of chronic pain, risk of suicide among those with a history of violent TBI and chronic pain, and benefits and harms of interventions for chronic pain for veterans and service members with a history of mild TBI as it says in our aims.

And then our next slide has our key questions. These are the overarching key questions that we covered in this report that we also looked at multiple sub questions to drill down into areas of interest such as comparisons based on TBI ideology like blast exposure. Our overarching questions, as you can see though, we were looking at the prevalence of chronic pain for US veterans or service members with a history of mild TBI, we were looking at the risk of suicide in US veterans or service members with chronic pain and a history of mild TBI; and then our final key question, we were looking at the benefits and harms of interventions to treat chronic pain in veterans or service members with a history of mTBI--and as I’ll note in a minute, that was not limited to just folks in the US, whereas the first two questions were.

We conducted a comprehensive search, and details about the search strategy and databases are included in our full report, but I’ll briefly summarize them here. So, our search is current to just under a year ago, so some very recent literature might not be included and we included studies providing prevalence estimates of chronic pain in US veterans and service members with a history of mild TBI, reporting estimates of suicide risk among those folks as well.

So, for Key Question 3, on interventions, we expanded our search to include trials in other countries assuming that these interventions, as long as they were focusing on a military or veteran population, would also be relevant to our US veterans and service members.

This slide summarizes our inclusion criteria by key question, highlighting the populations, interventions, comparators, and outcomes of interest. So, in general, we focused on mild TBI because prevalence, estimates, and interventions could differ significantly for folks who've experienced a TBI of greater than mild severity. So, if a study didn't very specifically separate out all the folks with just mild TBI from folks with any greater severity, we couldn't include that study unless they did that.

So, for our first two key questions, we focused on prevalence, we examined comparisons including type of mild TBI etiology and direct comparisons to civilians; so, Kathleen's going to tell you more about what we found there in a minute. For intervention studies, we examined controlled and uncontrolled trials of any type of intervention: it could be pharmacologic, non-pharmacologic, complementary and integrated health, pretty much anything. We searched for any types of comparators too, casting a broad net to include studies with placebo comparisons, some active comparators, the usual care waitlist, even pre-, post- comparisons. We wanted to be really broad to see if we could find absolutely everything out there on this important topic, and Ben's going to tell you about those results in a minute.

Another important piece about our methods relates to the definitions we used. So, I’ll walk you through this slide for a second. As you can see, chronic pain was defined as pain lasting or recurring for more than three months; the definitions definitely varied across the studies and I think Kathleen will tell you a little bit about that and why that's very important to consider for some of the prevalence estimates. Pain not explicitly referred to as "acute" was considered to be chronic pain and was included in this report, so we weren't super, super specific; we also included proxy definitions. So, you can see their health record diagnosis, analgesic medication use, et cetera. Those were things that we included in our broad net of sort of chronic pain definition.

For mild TBI, we defined that, as you can see there, a pretty standard definition of mild TBI. Again, definitions varied across the studies, some people used one very specific definition or another, but we generally tried to stick to those criteria. Again, we used proxy definitions as well, so that could be health record diagnosis or clinical intake forms. And the key piece here is as long as authors reported a clear definition for mild TBI differentiated from and excluded moderate and severe TBI.

Some additional methods are described on the following few slides. So, here, we summarize the variables we have extracted from the studies, essentially searching for these and documenting them in the report in a standardized manner across all the studies. All of these data were dual-reviewed and that means that at least two members of our team checked the studies for these data and separately documented them before comparing and combining them for the report tables and summaries.

Similarly, we examined all the studies for the risk of presenting biased results and that's called quality assessment or risk of bias commonly done in systematic reviews; this was also done by two independent reviewers using standard methods. So, because different factors can influence bias in different study designs, we looked at these separately for each study type. So, for example, in prevalence studies, we paid particular attention to whether a study included all participants in a given sample, meaning that it would potentially be less biased than a study that didn't include everyone in a particular group for some systematic reason. For intervention studies, these factors that can influence the potential for biased results include things like participants or assessors being masked to the treatment group assignment, for example. So, we looked at all those factors, again dual independent review there.

The overall strength of the evidence was rated for each question based on a wide range of factors we considered. As you can see here, those factors included things like study limitations, directness, consistency, precision, et cetera. The ratings ranged from high to insufficient; and as you can see, the high ratings of the strength of evidence imply that we're very confident that the estimate of the effect is close to the true effect for this outcome; whereas an insufficient rating means that there's just no evidence or we're unable to estimate an effect or have no confidence in the estimate for this outcome due to all these factors.

So, often, this comes down to there being very small preliminary studies in an area and indicates that more research is needed in order to feel confident that results are giving us an accurate picture of what's going on, and this could be in terms of prevalence estimates or estimates of the effectiveness of an intervention, so Key Question 3.

So, so in this slide, you can see our literature flow chart, and we're going to start launching into the results that we found. So, Kathleen, if I can remember how to do this--which I think I can--let me see, I have to find you on my panel up there. I’m going to turn it over to you so you can start talking through our Key Question 1 results. So, give me one second and I’m going to make you the presenter.

Kathleen Carlson: Thank you, Maya. Thanks so much, Maya; thank you, Dr. DePalma, and Whitney, and CIDER for having us.

So, just quickly to attach on the literature flow through our study, you can see here that we had over 2000 citations that were identified by our research librarians, we added another 21 through pooling or identifying relevant articles and reviews from the reference lists of included studies, and that meant that we had over 2100 abstracts and titles to review for this evidence review. After reviewing all of those abstracts, we boiled down to 174 manuscripts that we would review at the full-text level--and this is a lot of manuscripts to review and, ultimately, we ended up with only 30 studies that met our inclusion criteria which was a big drop off at that level. But the take-home message is that we erred on the side of inclusivity for these studies.

So, at the abstract to full-text level, we didn't want to run the risk of excluding any studies that might contain some important information on pain prevalence or pain intervention and treatment, and so until we got to the full-text review, we didn't exclude studies that we suspected may not report information of interest for this review. But ultimately, when we excluded studies, it tended to be because they didn't focus on our population of interest, these might have been non-service members or veterans, they might have even been animal studies in some cases; we also included a group of studies that were not an inclusive--or an included publication type; these tended to be non-systematic reviews or maybe commentaries, and we also had a handful of studies excluded because they didn't report an outcome of interest.

In here, we sometimes included studies that did report on pain-related outcomes, but it wasn't in a way that we could extract information relevant to prevalence or proportions of individuals with chronic pain. So, this might have been a mean or median pain measure score and, ultimately, would be interesting and important information relevant to pain in this population, but didn't address our Key Question related to prevalence.

So, in the end, we had 30 publications that were included--and you can see at the bottom here, that 27 publications representing 26 studies were included for Key Question 1 related to prevalence; only one study was included relevant to Key Question 2, and that was pertaining to suicide risk among those with mTBI; and only three studies relevant to Key Question 3 pertaining to treatments or interventions for pain in this population.

So, as you'll recall, our Key Question 1 addressed what is the prevalence of chronic pain in US veterans or service members with a history of mTBI? This question also addressed the prevalence by pain type and location, also by mild TBI etiology, so that blast versus other types of mTBI ideologies, and methods used to define or measure chronic pain. For this, we included any primary study except for those that were just case studies or case reports as long as it reported the prevalence of chronic pain in this population.

So, as I mentioned, we had to exclude some non-systematic literature reviews or non-human subject studies because they didn't report on humans in US service members and veterans; and, ultimately, we had 26 studies represented in 26 articles--or 27 articles, sorry about that.

So, this presents the proportions of these 27 articles that reported data on each of these pain locations; and you can see that the majority--or the largest proportion of these articles reported on head pain which included migraine. We also had a large group that reported on back pain, on arm, leg, or joint pain, or on general chronic pain, and these will be the ones that I tend to focus results on today. But we have data from all of these studies in the full report available online in a pretty granular detail.

So, this slide shows you the range of pain prevalence levels that we extracted from across all of the studies, and I have, here, circled the studies related to general chronic pain because I’m going to present more detailed information on these studies in just a bit. But you can see that for the majority of studies, there's a pretty wide range of prevalence levels that we extracted from across the studies. So, that ranged from 38 percent all the way up to 82 percent for studies reporting data on general chronic pain in this population; for head pain, that was almost the entire spectrum going from 3 percent all the way up to 98 percent of participants with mTBI reporting head pain or migraine.

We do have a fairly consistent group of studies for these pain types where there were fewer publications reporting outcomes. So, you can see here, a little bit lower down, the abdominal and stomach pain, chest pain, and sexual pain or problems; there's pretty more--a more narrow range of pain outcomes for those studies, but this may have to do with the fewer number of studies that recorded these outcome types.

So, this slide and the next two slides report the details that we extracted for studies reporting on the prevalence of general chronic pain. So, this is general pain or any pain reported in these studies. And there were eight total studies, this is just a sample of the variables that we extracted from across these studies and I wanted to present this. It's a lot of detail, but just to give an idea of the variation across the studies that we were seeing and this is just in one pain location or pain outcome type that we extracted.

So, this first study, you can see from Rachel in 2014, this is a study of 167 service members treated at Walter Reed Army Medical Center, and this was one of the few prospective cohort studies that we identified, and this study followed service members who were diagnosed with mild TBI treated at a polytrauma TBI clinic, and they were followed over time to assess the prevalence of bodily pain other than headache reported in the past month, and this was assessed at six months all the way up to 60 months. And you can see that, overall, these were quite high proportions of these service members that reported bodily pain over time.

Next done was Hoot et al, which was the Chronic Effects of Neurotrauma Consortium analysis from four of the original study sites, and this study includes both veterans and service members from post-9/11 combat era and who all reported on the level of pain intensity or discomfort of moderate to extreme, and we see that 60 percent of these study participants reported pain at that level.

We then had a series of studies that were based on VA administrative data, so these are electronic health record data from different regions or nationally across the VA and from different time periods. So, this one reported on cross-sectional information, so these veterans treated in the VA who had relevant diagnoses at any time period from 2001 to 2011; and this study by King et al was based entirely on ICD code, so both mTBI was identified based on the ICD code for post-concussive syndrome and then pain diagnoses were also identified using ICD codes. And in this study, the presence of pain treated among those with mild TBI was 76 percent.

And I will not go into detail on all these studies, except to point out in this first study here by [Pulis] and Rosenheck, this is one example of a study that reported on pain diagnoses separately for veterans with mTBI and comorbid post-traumatic stress disorder compared to veterans with mTBI but no more comorbid PTSD. And you can see here that pain prevalence among those with both mTBI and PTSD was higher than among those without, and this is something that we tended to see consistently across studies that compared groups with the comorbidity to those without the comorbidity.

And one final slide and then a summary of these eight studies. So, all of these eight studies reporting on general chronic pain tended to focus on the post-9/11 veterans, so this wasn't necessarily our target population for the evidence review overall. Of the eight studies, we had three that were retrospective cohort studies that were based on VA data. And so, this first one, I didn't talk about in the previous table, but the Seal et all study, we considered one of our most robust of the studies, if we're looking at veteran VA users who are evaluated for mild traumatic brain injury. So, this is a study that reported on over 65,000 veterans that had undergone the comprehensive TBI evaluation in the VA, so this is a systematized templated evaluation for traumatic brain injury among those who screen positive for TBI.

And among those who were confirmed or identified to have incurred mild TDI, 59 percent had been diagnosed or had received pain diagnoses, and this was a relatively robust operationalization of pain as well. They had to have one or more of the same ICD code for pain diagnosis that was 90 or more days apart, reflecting a definition of chronic pain. So, 59 percent. Seal et al also reported a pain functioning measure from the comprehensive TBI evaluation itself, and 75 percent of those with confirmed mild TDI reported moderate to very severe pain interference in their daily functioning.

Somewhat similar to the Seal study, we had the Pulis and Rosenheck study that used administrative data from the VA. And in this study, as I showed earlier, 82 percent of those veterans with co-morbid mTBI and PTSD versus just 71 percent of those with mTBI but without PTSD were diagnosed with pain. And then in King et al, we had 76 percent of veterans with an mTBI diagnosis versus 52 percent of those without mTBI who are diagnosed with pain.

So, across these three studies focused on VA data, there's still some wide variation in the prevalence of pain diagnosis, but overall, the take-home is that a very large proportion of veterans with diagnosed or otherwise identified mild TDI are also diagnosed with pain. Similarly, the Hoot et al study from the Chronic Effects of Neurotrauma Consortium longitudinal study found that 59 percent of veterans identified with mild TDI had moderate to extreme pain discomfort, so another functioning or pain severity measure, but this did not differ from the veterans who were not identified with mild TBI in this study.

So, let me move on to the prevalence of head pain. I’m summarizing a lot of information from across 23 studies in just one slide here, but I think one of the main take-home points is that the assessment methods across these 23 studies reporting head pain or migraine pain were widely different; so these included EHR data, outcomes of the Neurobehavioral Symptom Inventory, or the 15-item Patient Health Questionnaire, the 6-item Headache Impact Test or HIT-6, and the Post-Deployment Health Reassessment and Reassessment measures. And this may help explain why we have that enormous range of outcomes from 3 percent all the way up to 98.

But again, across the VA administrative data studies, we see some consistency in that veterans with comorbid mTBI and PTSD relative to those with TDI but not PTSD, 48 percent versus 36 percent had been diagnosed with headache; and in the King et al study, we had 51 percent of veterans with comorbid mTBI and PTSD versus just 38 percent of those with mTBI but no PTSD diagnosed with headache. So, again, higher proportions of those with the comorbidity versus those without. But overall, nearly half of veterans with mTBI are diagnosed with a headache or head pain.

Pugh et al, in a 2019 study, reported that 20 of veterans with mTBI have been diagnosed with pain in just their first year of VA care; and then a study by Besswick in 2016 reported that 15 percent of service members with mTBI were diagnosed with head pain within one year of mTBI.

Looking at the prevalence of back pain, we had ten studies and, again, a wide variety of assessment methods and study sizes that range from 260 all the way up to 93,000 individuals. And prevalence estimates similarly ranged widely from 27 percent to 61.

But in this analysis of pain location and in a couple of other specific pain locations that we looked at, we have three studies that use similar assessment methods. And in this case, this was the PHQ-15; and I report here, incorrectly, that we're looking at veterans with mTBI, these three studies all looked at service members with mTBI, and so they were similar in that way as well. And in these studies, Wilk et al, in 2010, and then a separate study in 2012, we had 37 percent and 44 percent of service members with mTBI who reported on the PHQ-15 that they were bothered a lot by back pain. And similarly, in a 2008 study by Hoge et al, we saw that 32 percent of service members with mTBI were bothered a lot by back pain.

In the Wilk 2012 study, we did report--or we did extract the data specific to veterans with mTBI and comorbid PTSD versus those with just mTBI but no PTSD. And again, you can see this higher prevalence level among those with the comorbid mTBI and PTSD versus those without.

Seal et al reported that 56 percent of veterans with mTBI had back pain in the past 30 days; similar for King et al, and Pugh et al in 2019, we had 27 percent of veterans with mTBI diagnosed with back pain in just their first year of VA care. So, overall take-home again, that high proportions of these veterans are diagnosed with mild TBI--and even service members who are identified with mild TBI--report back pain.

So, we were trying to identify which of these pain types or the pain locations were most prevalent in veterans or service members with a mild TBI history, and this would rely on studies reporting multiple pain locations or pain types across the same study populations. And there were a few studies that did that. In particular, those that reported outcomes of the PHQ-15; and as an example, Hoge et al reported multiple pain locations in the 384 service members with mild TDI and reported that 40 percent said they were bothered a lot by arm, leg, or joint pain, so that was the most prevalent pain type in this population followed by 32 percent being bothered a lot by back pain, and 22 percent by head pain.

So, overall, across these studies that reported different pain types or pain locations in the same populations or same samples, we found that back pain, head pain, and arm, leg, and joint pain had the highest prevalence levels.

We found three studies that compared pain prevalence among veterans with mild TDI that was associated with blast versus those with mild TBI from non-blast causes, and there wasn't a lot of consistency across these studies except for one study by Wilk et al, this 2010 study, that broke out head pain by those with blast-related mild TBI versus non-blast mild TBI when a loss of consciousness occurred. And it was only in this finding where they compared blast-related mTBI to non-blast mTBI with loss of consciousness where we saw a higher prevalence or a higher proportion with head pain among those with blast TBI versus those without. When they compared those with blast TDI with only alteration of consciousness-- so not a loss of consciousness--there was really no difference between those with blast-related mTBI and those without or with non-blast TDI.

Similarly, for Hoot et al in the Chronic Effects of Neurotrauma Consortium study, there was a small difference in the pain prevalence, just 63 percent versus 56 percent among those with blast versus non-blast mild TDI. So, blast didn't appear or didn't have strong evidence showing that there were higher pain prevalence outcomes in those exposed to blast versus non-black sources of mTBI, at least in these studies that were included here.

And again, we were interested in prevalence outcomes by the type of pain measure or the operationalization of pain. And, in general, across all of the studies that we looked at, those that tended to rely on the more stringent pain definitions or comprehensive diagnostic measures tended to report lower levels of pain prevalence, and I don't know if this is really evident across this slide here, but maybe if I point out the orange bars in the middle, these are higher prevalence levels than some of the other assessment methods and these were three studies that reported on the outcomes reported, reported pain prevalence levels among veterans who had been assessed with the comprehensive TBI evaluation.

So, in general, a more treatment-seeking veteran population that's identified with symptoms that are likely sequelae of mild traumatic brain injury and are getting an evaluation and potential workup for these symptoms, and thus may have higher pain prevalence levels than among some of these other populations and pain assessment types.

Okay. And I’m going to hand it over to Dr. Morasco now to present results from our Key Questions 2 and 3.

Ben Morasco: Okay. Great. Thank you very much. So, we'll talk about Key Question 2 looks at what is the risk of suicide in US veterans or service members with chronic pain and a history of mild TBI? So, unfortunately, there was only one study that was available to answer this question; this was part of the CENC epidemiology study, the retrospective cohort study examining EHR data from VA databases, they examined OEF, OIF, and OND veterans who entered VA care between October 2001 through September of 2011, and they included people who had received five or more years of VA care before 2014, these were users of VA.

So, all the study results were based on documentation in the EHR; they examined ICD diagnostic codes to identify pain-related diagnoses and suicide-related behaviors that were examined included suicidal ideation or attempts, which, again, were based on ICP codes.

Participants were categorized by phenotypes which were based on the results from latent class analysis; they ultimately identified a polytrauma group which was characterized by having consistently high comorbidities and mental health disorders, post-concussive symptoms and pain-related disorders in comparison to the moderately healthy--just the term they used--comparison group included those with a history of mild TBI and had low rates of these comorbid conditions.

They examined the rate of suicide-related behaviors among participants with the polytrauma phenotype, 6 percent had medical record documentation of suicidal ideation or suicide attempt, and this rate compared with 3 percent of participants who were characterized in the moderately healthy phenotype.

Key Question 3: What are the benefits and harms of interventions to treat chronic pain in veterans or service numbers with a history of mild TBI? The included studies must have consisted of an intervention delivered in a research context. So, while Dr. O'Neil was mentioning at the beginning we were trying to be inclusive of studies, we did not include studies that examined usual care processes or if a clinic had developed a new intervention but that was now their standard of care, those types of studies were not included. So, it must have been identified as a research.

And so, we identified two randomized control trials and one pre-post study were included.

So, of the studies, I’ll kind of go through the descriptions of the studies and then we'll get into results. So, there are two by Liang et al, the first was an RCT with 24 participants including veterans ages 18 to 80. To be included, participants must have had a history of mild TBI, current diagnosis of post-traumatic headache based on International Classification of Headache Disorders diagnostic criteria, which includes self-reported headaches, history of head trauma with loss of consciousness less than 30 minutes, GCS scale greater than equal to 13, symptoms of concussion, the headache must have developed within seven days of the head trauma and the headache persisting for three or more months after the head trauma.

To be included, participants had to report chronic persistent daily headache intensity greater than 30 on a scale of 0 to 100 during the baseline screen, and the average intensity of this chronic persistent headache had to have been greater than 3 out of 10 on a 0-10 numeric rating scale, and that was reported in a headache daily diary.

And they examined two headache characteristics-- which we'll get into in the results--the persistent headache, examined the outcome of the interventional persistent headache, as well as debilitating headache exacerbation.

The intervention consisted of three neuronavigation-guided rTMS sessions--rTMS stands for Repetitive transcranial magnetic stimulation--the active rTMS consists of pulses delivered to the targeted treatment area and they delivered a total of 2,000 pulses per session. And for this intervention study, there was a sham rTMS where participants had the coils attached to their head, the participants could visualize the movement of the coils and the treatment beamed over their own courses on the monitor, and they heard the sound and felt the vibration of the stimulation, but they did not receive any magnetic flux penetration. And so, then, we see the description of the sample participants--and there were no differences between groups.

In the 2018 study, it was slightly larger, 29 participants--they enrolled more, but 15 dropped out and they didn't have follow-up data available. The 2018 study had the same inclusion/exclusion criteria as the prior and participants were randomized to receive either real rTMS, which again consisted of 2,000 pulses per session at the left prefrontal cortex, and they received four sessions, each one to three days apart. And then, again, there are no differences between groups and characteristics.

There is also one pre-post study by Nelson and Esty in 2015. They included US veterans with wartime deployments in Afghanistan and/or Iraq who experienced a service-connected TBI and had chronic daily headaches following TBI. The treatment consisted of a proprietary neural feedback system, this involved subtle minute pulses of electromagnetic energy stimulation which was computer-adjusted based on EEG feedback. Participants received a total of four seconds of stimulation spaced over a period of four minutes, and they had two to three of these sessions per week until they had 20 sessions completed. And then we see the sample characteristics as well.

If we get into the results from these studies, from the first Liang study, if we look at the outcome of persistent headaches, the real--the group who received the rTMS--demonstrated a significantly-higher percentage of persistent headache intensity reduction relative to the sham group; they had a 56 reduction versus 15 percent, and a significantly higher percentage of the real rTMS participants demonstrated at least a 50 percent headache reduction compared with the sham group, 58 percent relative to 17 percent.

The second outcome of debilitating headache exacerbation, that was also reduced at the four-week post-treatment visit for the real rTMS group while the sham group remained elevated. They also asked for a global measure of pain intensity and pain interference with the BPI, there were no differences between groups on the BPI.

Adverse events. What you see there is that one person recorded mild scalp discomfort.

For the second Liang study, average persistent headache intensity at the final four-week post-treatment visit, the rTMS group had a 23 percent decrease in average headache intensity score, while the sham group had a 2.3 percent reduction. Regarding prevalence of headache, 57 percent of participants in the rTMS group and 20 percent of participants in the sham group no longer experienced persistent headaches at the four-week post-treatment assessments.

There were no significant differences between groups for a debilitating headache on a composite score, but it looks like, probably, this might have been a power issue as the rTMS group decreased by 58 percent and the sham decreased by about 10 percent; the key was 0.06. And then, again, they also had a global measure of pain intensity, pain interference and that score did not differ between groups.

Noting that both studies had had high risk of bias due to high rates of dropout and kind of some other outcomes. In one of the first studies, I think there were some issues with blinding between participants and researchers.

And then for the outcomes for the pre-post Nelson and Esty study, scores for participants generally improved between pre-treatment and the post-treatment assessment points; the headache, the worst pain in the past week reduced on a scale from 0 to 10, reduced from seven at baseline to about a three at Session 20. The headache average pain in the past week reduced from 4.5 at baseline to 1.5 at Session 20; and then node scores of PTSD--PTSD was not an inclusion criterion, but if you saw on the baseline slide, there was a high rate of PTSD in the sample. But PTSD checklist scores decreased markedly between baseline and the post-treatment assessments.

If we look at the summary of the chronic pain intervention studies, there were, unfortunately, only three trials on that our inclusion criteria, the two studies examining rTMS identified significant reductions in persistent headache relative to participants randomized to sham. The small pre-post trial found a consistent decrease in headache scores over time after 20 sessions; all three trials were rated as having a high risk of bias.

So, if we were to summarize them, all three studies investigated a population of interest, they all had a high risk of bias; and then that, in combination with a small number of studies and the small sample sizes, resulted in a strength of evidence rating of [insufficient], thus we were unable to estimate an effect for this outcome.

So, I’m going to switch things back to Dr. O'Neil, who will talk about sort of the context for all this. So, Maya, it's back to you.

Maya O’Neil: Perfect. Thanks so much. I think I got it now. So, I’ll just provide a little bit of a summary and discussion of some of the points that were discussed for our key questions, though these things have been mentioned already in the presentation. So, as you can see here, many chronic pain studies were excluded because they didn't record prevalence levels, that was really important for our Key Question 1. So, rather, a lot of those studies use pain measures that were on a continuous scale; so, as Kathleen was talking about, the means and medians, and that precluded the ability to estimate prevalence.

Though we want to mention that these studies definitely can provide other important information on pain severity, frequency, interference, things like that. So, we're not trying to sort of throw out those studies and say they're not good, it's just that they don't give us the information we need to estimate prevalence in particular.

As we noted, we also used a relatively flexible definition of chronic pain so as not to exclude potentially useful data. So, we included studies even if chronicity and severity of chronic pain was unclear, and that can probably explain some of the variation that we saw in the prevalence estimates from those studies.

In terms of pain prevalence, chronic pain, particularly head and back pain, unfortunately, is quite common in veterans and service members with a history of mild TBI, that's one of the big take-home messages from this report. It's quite common and then, as Ben was talking about, we don't have a lot of information on interventions and so we really probably want that and I’ll hit that point home again shortly in another slide as well.

So, the pain prevalence estimates are consistently higher among those with versus without mild TBI history--and importantly, for those with comorbid mild TBI and PTSD when we compare to those with just a mild TBI but no PTSD. Pain prevalence may be higher among those with loss of consciousness versus those with just alteration of consciousness. So, potentially, something about a severity difference even within that grouping of mild TBI results regarding blast versus non-blast etiology were inconclusive, at least with the studies that are available at this point.

Precise prevalence estimates are hampered by heterogeneity across the studies really in a lot of different ways. So, as Kathleen was talking about, all the different kinds of measures used, the different populations, the context in which these data were collected, et cetera. So, please keep that in mind.

In terms of risk of suicide, such an important outcome that, obviously, so many of us in the VA care greatly about. Unfortunately, there's very little current research that provides data on prevalence of suicide-related outcomes in US veterans and service members with chronic pain and a history of mild TBI. Given the higher rates of suiciding veterans as well as the evidence suggesting increased risk among veterans with mild TBI, it's pretty clear that more prevalence and treatment research is urgently needed for those who also experience chronic pain.

And similarly, very little current research on interventions for chronic pain in this population, even when we expand that to any country. So, we definitely think that more intervention studies are needed in veterans and service members who have a history of mild TBI.

I guess one thing I should mention is we are also in the process of taking a look at what studies are ongoing, so looking at clinicaltrials.gov, and it does seem like there are a few studies that are ongoing, but definitely some things that could be focused on in intervention research.

And one final point about the evidence that is available is due to the preliminary and positive findings from those rTMS studies, it seems like larger rTMS trials in veterans and service members with chronic pain and mild TBI are probably warranted. So, for those of you who are writing grants and interested in that area, feel free to cite our report; hopefully, we've done some of your work for you there.

At this point, I will leave up our contact information so you can ask us any questions afterwards. We have just a couple minutes left--it looks like we have about ten minutes here--and so I want to get at some of these questions that folks have been asking in the Q&A. So, Kathleen, this first question is specific, but maybe there's a broader answer to it. First question is about migraines, tension headaches, and facial pain, if those were considered separately? And so I think it might be worth speaking to how it's difficult in a systematic review to figure out how to lump things together or keep them split apart. Can you speak to whether those were examined separately in our review?

Kathleen Carlson: Sure. We reported the pain measure that the authors reported in their studies, so I can say that there were a handful of studies that reported prevalence of migraine separate from tension headaches or post-traumatic headaches for that matter. I don't think that we had any that reported facial pain separately, at least that I can think of. And I’m just looking over some of our results in our table right now, and I don't see a really consistent pattern of prevalence outcomes in the studies that compare migraine to other types of head pain, but that's just a quick look at those studies. But the details are presented in our headache pain table in the full report.

Maya O’Neil: Great. Thanks. The next question is about how mild TBI was inflicted in each of the studies that we included. So, I can say a little bit about that, which is that it definitely ranged in the studies, and it wasn't--these weren't studies that were necessarily limited to just folks that had TBIs related to blast exposure, there was quite a range--and I don't know, Kathleen, did you want to say anything else about the Key Question 1 result in terms of how mild TBI was inflicted?

Kathleen Carlson: Well, I would say it was the wide variety, distribution of all types of sources of blows to the head. So, a lot of motor vehicle crashes like the Humvee crash and blows to the head or the blast exposure, falls, and so on. And we didn't have that separately reported across a lot of the studies, so I’d say that just the studies that focus on blast versus non-blast would identify the source of the mTBI; a lot of the other studies might have just started with a sample that is diagnosed with mTBI and doesn't necessarily give us information on how the TBI was incurred. But that was kind of a sub-question of ours was whether pain outcomes differed by the cause of the mTBI; and basically, we really only had enough information and that was few studies as it was, that report reported outcomes comparing blast to non-blast sources of mTBI. But even within the non-blast sources, that wasn't distinguished by different causes. Does that make sense?

Maya O’Neil: Thanks. Yeah, that does make sense. And we have a similar question following that about gender differences, if any of the studies looked at gender differences.

Kathleen Carlson: Off the top of my head, I don't think they did. In our descriptive table of all of the studies, you can see that the proportion of the overall study sample comprised by women was relatively small in most of the studies, and that reflects the proportion of women in the overall military or the overall samples of veterans that tend to be injured. But it would be fantastic to have studies going forward that sampled or oversampled for women with an mTBI history and then could compare the pain outcomes between women and men who were otherwise similar in terms of exposures and demographics.

Maya O’Neil: Definitely. I totally agree and I was trying to take a look at our tables too. I don't remember any studies that specifically did that comparison either. We have a question about veterans that had reported back pain and joint pain. Were you finding that they were being treated with opioids?

Kathleen Carlson: Oh, we did. I would not say necessarily specific to back pain and joint pain, but we did have a couple of studies that reported opioid use among the samples with mTBI. And yes, there were fairly high proportions that were receiving opioids--and I want to say those were somewhere in the range of 25 percent up to 50 percent of the specific samples. And now, those samples could vary greatly, so these may be treatment-seeking samples specific to pretty severe chronic pain. But yes, relatively large proportions in a couple of studies that were reported to be receiving opioids.

Maya O’Neil: And one other question that relates to Key Question 1 again. So, the question is, "In identifying prevalence estimates for sites other than the head, so location of injury other than the head, was the confounding of injury to that site concomitant with the mTBI considered as a factor?" So, does that make sense, Kathleen?

Kathleen Carlson: Yeah, so like back pain, for example, could be a chronic overuse injury not resultant from mTBI, is that what that's getting at?

Maya O’Neil: Yeah.

Kathleen Carlson: So, no, we don't have the information necessary to disentangle the cause of the pain from the mTBI itself. So, basically, the bulk of the studies that we have available now tell us who has mTBI and among those, who have a chronic pain diagnosis not specific--not necessarily specific to the mTBI itself. So, I think that's a confounding factor in a lot of these studies that examine comorbidities of our veteran or service member population with mTBI, is that the source of their mTBI is exposure to combat, or high-intensity combat or work environments, and overuse injuries occur, pain from other injuries occur, and I can't think of studies that really have been able to disentangle the cause of the pain outcome and whether that is mTBI-specific itself or specific to other potential causes of injury and pain.

Maya O’Neil: Alright. And I’m going to notice the time here--Ben, I want to throw one question your way and then I think we'll turn it back over to Whitney. So, just in the last couple of minutes, we had a question, "Given that there's little current research on interventions for chronic pain and veterans and service members, do you think they may be more likely to self-medicate for their chronic pain issues?"

Ben Morasco: That's a good question. I don't really know that answer. I guess one thing that we think about is there's not--to me, and I think we've talked about this when we were writing up the summary of the report, we were disappointed that there's not adequate research--but I guess to the extent to which that how much that represents how much clinical services are ongoing, we don't know--I mean I’m speaking of my end or one view that I’m accustomed to. We have a clinic that--we have a polytrauma that provides care for this patient population, we have specialty pain medicine and such and such. I’d like to think that people with mTBI and pain are being able to receive sort of--I guess I was about to use the terms traditional multimodal services for chronic pain particularly consistent with sort of staggering it in terms of intensity levels of pain needed. But how much that's occurring across VAs? I don't actually know. I would assume that probably there's more care happening for this patient population than what the research literature indicates.

As Maya also intimated earlier, one of the things we're doing is we're checking sort of about ongoing trials in this area--and there is a lot more active work, but it is disappointing that given that we've known that pain, PTSD, and TBI has been an issue in OEF/OIF veterans for years, it is surprising not to see more research in this area. I started talking about more, but I realized the time and I feel like we should wrap up. But that's a great question. Thank you.

Maya O’Neil: Thanks so much for those questions, I agree. And Whitney, I think at this point because of time, we'll turn it over to you, and any additional questions we can try to follow up with people via email. Don't hesitate to reach out to us via our emails as well, we all love chatting about this stuff and really enjoyed doing this report. Thanks so much. Whitney?

Whitney Lee: Great. Thank you. Thank you to you all for taking your time to prepare and present this. At this point, I’d like to ask Dr. DePalma, if you have any remarks, and then also to your team, Maya, if you guys have any closing comments.

Ralph DePalma: We would like to thank the team for this very carefully detailed analysis of this; the deficiencies in the research will serve to guide future VA-wide research to improve veteran care; and it was particularly interesting to see the effects of TMS, and I’m really glad you emphasized it.

In closing, we would like to ask when a publication will be forthcoming. And thank you very much again.

Maya O’Neil: Thank you so much for having us. We're working on converting our report--which is available to all VA users on our VA internet, so feel free to download our full report; that's already available now. But we're working on getting those out into publications and, as we were talking about, trying to update those publications with some clinical trials.gov info, things like that. And basically, our take-home message for folks in the field is we hope that you find these reports useful; for those of you writing grants, we hope that the sections where we're highlighting things like the research needs are really helpful for you as you're writing grants and we can help try to move the field forward and highlight the ways that we need to do some more great research on the interventions that are, hopefully, already being conducted and studied out there, and then also getting better prevalence estimates for--obviously, for some important outcomes like those suicide-related outcomes. So, hopefully, we'll see more work on that in the future.

So, thanks again so much for having us; we've really enjoyed putting this together for you all.