



Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Webinar Series

May 8, 2014, 1-2:30 p.m. (EDT)

Diagnosis and Management of Post-traumatic Headache

Welcome, and thank you for standing by. At this time all participants are in a listen only mode until the question-and-answer session. I would like to inform all participants that today's conference is being recorded. If you have any objections, you may disconnect at this time.

I would now like to turn the conference over to Dr. Christian Shenouda. You may begin.

Dr. Shenouda, we are unable to hear you in conference. Your line is muted. Would you please – thank you.

Good afternoon, and thank you for joining us today for the DCoE Traumatic Brain Injury May webinar. My name is Dr. Christian Shenouda. I'm a Traumatic Brain Injury physician providing contract support to the Defense and Veterans Brain Injury Center, DVBIC, a Center of DCoE. I'll be your moderator for today's webinar.

Before we begin, let's review some details about the webinar. Live closed captioning is available through Federal Relay Closed Captioning. Please see the pod beneath the presentation slides. Adobe Connect and Defense Connect Online are the technical platforms hosting today's webinar. Should you experience technical difficulties, please visit deco.mil/webinars to access troubleshooting tips. If you cannot connect via Adobe Connect or Defense Connect online, please continue to listen via phone and go to dvbic.deco.mil/online-education to download the slides.

There may be an audio delay as we advance the slides in the presentation, so please be patient as the connection catches up with the presenter's comments. During the webinar, please feel free to submit technical or content-related questions via the Question box. The Question box is monitored and questions are forwarded to the moderator for response during the question-and-answer session during the last half hour of the webinar. Our presenters will field as many questions as time permits. Please feel free to identify yourself to others via the Chat box, but refrain from marketing your organization or products.

The presentation today and the resource list are available for download from the Files box below and will be archived in the Online Education of the DVBIC website. If you preregistered for the webinar and want to obtain a CE certificate or a certificate of attendance, you must complete the online CE post-test and evaluation. After the webinar, please visit <http://continuingeducation.dcri.duke.edu> to complete the online CE evaluation and post-test and download your CE certificate or certificate of attendance. The Duke Medicine website online CE evaluation and post-test will be open through Thursday, May 15th until 11:59 p.m. Eastern time.

Throughout the webinar you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. Please do not submit technical or content-related questions via the Chat pod. The Q&A pod is monitored during the webinar. Questions will be forwarded to presenters for response during the Q&A session after the presentation.

Headache is one of the most common presenting symptoms after TBI across all levels of severity. Research in the civilian and military populations has improved our understanding of the prevalence of headache after TBIs. However, further research is still needed to help better elucidate the pathogenesis and treatments.

The webinar today will review the current research on post traumatic headache and how symptoms of headache can assist with diagnosis. Current recommendations for treatment of post traumatic headache will be described. At the webinar's conclusion, participants will be able to describe the incidence and prevalence of headache after TBI, relate critical elements for the diagnosis of post traumatic headache, and identify and employ current treatment approaches for headache after TBI.

Now I'll introduce our speakers Our first presenter is Dr. Jeanne Hoffman. Dr. Hoffman is an Associate Professor at the Department of Rehabilitation Medicine at the University of Washington in Seattle. She's a clinical psychologist who provides patient care at the University of Washington Medical Center in Seattle. Dr. Hoffman has been involved with the TBI Model Systems research projects for the past ten years. She is the Principal Investigator for the TBI Model Systems Module Project Examining the Natural History of Headache. She is also the Principal Investigator for a field-initiated Neider (sp) Grant to extend the natural history headache project to individuals with mild TBI. She has extensive experience with the design and analysis of intervention programs for individuals with TBI including projects to evaluate the impact of exercise on mood after TBI. We're pleased to welcome Dr. Hoffman.

Our second presenter, Dr. Sylvia Lucas, is a Clinical Professor of Neurology, Neurological Surgery, and Rehabilitation Medicine at the University of Washington Medical Center in Seattle. Dr. Lucas is the founder and Director of the University of Washington Medical Center Headache Clinic. She is the recipient of the Wadsworth Clinical Term Professorship in Headache Research and Practice. She is also a member of several organizations including the American Academy of Neurology, Washington State Neurological Society, American Headache Society, and the International Headache Society. She is also a member of the Board of Directors of the Headache Cooperative of the Pacific.

Her research interests include post traumatic headache and headache therapeutics. She has published in multiple peer review journals, and she has received the Harold Lamport Biomedical Research Prize.

We're very pleased to welcome these two distinguished speakers. We'll now proceed with the presentation.

Hello and welcome. Thank you very much. This is Dr. Jeanne Hoffman, and I'm going to be starting the presentation and then reviewing the research and the research that we've conducted on headache after traumatic brain injury, and then I'll turn it over to Dr. Lucas who will talk more about the specific recommendations right now given the lack of research that we have right now on treatment of post traumatic headache.

As I have the disclosure slide, which, of course, the views are those of us, the presenters, and I have no disclosures and Dr. Lucas's disclosures are noted on the slide.

We also want to recognize funding from Neider for the research that I'm going to present today, and the specific information is on the slide.

I also want to acknowledge our wide group of research colleagues who have contributed to this research, those at the University of Washington, as well as through the TBI Model System.

So first I want to review some of the research on post traumatic headache. One of the things that is important to keep in mind is that headache diagnosis has really been divided into primary headaches and secondary headaches, with the difference being that post traumatic falls under this idea of secondary headache which is caused by some other event other than being a primary diagnosis or underlying genetic issue. In terms of definition of post traumatic headache, the International Headache Society classification really describes these headaches in terms of the head injury rather than any specific symptom criteria. The individuals need to meet the criteria for the severity of head injury, and there's differences based on mild versus moderate to severe. The headache needs to develop within seven days of injury or regaining consciousness after injury. There's the difference between acute and chronic, which is based on the three month mark. However, again, as I mentioned, there's no distinct clinical presentation or unique signs. And the timeline for development may be problematic, and I'll speak a little bit more to that later.

What's important, also, is that in the literature, post traumatic headache is really widely described and often it's really referred to any headache that's temporally related to traumatic brain injury. They often don't include specific information on when a headache occurred, or when a brain injury occurred, and it's simply anything that happened after traumatic brain injury.

Some studies have followed primary headache diagnostic criteria, and the latency issue comes up broadly and often isn't included in the literature. Sometimes due to the fact that people are unable to assess people early enough after injury, but also sometimes just because it's a very complicated criteria to apply.

So ultimately we know that post traumatic headache is one of the most common persisting symptoms after injury. In service members there's been quite a lot of research over the past few years, just due to the high rate of traumatic brain injuries, and there have been multiple studies that have been conducted with some individuals reporting up to 40% of those with traumatic brain injury reporting headache within one week of injury, with more reporting, 20% more at one month, and again, another report of 40% more than one month after injury, which, again, really speaks to the timeline of that seven days. Do we really think that those early headaches are the only ones related to the traumatic brain injury or the later-developing ones as well.

Of those who have been found to have concussion, Theeler and Erickson found that 98% also reported post traumatic headache at some time in the year after. And, of course, there's been other reports of lower rates, such as about 32% in research done by Hogan and his colleagues.

In terms of classification, migraine has been the most frequent classification applied in the current research. This is sometimes related both to – in the research – to following traumatic brain injury, but also just in broad people may have a migraine disorder even prior to receiving a head injury. So up to 36% of soldiers in a combat brigade reported the migraine headache, but it was also found to be 5.4 times more likely after a mild traumatic brain injury with, again, high rates of 89% to 95% of those with post traumatic headache meeting criteria for a migraine-like headache.

In civilian samples, early research really range from 30 to 90% depending on the study. And some of that is related to the time post injury, as well as the focus off and on clinical samples who are presenting with problems and one of those problems being headache. In the prospective studies that have been done, the range has been from 65% at one month to 26% at one month. Some studies said as much as 100% at the time of injury down to 15% at three months. And another study done by (inaudible) Kamal and colleagues suggesting that 66% had headache within the first ten days after injury but then no one reported headache at three months post-injury in their sample. So really highly variable. And we believe that a lot of this is due to the fact that the samples that people are looking at.

There's been very limited research in athletes, although an older study found that about 85% of people with sports-related concussion reported post traumatic headache. And there is a lot of evidence that headache can become persistent with from 19% to 22% of people in previous research before the research that we're going to talk about today.

So we conducted two studies that were funded by Neider. One was done as a module study under the TBI model system where we worked with six other centers and were able to enroll a total of 452 people and follow them over the course of a year. And these were all individuals with moderate to severe traumatic brain injury. Because this group was obviously more severe, we also wanted to do a sample of individuals with mild TBI, and we were able to get funding for a field-initiated program and were able to use a similar methodology for 212 individuals with mild traumatic brain injury at the University of Washington. In both studies we had similar assessment although baseline assessment did differ between the two because those with moderate to severe traumatic brain injury we were able to enroll during their acute inpatient rehabilitation stay, whereas with the mild cohort we were actually able to get them within seven days of injury.

Both groups, though, we follow at three, six and 12 months after their injuries by telephone. And we assessed incidence and prevalence as well as characteristics of the headache so we could understand more about what type of headache was happening for this prospective sample. What we found is that early after injury a lot of people had headache. In those with moderate to severe traumatic brain injury, 41% had headache during inpatient rehabilitation and there was a cumulative incidence of 71% who reported headache across the first year.

With mild TBI, rates were a bit higher. About half the people, a little over half the people assessed, had post traumatic headache within seven days of injury, but the rates were even higher with 91% of the population experienced headache at least one time across the first year.

So in order to kind of compare these two samples, we chose to look at people with new or worse headache because about 18% in both groups had a history of headache prior to their injury. And, by the way, this is one thing that has typically been left out of early research that people haven't asked about headaches that happened before their injury and may be complicating things in terms of numbers of people with headache.

So we then compared the groups at three, six and 12 months since those were the ones that we could compare to. What we found is that the groups were generally the same in several areas although there were differences in race categories, and while you can't see beyond this, it looks like a similar percentage of white in both groups. In the moderate to severe group, there was more blacks and less Hispanics than in the mild TBI group. The mild TBI group had higher education, and we believe this is really related to the fact that the mild TBI group was assessed in Washington, and in the King County area we tend to have higher levels of education. Cause of injury also was different with those folks in the mild TBI group having more vehicle crashes and less assaults involved than in the moderate to severe TBI group.

So you can see that when you look at prevalence of new and worse headache in the year after TBI, this really begins to think about the number of people that may be continuing to have headache over time, that it really is maintained for those with mild TBI at high rates, a little bit lower rates, but still, over a third of the sample having headache across the entire time period after headache.

In addition, going back to that issue of is it only within seven days of injury, you can see with cumulative incidents, you still have new incidence of headache that occurs over time, so there's more people having new headache at six and 12 months for both groups, mild and moderate to severe TBI, and when we think about beginning to approach treatment, we think that those are important groups to consider as well rather than only defining very narrowly.

Headache persistence is also an issue, and what we found is that there were generally more people in the mild TBI group who had headache and that we see that in incidence and cumulative incidence. However, the interesting thing is that those with moderate to severe headache tend to have also some persistence in headaches, but they also move into more severe types of headaches, which I'll be talking about.

We did look at headache classifications in terms of describing who was in the categories. We looked at people as assigning them to migraine or probable migraine if their pain was moderate to severe and if

they had at least two of the following criteria of significant disabling impact, unilateral throbbing or pulsating pain worsening with movement, and then either nausea or vomiting or sensitivity to light and sound.

For a tension headache, we defined those whose pain was mild to moderate, who had bilateral pain, vice-like or minimally disabling impact. And cervicogenic was pain that had the whole range from mild to severe, was unilateral and they had neck pain involved. Anyone else we put into the unclassifiable because there are, obviously, many different ways to diagnose headache, but those tended to be the three that we felt like were the most relevant for this group. As you can see, migraine and probable migraine was the highest category for all those folks across time for both moderate to severe and mild.

Tension headache was much more common for those with mild TBI compared to moderate to severe TBI. However, again, as we see, that this tendency for those who had moderate to severe TBI to have fewer headaches but those headaches that they have tend to be more severe. And, in fact, they're more frequent as well. So by at one year, those with moderate to severe tend to have more headaches several times a week, whereas those with mild TBI are much likely to have on the one-per-week or one-per-month range.

Impact of headache also is different between the two groups. The pain ratings are actually significantly different between those with mild TBI and moderate to severe TBI. And for the Headache Impact Test, which is the HIT-6 that we use, what you see is that at three and six months those with moderate to severe are much more likely to be impacted by their headache and that difference at 12 months was not significant.

We did examine risk factors because we know in the general population that, for example, women tend to be more likely to have headaches than men. However, we did not find any difference in those with traumatic brain injury. Now if you look at people who had a history of headache, they also tend to have a headache after traumatic brain injury, and there you'll see some difference with, of course, more women having headache. But if you just look at those with new and worse headaches, there is no significant gender difference.

We did, however, find a risk factor for age that we're still trying to really make sense of and understand, which is that age appears to be a bit of a protective factor. And this is something that has been found previously, for example Dr. Dickman in looking at symptoms of brain injury found that headache was less frequent in those 60 and above, and we also found out both for those with moderate to severe TBI, at least for three and six months, and definitely true for those with mild traumatic brain injury across time.

So ultimately what we have found is that headaches are a frequent problem after traumatic brain injury, with a higher prevalence after mild than moderate to severe TBI. However, headache is more severe in those with moderate to severe TBI. And the majority of these do meet ICHC classification as migraine and probable migraine. And age appears to be a risk factor for the development of headache with those who are younger having more likelihood of developing headache.

I also want to cover a little bit on the work that we've looked at in terms of treatment of post traumatic headache in our research. In previous research there was a review of interventions for post traumatic headache that was conducted in 2012, and there was really only one Class Two study. The rest were Three or Four. These are typically pharmacotherapy based, but there's also been some biologically-based and behavioral interventions, but there really is no evidence-based guidelines that exist.

We found that in those who were able to report on their treatment of headache with mild TBI, that the vast majority of individuals across time are using NSAIDs and acetaminophen. There are some higher rates, a little bit, of opioids, but very low rates, especially given the number of people who met criteria for migraine-type headache, very little use of tryptans or any other types of medication.

We also found that for those individuals who did take medication, that the medications were typically not very effective, whatever they're taking, and especially if they're probably not being directed, really, towards the type of problem that they're having. So those with tension headaches seemed to be best served, which is somewhat understandable about, but only about half the people who have tension headache are even trying to take any medication at all.

So ultimately, for those with mild TBI, and we were not able to get good data from those with moderate to severe TBI, unfortunately, but the majority are using just over-the-counter medications, and it's not clear whether they're actually seeking treatment for headache or not. Very few people use alternative treatment, so the most that we saw was about 21% of those with migraine or probable migraine use massage, but yet you would not necessarily expect that massage would help necessarily a migraine headache. Medication doesn't appear to be all that helpful, at least what's been used so far. And the recommendation in the literature are typically based on primary headache, but we're not really sure and are just now beginning to do some work on using some of these methods with post traumatic headache in more structured, randomized trials to begin to look at that.

So now I'm going to turn it over to Dr. Lucas.

Thank you, Dr. Hoffman. And now for something completely different.

I want to start talking about the clinical management of post traumatic headache, and just piggybacking on what Dr. Hoffman said, keep in mind that there are really no evidence-based clinical trials that really are helping us with this. And also back to the beginning of the conference, I'd like to review post traumatic headache. And here the big point is that post traumatic headache is a secondary headache disorder. Health criteria define the severity, the latency and the duration of the headache, but there really isn't any distinct clinical presentation for post traumatic headache, so we've been talking about post traumatic headache in terms of migraine types or pheno types or attention type type, or pheno type. But keep in mind that we're really using the words that have been developed for the primary headache disorder to describe a symptom complex which is post traumatic headache as a secondary headache disorder. So post traumatic headaches really have been defined, there's no specific pheno type for post traumatic headache. The location can be anywhere. Characterization of the pain is variable. Severity varies widely. And disability may be greater relative to non-post traumatic headache for a variety of reasons. Even the frequency, as we've seen, is very variable. And other injuries may complicate the clinical presentation.

So we're really using characterization to help us define a diagnostic framework for post traumatic headache. Of course, the most important thing is to recognize that someone has post traumatic headache following a TBI. There's really little value in asking someone have you had this for two months or four months but it gives you some idea of timing. And sometimes whether you need acute or preventative therapy.

The latency requirement, as we have heard, probably contributes to an under diagnosis, so clinical judgment here is very important. You don't rule out a post traumatic headache because it's eight day, or perhaps one month, and in both the civilian and the military populations, up to a third of these patients could present after a week.

After recognizing it, then evaluating the clinical features is important, and part of this also gets back to why people – or what people are self-treating with. You're using over-the-counter, nonspecific, low efficacy drugs, that may be used to treat a moderate to severe disabling headache. So trying to gauge severity, trying to gauge its features including location, characterization and associated features really helps you point to what a good therapeutic regimen could be. And the frequency, of course, helps in determining whether preventative as well as acute therapy are necessary.

So what we're really trying to get you to do is recognize the certain type or pheno type headache using primary headache criteria so that you can treat the pheno type and help to narrow in on, hopefully, a more efficacious therapy for your patients.

The other thing that's quite useful, we've found, in primary headache disorders, and probably even more so in post traumatic headaches, is to recognize comorbid conditions that are seen as migraine, and we'll talk a little bit about those later.

This slide on differentiating migraine from tension-type headaches is probably one that follows the international classification of headache disorders fairly closely, but keeping this in the back of your mind might be helpful when you're trying to categorize a post traumatic headache patient and also help you decide what medications you may start with. The single most important criteria in differentiating a migraine and a tension headache is the severity. A tension headache will be a flat headache. It's mild to moderate. And it's a low-impact headache whereas the migraine can be moderate to severe. Of course, it depends when you catch that headache as you're asking people to describe it, but untreated many of these headaches will be severe and disabling.

The unilaterality has been a little bit controversial. And unilaterality is not a definite requirement for migraine. They're often unilateral, about 60% of the time, but that means 40% of the time they won't be. So bilaterality is fine. There's an aura in a minority of patients, at least in the primary headache population, and that's about 18% or so.

But migraine is made worse by routine physical activity. We think that's due to a peripheral sensitization. So things like bending over to tie your shoe or running up the stairs just make people go, ooh, you know, their headache is just a little bit worse, and they really want to lie still. Throbbing or pounding, again, a manifestation of peripheral sensitization. It's like everything is -- again is increased for a lot of sensory issues including feeling the pulse in your carotid artery, a throbbing, pounding, pulsating character is quite common although it isn't always there. Some people can feel an explosive, like a balloon blowing up in their head, or somebody crushing their head from the outside. But, remember, the severity is the most important thing.

Typically there are associated features in migraine like nausea or vomiting, but photophobia and phonophobia usually co-occur. Tension-type headaches, again, usually low-impact, bilateral, squeezing vice-like tight. Usually don't have all the associated symptoms. No nausea or vomiting.

So once you've decided, is this a migraine, is this a tension headache, can you classify it at all, you tend to treat it as a primary headache disorder. Is this a hard and fast rule? No. We don't have any evidence-based medicine for that, but there are some indirect evidence. Is this indirect evidence from animal-based models that there may be some overlap between trauma-causing headaches and the primary headache disorder.

If you have a young person who isn't even in the running for a prior history of headache since peak prevalence of primary headache disorders is about 25 to 44, family history or headache may get to be very important there, and I think this is also one question to ask.

Severity of headache determines the need for non-specific or specific migraine therapy, something that I want to talk about in the next few slides.

And, again, frequency can determine a need for preventative therapy.

One thing that we need to keep in mind in post traumatic headache is the fact that the severity of the TBI may also bring an other issue into choosing medication, and that may have to do with the more complicated the medicine is to take, perhaps it's not useful for someone with traumatic brain injury, and also if there are side effects of cognition or confusion or word-finding difficulty, this is also something we might think about again.

The strategies for migraine management can really be divided into three. Most of us are used to thinking of treating a headache with acute therapy. You take something when it hurts to stop the pain. And we recognize the headache type to help us zone in on this. But even before thinking about acute treatment,

at least in the primary headache disorders, recognizing and avoiding triggers is quite useful. We don't have as much data for post traumatic headache in recognizing and avoiding triggers, but I think the same principles will apply. A headache diary is going to be the single most important thing to help you decide if your patient's therapy is working. It also is extremely important to determine predictable, possibly changeable, triggers. Some triggers are things such as the menstrual period, which is physiologic, but there are also other external triggers such as alcohol, poor sleep, skipping meals, stressful situations, strong smells like cigarettes, diesel. So, again, many things that are worth a discussion with someone who is suffering from these headaches.

Preventative therapy for frequent headache is something that I'll talk about in a few slides as well, but we need to remember about individualizing care and recognizing comorbid conditions. There's really no list about this is the first preventive drug you're going to try, and if that doesn't work, this is the second one you're going to try. It really needs to be individualized.

The goals of acute therapy is to restore the ability to function. We stratify care based on attack severity and disability, so, for example, if someone wakes up with an eight over ten headache, probably acetaminophen is not going to work. Probably three ibuprofen is not going to work. You need to match the efficacy of the initial headache therapy to the treatment need.

Treating a migraine attack as soon as possible after the onset has been proven in primary headache disorders to have better efficacy. And it's kind of a race between the migraine growing, called the wind up phenomenon, and the medication being able to help. There is evidence in the primary headache disorders that if you treat a headache after an hour of its onset your chances of being pain free at two hours are less than ten percent.

Also, if a headache reoccurs, it's okay to retreat. Many of these drugs do not turn off the headache, at least what we think of as a headache modulator or generator, and if someone is used to having a two-day or a three-day headache, sometime people need re-treatment.

The reason to have good efficacious therapy up front is to minimize the use of back up, rescue medications by making sure the initial drug is effective. This can avoid urgent care or emergency care therapy. But also we want to limit acute therapy to avoid medication overuse.

It's very good to optimize self-care by patient education, and sometimes, not only for people with post traumatic headaches, but in the primary headache disorders, a handwritten note or something typed out, if you have this headache and it's moderate, you can do this, but if that doesn't work, here, use this injectible. So, again, it's an individualized treatment but people need some help in their migraine toolbox or tool kit.

And, once again, avoid or minimize side effects by choosing a medication with really good tolerability so patients don't quit.

We divide acute migraine medications on the basis of their specificity. There's nonspecific and specific therapies. Nonspecific can be prescription or over-the-counter products, but they tend to be simple analgesics. Aspirin, acetaminophen. Combination analgesics, sometimes coming under the trade names of Excedrin, Excedrin Migraine, Excedrin Tension, Excedrin Extra Strength. They're all the same thing, by the way. A combination of aspirin, Tylenol and caffeine. There's a plethora of nonsteroidal anti-inflammatory medications available over the counter. Typically the directions are low in terms of therapeutic dose, but, of course, guidelines are very useful there.

Opioids are quite nonspecific, and I'll talk about those a little bit more.

Corticosteroids are not useful in headache by and large. There is some evidence from the emergency department treatment that a course of corticosteroids may decrease the recurrence of a headache, but that's one study.

Specific drugs really turn off the working end of a headache. The tryptans, the gold standard being sumatriptan that was out in the United States in 1993 followed by six more and known as a class of triptans, block serotonin type one. They work as serotonin 1B and 1D agonists. They do bind on the serotonin 1B and serotonin 1D receptor. And I'll be showing you a slide in the next couple of ones to explain where those are.

It's always worth it to also ask about what goes on with a headache in order to know if someone might need an adjunctive therapy. If you have a patient who has a lot of nausea or vomits, there's a couple of problems there. One, they could certainly get dehydrated. Two, they can't keep their pills down. So it's certainly worth to maybe give someone an anti-emetic such as prochlorperazine or chlorpromazine or metoclopramide. If they're vomiting, suppositories are ideal. They can keep those in the refrigerator for a year. Sometimes if you want to get people back to work, things like ondansetron that aren't sedating are very useful.

This is an often-used slide that presents acute anti-migraine targets. It's a little bit complicated, but bear with me here. That's the brain on the left. And I do want to point out one area where the trigeminal nerve pathway starts. So what you see on the left is the brain with some pain pathways there, but towards the right of the slide you're going to see the trigeminal nerve. And you'll see the trigeminal ganglion right in the middle. Remember that this nerve innervates the dura and it innervates most of the face, part of the eye, part of the ear. It is really the nerve that serves the sensation from about the mid-head forward. And most people who get a migraine will have a headache in the V-1 distribution, so in the eye, kind of up one quadrant, sometimes both quadrants. Sometimes they'll get it in V-2 over the cheek, so a lot of people come in saying, oh, I have a sinus headache, wherein that's not the truth. Some people can even get the headache in their teeth or their chin, V-3. But by and large, it's going to be the eye and above the eye radiating to the temple.

When the headache begins, and we think it begins in the back of the brain in an area called the pons, if this pathway is stimulated, then what's going to happen is towards the end of this pathway you'll see the release of neuropeptides. And probably the single most important neuropeptide that mediates headache is going to be CGRP, calcitonin gene related peptide. This is the most potent dilator seen in the body. And CGRP will diffuse over to these middle meningeal arteries and cause vasodilation, not only does the artery get bigger, but it also dumps fluids, probably histamine, probably serotonin products, and other (inaudible) products. Now that signal is going to go back into the – through this pathway – the trigeminal nerve pathway – back to the brain stem, and then through pain pathways to the thalamus and probably the anterior cingulate, which is the perception area for pain.

So I think it's important to note that 5HT_{1D} receptors are where CGRP is released, and 5HT_{1B} are in the blood vessel. So the triptans, as specific drugs, will block the release of CGRP and other neuropeptides and because they also bind on 5HT_{1D} inside the blood vessel, will also vasoconstrict that blood vessel. There is some evidence that these also may get into the brain, but they're not highly penetrant.

I'm not going to go through all these migraine-specific treatments, choices. I think you've heard of most of these. There are seven triptans. As I said before, most of these are now generic. They come in various forms such as tablets, orally disintegrating tablets, but it's certainly worth noting that with Sumatriptan you have several injectible devices, a stat dose, a needle-less injection system modeled after what's used in the Army to give people lots and lots of vaccines at the onset using an air gun approach. And also recently there was a patch that came out delivering a low but steady dose of Sumatriptan through a battery-operated arm patch.

DHG45, dihydroergotamine, and migranal nasal spray, which is also DHG, are not as widely used but they're highly effective drugs, and in the clinic, in a primary care setting or a neurology setting, and certainly in emergency settings, this might be the second drug of choice if someone's already used triptan.

Guidelines for initiating preventative medications in post traumatic headaches really are based on the guidelines for primary headache disorders. And it's arbitrary. If the frequency of a headache is greater

than four to six a month, if disability is very high, that interferes with quality of life, one may consider preventatives. Also if acute medication is more than two or three times a week, or if it's escalating use, I certainly would consider adding a preventative. Some patients say that their acute therapies work better as well. And there are some contraindications to the triptans and dihydroergotamines, both categories which are vasoconstrictive, so if someone has coronary artery disease, peripheral vascular disease, evidence of vasospasm, they're not indicated.

Sometimes comorbid conditions help to select preventative therapy, and the difference between primary headache disorders and post traumatic headache may involve cognition, so, of course, side effects, compliance, memory issues, might make it more complex.

Migraine preventative medications are varied. We borrow them from many facets of medicine. It doesn't have anything to do with their primary usefulness by and large. So, for example, for antidepressants, we're really not using their antidepressant effect but many of these will have effects on serotonin, dopamine, even norepinephrine, and we don't know how specifically they work in headache.

The tricyclics have been very useful, particularly amitriptyline, nortriptyline, for which data is the best. The SSRIs, or the SNRIs, have been useful. There is some evidence that SSRIs have been useful in small studies.

The cardiovascular drugs were probably the first drugs to be actually approved by the FDA for migraine prevention. For example, propranolol and timolol, which are approved, but there's also very good evidence that natolol and latoprolol (sp) can work as well.

Calcium channel blockers, the data isn't as good. They're typically more useful in cluster.

And the antiepileptics that many of us know and love. The Depakote, Topamax, to use two of the brand names.

I'm not going to go into these in detail. If there's time for questions at the end, I'll be glad to answer questions about Botulinum Toxin Type A, some of the anti-spasticity agents and their use in headache. Magnesium, which is a hot topic. Some of the glutamate blockers like memantine.

A couple of polling questions.

Yeah.

We have a couple polling questions right now that you can respond to.

Thank you. I think it looks like everybody is done.

Can we return to the slides?

I want to talk about a case of post traumatic headache in the few minutes that we have left. This isn't quite a simple case, but none of your cases are going to be quite simple cases. This is a 32-year-old woman who was referred to a concussion program six months after she had an injury during a city league soccer game. She was shouldered in the right temple by an opposing player, thrown to the ground, hitting the grass with the left side of her head. She saw stars, doesn't remember a conversation immediately after the event. Rested on the sidelines with ice and had an immediate onset headache and that evening her neck became stiff and painful.

The next day she had a little bit of trouble walking, she felt like she was off, and went to a local emergency room who diagnosed her, of course, with a mild concussion. She was treated by her primary care provider with physical therapy. She thought that made her headaches worse. It was pretty close after the injury. She was also given cyclobenzaprine, a muscle relaxant, ten milligrams up to three times a day,

and also a prescription for Hydrocodone/APAP known in some places as Norco or Vicodin, ten milligrams/325 milligrams of APAP up to four times a day. She can't work if she takes those medications, so she usually takes ibuprofen 800 milligrams three and mostly four times a day, and the other medications when she gets home.

Her headache has been a 24/7, with a severity five to six over ten to ten over ten. It's cap-like over the vertex, stopping at a band around her head with bilateral orbital pain. She gets allodynia or change in sensation, very tender over her head with severe pain. And it squeezes and throbs when it's very severe. She also has nausea, vomiting, light and sound sensitivity, and her neck pain gets worse when she's bending at work to try to use her computer. She's missing about one day of work a week and she's trying to avoid social activities and housework and just lays on the couch when she gets home. She has trouble getting to sleep.

She also has a prior history of mild headache around the time of her menstrual period. Family history of headaches. Recent weight loss. Poor sleep. Feeling anxious and unhappy. Her other medications are oral contraceptives, Vitamin D, she lives in the Pacific Northwest, and levothyroxine.

What's her diagnosis? Probably the easiest diagnosis to make is chronic post traumatic headache. It's been after three months of the injury when she was seen, and it follows a mild TBI with concussion. The headache increases in intensity at work because she's trying to focus on the computer. If we evaluate the clinical features of her headache, we'll see that with some headaches, particularly when they get severe, there's throbbing, physical activity makes them worse, they're moderate to severe. She has nausea and occasional vomiting and light and sound sensitivity, so this is consistent with primary headache features of migraine.

She also has comorbid conditions that are seen with migraine and that are seen with concussion. She's having difficulty sleeping, she's having some anxiety, and she's feeling down.

So the decision was made to treat her with drugs commonly used for acute and preventative therapy of migraine. Acute therapy for her most severe headaches, triptan (sp), was chosen. And it was decided if a triptan didn't work on its own, to add non-steroidal anti inflammatory medication. In this case we chose naproxen sodium 550 milligrams, and I'll tell you why in a little bit.

For preventative therapy we chose amitriptyline 10 milligrams at bedtime. She's having sleep issues. You might argue that ten milligrams, not much of a pain blocker, but it's reasonable. An alternative drug could be tizanidine based on a couple of papers for primary headache disorder, both in treating migraine and tension headaches. Fluoxetine was added in a low dose for mood and headache chronicity since there's some papers showing it has some effect. And it could be synergistic with a tricyclic. Alternative therapies in that case could be duloxetine or an anti-epilepsy drug if these don't work.

Can another diagnosis be made? Many of you probably noticed she was taking ibuprofen three and four times a day. She was taking Vicodin at least once a day, ten milligrams, and cyclobenzaprine, quite frequently. So yes, she has chronic post traumatic headache, but also, does she have chronic migraine? A headache that's gone to episodic to daily, more than 15 days of headache a month. Does she have medication overuse headache? Does she have cervicogenic headache?

Well medication overuse headache is probably the most likely there. Chronic migraine doesn't really fit the bill because she never really did have episodic migraine and then switch over. Cervicogenic headache is controversial, and if there's questions about that we can talk about it later, but a cervicogenic headache is not a migraine. And medication overuse headache, there's several reasons for her to have that, primarily using ibuprofen several times a day, Vicodin every day, and cyclobenzaprine, all drugs that can cause medication overuse headache.

Avoid medication overuse. Education is really important here. It can occur in patients with preexisting primary headache disorders, but also people that might be on the way to those as well. The pattern of

headaches in overuse of analgesics is predictable and the frequency escalates. People typically wake with a headache. They might get it in the middle of the night. Whenever their drugs wear off, they get that headache. So the way to prevent that is to limit frequency of medication use. It's ideal to keep any acute therapy to two to three days a week on average.

Refractory to otherwise appropriate acute and preventative therapy is the big problem with medication overuse. If someone's using ibuprofen four tablets three times a day, you can put them on anatriptol (sp) and you can put them on topramide (sp), you can put them on anything and it won't work. You have to get rid of the offending medication. You got to taper people either cold turkey or you can do it in a tapering dose, and you have to be a really careful if it's an opiate or a barbiturate because in that case you want to do it slowly and be very careful.

There's going to be more headaches during withdrawal. You can start acute therapy that's not anything like what they're overusing, or really start bridge therapy with preventatives keeping in mind that they're not going to work well until they're off the offending drugs.

Some comorbidities of the primary headaches disorders, specifically migraine, are found also in people with concussion, so depression, anxiety, phobia, bipolar disorder, irritable bowel, sleep disorder, fibromyalgia, all found more commonly in those with migraine than in those without migraine. So use the comorbid conditions to assist with selection of preventative therapy. There's no evidence for the post traumatic headaches, but people with the primary headache disorders are starting to look at the holistic approach if you will. It's not just the headache that someone has. They have headache. They have poor sleep. They have some depression. So you might want to choose a tricyclic and an SSRI or an SNRI. Tricyclics helping with the insomnia, for example.

So in conclusion, it's a significant problem after traumatic brain injury. A large number of individuals report severe, often disabling, headache even up to one year following injury. Headache characterization was most frequently consistent with a migraine type. Please classify headaches according to primary headache criteria. It may help determine acute and preventive therapy. And, of course, we need more studies to determine whether TBI can be treated more effectively as some of the evidence we have for the primary headache disorders.

Thank you very much.

Great. So it's Christian Shenouda, the moderator. Thank you both for your presentation. To the audience, if you have any questions for the presenters, please feel free to submit them via the Question box on the left of the screen.

As attendees submit their questions for the presenters, I'd like to mention that DVBIC will soon begin development of a headache clinical recommendation with a projected release date of early 2015.

Each month we take a moment to briefly highlight one of several free educational materials available. This month's debrief highlights the free DCoE downloadable neuroimaging resources. The clinical diagnosis of mild TBI is based on history of TBI in the context of a change in alteration of consciousness. Neuroimaging findings are not typically included in the diagnosis of mild TBI, however, neuroimaging is recommended in the setting of clinical red flags, new onset or persistent or worsening symptoms, or individuals whose recovery is not progressing as anticipated. In addition to a history and physical as well as clinical judgment, these standardized recommendations of neuroimaging testing parameters can aid care across the military health system by decreasing neuroimaging when not indicated and creating the capability to compare similar studies regardless of their origin. The DCoE neuroimaging following mild TBI clinical recommendation offers military health system providers an evidence-based standard approach to imaging in the acute, subacute and chronic stages following TBI. This guidance represents a review of currently-published literature and contributions from clinical subject matter experts representing the services, Department of Veterans Affairs, as well as academic, research and civilian sectors.

The clinical imaging modalities included include CT scans, MRI, PET and SPEC scans. This clinical recommendation and its companion resources, the clinical support tool and provider education slide deck, are all available at the DVBIC website, dvbic.dcoe.mil, and can be downloaded from the Files box in the lower left of your screen. You can also access the February 2013 DVBIC webinar, Overview of Imaging for TBI by visiting the DVBIC website and selecting Educational Materials. From there select Online Education to access the webinar.

Now it's time for some questions from the audience. We're monitoring the Question box, and we'll forward the questions to the presenters for response. If you haven't already done so, you can submit your questions now via the Question box located on the screen. We'll respond to as many questions as time permits.

So I think you guys did a great job of addressing some of the questions that were already asked, and I'm going to try to group these together so that we can fit as many of them in. The first question that we have is about rates of TBI in mild TBI or concussion. One of the earlier slides showed a rate of 60% to 80% rates of concussion. The question is, is that in all concussion or is that only for those who displayed post-concussive symptoms?

It's for the rates were for anybody who had the diagnosis of mild traumatic brain injury, so yes, the rates are very high, but it's – we followed people prospectively so we didn't just select people who had other symptoms. This may have been their only symptom. But it is that high. I mean I know that it's surprising for some people, but that is true.

Exactly. And I think one of the things that's always surprising to everyone is when mild cases display more symptoms than moderate or severe patients. Can you comment on that? Is that because the severes have more medical issues or decreased awareness? What has been your experience?

I think that's a really complicated question because we don't fully understand at this point. I think that a lot more needs to be done about looking about what the underlying issues are around headache, and I think that's still very unknown. There's some theories that are going around. Definitely one of the possibilities that has been put out is that simply because there are more medical issues that headache doesn't get reported. However, it also is interesting to me that I don't feel like that's necessarily as true due to the fact that for those people who do have headache, they're reporting a lot more problems with their headache. So I don't think it's just a matter of, you know, that they're not, they're just not aware of it. For example, if they're lower awareness.

One theory that had been put out early was the fact that maybe there's some protective factor about early intervention that's often done with more moderate to severe TBI. But, again, I think it's all theoretical at this point and more research needs to be done.

Okay. Thank you. So the next grouping of questions is about treatment, and we'll start off with non-pharmacological treatments. One of the audience is asking about hypnotherapy. Can you comment about how often you use alternative treatment like hypnotherapy, acupuncture or massage?

For primary headache disorders we use massage fairly regularly. It's a reasonable preventative. We also have used acupuncture. Hypnotherapy, some people will use. It's a little – and, again, all this is anecdotal because the best evidence for alternative therapies has come from a combination of cognitive behavioral therapy or biofeedback therapy, so everything else is kind of by the seat of your pants, and we don't have good data, I think, on post traumatic headaches for alternatives.

Yeah, I was going to say in our research what we found is that very few people were using any kind of alternative treatments, any kind of therapies of any sort within the first year. Now that might change, and we certainly have a lot more to learn about what people are using. And as far as I know I have not seen any specific studies that have actually utilized hypnotherapy specifically for headache after brain injury,

but, again, there's very little research that's been done on any kind of treatment for post traumatic headache.

So let's move on to pharmacologicals. One of the participants had a question about triptans, and I think you adequately addressed that by saying that triptans are effective if they are administered early on. Would you like to say anything else about the use of triptans?

There's, again, no evidence-based data for the use of triptans in post traumatic headaches, but I think there's a lot of anecdotal evidence and there's been published papers on the use of triptans there. I don't think one triptan is better than the other, but I think one of the questions that is quite, quite useful to ask your patients has more to do with not the triptan but with the dose type. So, for example, if someone has a headache that reaches peak pain in 30 to 60 minutes, you might consider an injectible than tablets it takes one to two hours to reach peak blood concentration.

Everybody is different in terms of their approach to which triptan they like. Sumatriptan might be the gold standard, but for many people it's not well absorbed, it has the lowest viability, so an injectible might be better.

A nice thing to remember is use an injectible if someone has a wake up, throw up, or back up headache. So, for example, if they wake up with it, it's probably gone on for a while. If you need it as a backup or if someone is very nauseous or vomiting. And if you use the pill and it hasn't worked, remember the injection.

There's also low, slow triptans, like naratriptan and frovatriptan that take a couple hours, even longer than the other triptans, to reach peak blood concentration. But there are advantages that they have side effect profiles much like placebo.

Okay. That's a great point.

Another question here is about the use of NSAIDs. In your presentation you alluded to that some NSAID dosages are sub-therapeutic. And then you went on to mention naproxen 550 milligram. Is there a typical dose that you use in practice?

A lot of that is going to depend on how a patient feels about taking NSAIDs. Obviously if there's GI issues, you're going to avoid those or use low dose, but when I talk about packaging, for example, take naproxen sodium 220 milligrams packaged brand as Aleve, if you look at the directions, it will say one tablet BID. If you use more than two days, go ask your doctor about it. But really, these doses are very low and typically they don't work. We've learned from the combination of Sumatriptan and naproxen known as Treximet, that 500 milligrams of naproxen was useful. If someone wants to go out and by an over-the-counter Aleve-type preparation, then I usually tell people to take two or two-and-a-half. Obviously you wouldn't want to do that all the time, but if you're treating an episodic migraine, I think it's okay to go high. And, of course you're going to tell them to take it with food or milk and not on an empty stomach.

There is also some evidence that combining naproxen, which has a different pH than the triptans, may even drive the triptan in a little faster. So they are useful.

Okay. We have a question here about a pediatric patient, 13 years old with chronic headache six months post concussion. Is there a specific medication class that you would recommend for pediatric patients?

I use the same rules in pediatric patients as I do in adults, and that's first look for the comorbid conditions. Other than the parents. No, I'm kidding. So sorry. But part of that is going to depend on the size of the child, how they do with medications. Of course the headache type. And how disabling they are. I'm not a pediatric neurologist, and some pediatric neurologists are a little bit concerned about prescribing antidepressants because of some warnings about increased suicidality and that sort of thing. So this

really has to be done in association with a psychologist if they're in on the therapy, and I can't emphasize more the usefulness of a psychologist for a child who has a chronic pain disorder. Typically it affects their social life, it affects their ability to participate in school. Sometimes you need a school program to give people extra time. So there's not one specific therapy. I will use anti-epilepsy drugs. I will use combinations of tricyclics and the SSRIs. We have used onabotulinum toxin for people under 18 as well.

Okay. Well that's a perfect segue because we have a few questions about Botox and injectibles. So for Botox, can you comment on patient selection and how you would arrive at the decision to use Botox as your therapy?

The use of Botox as therapy is really derived from the FDA's approval of using onabotulinum toxin for chronic migraine. That's great than 15 days a month of headache, more than four hours a day, and the failure of a response to treat categories of preventatives such as anti-epilepsy drugs, tricyclic antidepressants, calcium channel blockers or the beta blockers. It is approved for those 18 and over but in special circumstances with the parents' involvement we've used it in younger children.

It is painful, and it's probably a lot more painful in kids. It feels like a few little wasp stings. But it can be very useful. We do not think that onabotulinum toxin use in treatment of migraines stems from its paralytic effect, but you do get that. It is also taken up by sensory nerves and this is how we think it works, but it does have a paralytic effect, so there can be side effects. On the other hand, if there's a lot of tension involved in shoulders, maybe that's not such a bad thing and part of the therapeutic effect.

There are other things for preventatives that might be a little safer in children. The use of magnesium, for example. Magnesium is not well absorbed unfortunately. We know that from things like Milk of Magnesia and magnesium citrate. But there are some forms of magnesium that are better absorbed and don't cause diarrhea. But magnesium infusions can be very useful, and the naturopaths have taught us that, that kind of a high injection rate magnesium is really quite useful as an acute and a preventative therapy.

Some of the Vitamin Bs, such as Riboflavin at a dose of 400 milligrams a day have been found to be useful as have feverfew, which contains the active ingredient Puracol and can be found in a combination product. I think Migrelief, Migrahealth, among other things, have this triple combination of medications. And it is over the counter.

Okay. One more question about injectibles here is that of occipital nerve blocks. So occipital nerve blocks for cervicogenic headache, would they share the same indications, a couple failed headache medications?

I think occipital nerve blocks are really under used and it's certainly worth trying in people who have headaches in the occipital dermatomal distribution, so we're looking at the back of the head, we're looking at C2, C3, C4, and recall that if you're looking at the primary headache disorders, 80-plus percent of people will have neck involvement in their distribution of pain. So it can be the front of the head. It can be the quadrant. It can be the trigeminal. But also it's usually the neck. And these people usually have a tight, vice-like pain. So it can be two different types of pain in the same person. The referred pain to the back of the head and the neck is common. Whether or not someone has occipital neuralgia is irrelevant. And I think the receptive fields, you know, if the neck and shoulder are involved, it's sure worth trying occipital nerve blocks. Again, there's no evidence based data that these work in post traumatic headache, but whether or not there is a neck injury or not, whether or not C2, C3, C4 is injured, the occipital nerve blocks can work because these nerves innervate not only do they innervate the receptive fields, but they really go into the headache generator, they go into that long sensory nuclei, the trigeminal nucleus caudalis, and it may be, and we have absolutely no idea how the occipital nerve blocks work, but it may be that they just decrease afferent input and they break some sort of the forward loop, but it's an easy procedure. It can be done in your office in 15 minutes, and it's definitely worth looking at.

Okay. So we have a question that came through about biofeedback. Even though we already addressed non-pharmacologic, can you address biofeedback and your experience with that?

So biofeedback, again, I don't know that we have any research indication that it's been used very frequently, or if at all, and I don't know, Sylvia, if you ever make a recommendation for the use of biofeedback specifically?

In post traumatic headaches?

Yeah.

I have because I think post traumatic headache, like any other headache, if you look at biofeedback as a tool to decrease triggers, for example a lot of people will become anxious, they're going to get a headache, their day is ruined, it's just sort of, you know, getting more and more anxious about this. And then they start taking pills too often. This pill-popping behavior. And then before you know it you're in medication overuse. And that's just one of the reasons. But I think biofeedback, when used, if it's somebody that can utilize that behavior, is extremely valuable.

Okay. So one of my personal questions here that I've got – I've got to get this one in, is for judging the efficacy of treatments. You mentioned a couple of things. Headache diaries as well as the HIT-6 evaluation tool. Is there any other recommended tool that you would say that is going to help us judge our efficacy of headache frequency and severity over time after a treatment has been initiated?

The headache diary is the single most important thing you can use because that's what you really need for efficacy. And there are a lot of applications. In fact, just before this conference, you know, I just typed in my iPhone headache diaries, and you're going to see a plethora of these. I mean, there's some just for the iPhone. But you can download them for different types of smart phones.

There is also paper ones that you can get from the National Headache Foundation, WebMD, Head Wise, any of the pharmaceutical companies making migraine drugs. But the reason these are so important is you can ask the patient not only to give you the days of headache they have, but also ask them to rate their headache intensity on a one to ten scale and ask them to tell you what they've taken every single day. So in one diary you can look at whether any perturbation you've made has really made a difference in frequency or intensity of headache, and you can also – it's an easy way to look at overuse.

Scores that you get from HIT-6, the Headache Impact Test, and the Midas Score, which is a three-month disability score retroactive, they're good, but they're kind of non-linear scales, so typically if I see people with really bad headaches they're always going to have high numbers. And so it's not good, I think, from visit to visit if you're really looking at more subtle effects of starting a medication. That doesn't mean they're not useful because, again, their huge impact is right in the beginning when you're trying to see how bad is the headache really to that person. And so sometimes you can be really – you'll say, how are you, and they'll say, oh, I'm doing fine, and then you're looking at a disability score that's severe disability, so it's something worth talking to the patient about.

I also want to comment on headache diaries that I think one of the things that adds a complexity is people with cognitive disability. And so we're still trying to understand how easy it is to actually complete a headache diary on a regular basis and whether or not we need to enlist other people, other family members, caregivers in order to actually get the data that you need because one of the things that we've found in just some of the research that we're doing is that you can't always get people to do it on a consistent, daily basis and their ability to do an accurate look back of even previous day or previous week is often not very effective. So I think that the tighter that you can be in terms of the minimal amount of information and the easier it is to complete, so certainly if people do have kind of hand-held devices that tends to work better. But, again, I think we're still learning about how best to do this.

Okay. In order to finish within the allotted time, let me take one more question here. And this question is about aura versus non-aura. So there's a lot of talk about primary headache disorders having aura versus non-aura. Have you found anything with post traumatic headache that differentiates headache types between aura and non-aura?

In our studies we didn't specifically divide out aura and non-aura. I mean, having aura certainly put you in the migraine category right away, but we combined those two. There have been other reports in the literature that, again, small samples that may point to aura being a little bit over-represented in the post traumatic headache group than in the primary headache group. But we don't have any direct information on that. But that's still an area of great interest.

So we'll continue on. What I'll say is after the webinar please visit <http://continuingeducation.dcri.duke.edu/> to complete the online CE evaluation and post-test and download your CE certificate or certificate of attendance. Again, the Duke Medicine website online evaluation and post-test will be open through next Thursday, May 15, 2014, at 11:59 Eastern time.

Please help us improve future webinars. We encourage you to give us feedback. A survey will open in a separate browser on your computer if you'd like to give us feedback. To access this presentation and the resource list for this webinar, you may download them from the Files box below or on the DVBIC website, which is dvbic.dcoe.mil/online-education. An audio recording and edited transcript of the closed captioning will be posted to that link in approximately one week.

The Chat function will remain open ten minutes after the conclusion of the webinar to permit attendees to continue to chat with each other.

Finally, the next DCoE psychological webinar titled Understanding Changes in PTSD and Acute Stress Disorder Diagnosis and DSM5 is scheduled for May 22, from 1:00 to 2:30 p.m. Eastern time. The next DCoE traumatic brain injury webinar, Why Does Concussion Affect Men Differently Than Women, is scheduled for June 12th from 1:00 to 2:30 p.m. Eastern time.

Thank you again to our speakers and to our audience participants. The presentation has now concluded.

That does conclude today's conference. Thank you for your participation. You may disconnect at this time.