



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

**January 8, 2015, 1-2:30 p.m. (EST)**

### **“The Role of Sleep, Activity, and Nutrition in the Treatment and Recovery of Traumatic Brain Injury”**

Good afternoon and thank you all for standing by. At this time, all participants are in a listen-only mode. After the presentation, they will be conducting a question and answer session over the computer or over the tool. Today's call is being recorded. If you have any objections, you may disconnect at this time. I'll now turn the meeting over to Dr. Heechin Chae. You may proceed.

Good afternoon, everyone. This is Heechin Chae in warm Fort Belvoir, Virginia. It's only 19 degrees outside. I hope everyone is indoors in a warm place. We have the privilege to present to you about the role of sleep, activity and nutrition in the treatment and recovery of traumatic brain injury. Webinar details: live closed captioning is available through the Federal Relay Conference Captioning. And webinar audio is not provided through Adobe Connect or Defense Connect Online in the Question and Answer Session. We'll do that after the presentation, so please prepare to submit questions via the Q&A box.

The resources are available for download in the Files box on the screen or visit the website listed there. There are Continuing Education details. As you know, you'll receive CME credits for this presentation. And all registered participants prior to the deadline on Thursday at 3:00 p.m. and meet the eligibility requirements stated above are eligible to receive CE credit or a Certificate of Attendance.

If you preregistered for this webinar and want to obtain a CE Certificate or Certificate of Attendance, you must complete the online CE Evaluation and posttest; and that's very important. And I think you get 1.5 credits for this presentation.

Questions in Chat – 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 because we will not be able to answer that. The Q&A pod is monitored during the webinar. Questions will be forwarded to the presenters, to me, the moderator, for response during the Q&A session. Participants may chat with one another during this webinar through the Chat pod. The Chat function will remain open for ten minutes after the conclusion of the webinar.

This webinar overview, in 2013, Lieutenant General Patricia Horoho, the U.S. Army Surgeon General, launched an organizational initiative to improve the health, readiness, and resilience of the Army family. The performance triad is a comprehensive plan to promote the balance of sleep, activity, and nutrition among Army family members to improve health and wellness. The three key components of the performance triad are instrumental in the recovery process for service members with a TBI, traumatic brain injury, particularly those with persistent symptoms and chronic injury.

At the conclusion of the webinar, we hope to be able to help you discuss the critical role of sleep. Activity, and nutrition in brain health recovery; examine current evidence-based treatment practices associated with recovery care; and evaluate how sleep, activity and nutrition impact recovery care practices.

Right now we'd like to play a short video clip of Lieutenant General Patricia Horoho talking about the three-step pilot course designed to improve activity, nutrition and sleep. Now please adjust your speaker volume on your computer as we play the video. Thank you.

[Video]

So before we start the presentation, I'd like to introduce the speakers for today. First, that's me. I'll be serving as the moderator. I'm currently serving as the Director of the Intrepid Spirit Center in Fort Belvoir, as well as the Site Director of Defense and Veterans Brain Injury Center at Fort Belvoir, Virginia. I've treated – I think I've been doing this for a few years. And I moved from Boston to start this Department about four years ago. And I hold a faculty appointment at the Uniformed Services University of Health and Sciences. And I'm excited to serve as the moderator today.

The first presenter is Dr. Maulik Purohit. He's a board certified psychiatrist. He is also certified in brain injury medicine. He serves as the Director of Research, Neurorehabilitation and TBI for the Intrepid Spirit Center in Fort Belvoir. He also serves as the Senior Scientific Director of Defense and Veterans Brain Injury Center at Fort Belvoir. Dr. Purohit is an Integrated Medicine and Stress Management Specialist. He has served as faculty in the Harvard Medical School Department of Physical Medicine and Rehabilitation and established one of the premier sports concussion programs through Massachusetts General Hospital.

Thank you for joining us today, Dr. Purohit.

Dr. Emerald Lin is also a board certified Psychiatrist and also certified in brain injury medicine. She coordinates the interdisciplinary care of active duty service members with acute and chronic traumatic brain injury at the Intrepid Spirit Center here at Fort Belvoir and serves as the Course Director for the Continuing Medical Education Lecture Series for Intrepid Spirit Center staff. Dr. Lin also developed the Botulinum Toxin Headache Clinic at our clinic, and she also served in many leadership roles with regional and national psychiatrist societies including Program Director of the New York Society of PM&R and Program Director/Secretary and Fellowship Representative of the Residents and Fellows Council of the Association of Academic Psychiatrists.

Thank you for joining us today, Dr. Lin.

Before we start, I want to just disclose that the views expressed throughout the presentation are our thoughts and do not reflect the official policy of the Defense Department, DoD, or the U.S. Government. We do not have any intent to discuss off-label/investigative use of commercial products or devices, and we do not have any relevant relationships to disclose today.

This is the outline for today's presentation. I'll be talking first about the introduction, and Dr. Purohit and also Dr. Lin will follow afterwards.

As you know, traumatic brain injury is one of the signature injuries of the OEF and OIF. According to a RAND study in 2008, 19.5% of service members in those wars sustained a TBI. And 80% of these are the result of exposures to blasts. Because of the large number of service members involved in these wars, 19.5% represents a significant number of service members. And we should also keep in mind that many service members chose not to report their injuries after deployment.

And 76% of all TBIs that occurred in the Army from 2000 to 2012 occurred in garrison, according to the Armed Forces Health Surveillance Center Study, 2014. And this basically tells us that TBI is perhaps an inherent risk for service members just like it is in sports like football, ice hockey or soccer.

Also today's topic of discussion can be applied to all spectrums of traumatic brain injury. We want to focus on mild TBI because the majority of service members who sustained TBIs in the past ten-plus years and also in garrison had MTBI. We know that MTBI is very interesting and challenging because we assume

the majority of the people who sustain the injury will recover fully. But we also know through literature that, depending on studies, really 10% to 20% of those that sustain TBI do not recover fully.

And so like all clinicians who are faced with this, what we call "miserable 20%," who do not recover fully from the MTBI as expected, here at the Intrepid Center we struggle with questions like, did they really have MTBI? And if they did, why did they fully recover? Have they reached maximum recovery?

And most of the treatments that we are practicing today in TBI Clinic are of a compensatory nature, compensation to basically cope with their impairments and problems. It's not really geared toward perhaps like tapping into their potential for recovery or neuroplasticity and so on. So can this miserable 20% continue to improve even after, let's say, one year post injury? Based on this literature and our clinical experience, we've come to realize that perhaps there are things that we can do to improve their recovery or perhaps remove the barriers that prevented or stopped the neuroplasticity process.

And so because of that, our initial treatment is focused on removing the barriers or factors that prevent the potential recovery. More specifically, our treatments are based on four pillars: sleep, nutrition, physical movement, exercise and stress. And that's why we believe that the performance triad of the Army medicine can be applied to patients with traumatic brain injury.

And before we talk about this role of sleep, nutrition, exercise, it's important to talk about the context of the injury. We believe that this is very important. For example in deployment, we know that a person who gets a concussed brain or sustains a TBI, they're experiencing poor sleep even prior to the injury, such as I listed there, and poor nutrition.

And they are under a highly stressful environment, what the service members call they are in a different battle with them. And extreme environmental conditions – whether it be temperatures or carrying heavy loads – and all those things, we have to keep that in mind as the context and the time of the injury.

This slide is a complicated slide. It's just a reminder that even though the acute concussion or MTBI management involves rest and education, underneath -- microscopically and physiologically -- it's a very complicated process. There is a cascade of events that occur after the initial event that we are still trying to understand and also understand the implications a few days or a few weeks or even certainly months after the injury.

So at this time, I'd like to turn the podium to Dr. Purohit, who will be talking about sleep and exercise.

Thank you for allowing us to speak today and share this information. I wanted to express that the same disclosures that Dr. Chae stated earlier apply to this part of the talk as well.

For the outline for this talk, I'm going to discuss some of the background. Dr. Chae covered some of the TBI background. I'm going to discuss some of the physiology with stress and go through some of that background very briefly, and then talk about exercise and sleep and how they relate to the diagnosis.

For the next slide, metabolic changes with brain injury, I know for this audience there very well were some brain injuries in the background. But I wanted to present this slide and the next couple of slides because traditionally with brain injury, our diagnostic methods have been self-report because our neuroimaging and other biomarkers are not really up to par for diagnostics, which is very different than other diagnoses; for example, diabetes, which we have very clear lab tests of and other things to say yes or no, and we don't base it on self-report.

Clearly, our clinical diagnostic tools for TBI are really self-report. And I know for a lot of people that becomes a mixed bag, with different motivations and other things going on. But down the pipeline, we do have some things coming on that will help improve our diagnosis. One of them is looking at metabolic changes because this injury does have a definitive functional component in addition to a short-term component that we are able to see on clinical neuroimaging.

And this discusses the metabolic function in various areas of the brain after brain injury, looking at a cingulum bundle, lingual gyrus and cuneus. And the cingulum bundle is of primary importance because it's really important for emotional regulation, emotional processing; and it's also related to some cognitive function through (inaudible) functions. And so these are very important areas. With real injury, we can see a metabolic change after injury. TBI is not just a self-reported injury, but there are real changes going on physiologically and metabolically.

And then on the next slide, this is a very interesting study by Christine Mac Donald and others originally out of Washington University in St. Louis. And this is very relevant for this population because this is specifically the service members that came back from OEF and OIF and looking at white matter changes in some of the advanced neuroimaging that's coming down the pipeline with the diffusion tensor and diffusion-related imaging based on damage in the cingulum bundle, again, consistent with the previous study, and then the cerebellar peduncle, orbitofrontal white matter.

And on the next slide, the corpus callosum on the left and then the internal capsule and uncinate fasciculus on the right. Now, these are very important areas. The cingulum bundle, again, we talked about. The corpus callosum is very important; it's the largest white matter tract in the brain. It connects the right and left side. It's important for cognition, emotional regulation, and really a lot of functions between the right and left coordination.

The uncinate fasciculus is another very important area. It connects the frontal and temporal regions. It's important for something called interoceptive perception, which is the perception of things that are going on within the body and allowing the person to detect stress and other events going on. So interoceptive perception is very important, and damage to the uncinate fasciculus causes that perception to go down. And as a result, patients aren't able to detect changes that are going on within them, which is very important for diagnostic purposes and also for patients coming to be evaluated initially.

On the next slide, looking at the importance of the white matter, this is a slide comparing a control group, which is the black bars, to patients with TBI with good outcomes, which is the grey bar, to very smooth TBI and poor outcomes. The dichotomy from a disability scale splitting down the middle into good and poor outcomes; the sample size is below. The y axis is mean diffusivity, a marker of white matter integrity. And what we see is that the black and the grey bars at all the various white matter tracts, forceps major and forceps minor and so forth, those that had good outcomes were the same in terms of white matter integrity as those with controls, meaning no injury. The poor outcomes had significantly more mean diffusivity, indicating far more white matter damage compared to the TBI with good recovery and the control group, really lending a lot of support to the idea that white really is important and integral to identifying what the injury is and relating to the symptoms of injury and the disability that comes from it.

On the next slide, we talk about sources of stress and changing back to where stress comes into this role, as Dr. Chae mentioned in the introductory slides. These are some of the places of stress and sources of stress that people have: whether their pre-injury health is a big issue; a support system may or may not exist; career impact, especially in terms of whether patients will be progressing in their or not as a result of the injury, whether they'll keep their job or not as a result of the injury; financial status; company-morbid medical conditions, of course; and family obligations and commitments that they may have on top of the injury.

And so these are a lot of sources of stress. These are a source of stress for everybody, but they're compounded for patients with TBI and have a multiplicative effect in terms of their outcomes and their disability.

On the effects of stress on the next slide, we can see that stress affects all aspects of life. Now conceptually we break them down to body, mind, emotions and behavior. But really, it affects everything. Something that affects us in our emotions will affect our behavior and the way we feel and think and so forth. And so it really is a mixed bag, and we can essentially break them down to where it affects all aspects of life.

On the next slide, but it's a little bit complicated. We talk about stress and TBI. And PTSD is really a post-traumatic stress disorder. And so the effects of stress in TBI are very overlapping: cognitive function, irritability, impulsivity, other things – depression. There are some things that may or may not overlap.

But on top of the Venn diagram, there is the polypharmacy, meaning patient symptoms are treated with multiple medications. If you are depressed, you get an SSRI. If you have cognitive dysfunction, you might get neuro (inaudible) agent. If you have psychotic behavior, you might get an antipsychotic medication. So there are a lot of things going on with polypharmacy on top of the symptom management and the other diagnoses.

Along with that, there is the pain and suffering, which we don't talk about as often. But the chronic pain in some blast injuries will certainly have a lot of pain from that injury, and it will compound the diagnosis and the disability even further. So it's a very complicated picture by the time they get to us. And all of this is the significant minority that experiences this and affects them in a lot of ways.

On the next slide, we discuss the physiology of the stress response. When stress is detected, it's really first detected by the hypothalamus, which sends a signal to the pituitary, to the adrenal cortex, which causes the release of cortisol. Now, cortisol we've heard about a lot as the stress hormone. And it's a great hormone in many ways when it goes to peak and valley, meaning it goes up and then it goes down. That effect actually gives us stress fitness.

Unfortunately, when we have a chronic level of stress, meaning high levels of stress for an extended period of time, that cortisol level stays constantly elevated, and then that's where some of the problems happen. What cortisol does is it disproportionately affects the prefrontal cortex and the hippocampus. The prefrontal cortex is really important for personality mood disorders, attention, and it leads to memory. Hippocampus is the memory area, particularly for visual memory. Cortisol affects them and causes actually literally a shrinking of those structures, which we'll see on the next slide, which is a real effect of stress – not just a psychological effect of stress, but a real physiological and structural effect of stress.

On the next slide, what we're seeing is a normal patient on the left side. And we see the hippocampi right next to the green arrow and then the same contralateral structure on the left side of the same picture. And then on the right, we see the shrinking of the hippocampi. And we see that there is a literal shrinking of the hippocampi, and you can see that there is air in that picture, meaning that that structure is no longer there. And this is Alzheimer's disease, so this is really a study that looked at cortisol levels over an extended period of time to see what the effects are structurally on the brain. And so this is the long-term effect of cortisol in a pathological sense for a long time.

So moving on to what exercise and sleep can do, these are really designed to help with the stress response and the downturn effects of TBI to help recover some of that damage. And what Dr. Chae said is we're trying to build positive neuroplasticity to help redevelop the brain from the injury itself.

Exercise is broken into two categories, more for concept than anything else. The first part is traditional, what we think about as aerobic, like running and weight lifting, which are the traditional sort of exercises in the U.S., versus some of the newer information that's coming out, relaxation exercises with mind/body medicine such as meditation, yoga and tai chi. And this is defined based on the NIH definition of mind/body and what those things can do for patients with TBI as well.

The next slide, the role of exercise – the reason exercise has been studied is we know that exercise has tremendous health benefits across the spectrum for almost any ailment – weight management, blood pressure, depression and mood issues, pain management. If we could put exercise in a pill, it would be the best selling drug out there.

And then people looked at for specific (inaudible), for exercise on acute low back pain; and this is where the foundation of exercise for TBI came out of, is looking at pain patients, particularly low back pain. And they saw that exercise helped the recovery. And so we're trying to see if that challenges the concept of rest for mild TBI.

So the first thing we looked at was bed rest versus no bed rest and the effectiveness of bed rest after mild TBI. So one group received no bed rest; the other group received six days of bed rest; a total of 107 patients; 1:1 randomization. And then the outcome measure was the SF-36, saying patients symptom reports -- such as depression, anxiety, attention, memory, those types of things -- SF-36 is a standard quality of life measure.

So on the next slide -- and I apologize that this is small -- but I wanted to present the raw data that they presented. On the top one-third of the picture, what you see is at two weeks, there is a slight trend towards improvement with bed rest. But the statistical significance is zero, meaning that really there is no statistical difference between the two groups.

And at the next time periods, three months and six months, there is no difference in the groups at all; and they're both at the same level, whether they got bed rest or not. So outcomes after TBI, with bed rest or no bed rest, probably not a difference, although in the short term, in the first few days, it may be easier for patients to follow the bed rest recommendation just for a couple of days because of the symptoms of nausea, vomiting and other things that may be going on. But in terms of outcomes, there is no difference at three and six months.

On the next slide is an animal model study looking at exercise and is there any actual structural change in the brain and particularly looking at BDNF. BDNF is associated with neuroplasticity in the brain. It's sort of the funnel point and comes into the first step for helping with neuroplasticity, among other things involved. In animals, they started looking at rats with acute and delayed intervention of exercise.

On the next slide, what we see is on the left set of bars, on the first two bars, we have a SHAM group in the white bar and a SHAM group in the grey bar. On the left, the white bar is the group that did not get exercise, and the bar on the right is with exercise with the grey. So you see that there is beading up with exercise versus no exercise in rats with no injuries, which is expected; exercise helps with brain function.

In the middle two bars, with the yellow and the black, what we see is that in the short phase of TBI, those with sedentary, meaning no exercise, which is the yellow bar, you had a little bit higher beading up than those with exercise in the early phase, although that's statistically not significant.

But on the third set of bars on that same ipsilateral side, is the delayed injury, meaning delayed phase. And not in the acute phase but a few days out, about six days out from injury, there is more beading up with exercise than without exercise in a sedentary setting. So clearly in the acute phase, there may not be an advantage; but in the delayed phase, there may be.

And then the other side is the contralateral side, which actually shows similar results for the delayed phase, but the middle side actually shows more beading for the sedentary on the contralateral side. So it argues that in the short-term phase, exercise may not be helpful and possibly harmful; but in the delayed phase, it may actually have a pretty good benefit.

On the next graph, this is the cognitive function of the water maze section as a standard cognitive function in animal models. What we see is actually on the left is the time of the event. In the beginning stage, the exercise group with the acute phase injury had the longest time in getting to the water maze and getting to the finish compared to all the other groups, again arguing that functionally exercise in the early phase may not be helpful.

On the right side, in the delayed phase, in the interest of time, it sort of gives a summary. And the punchline is that in the delayed phase, exercise was much more helpful versus the acute phase in supporting the structure. The previous slide had the beading up as the protein was released (inaudible) functional event of the cognitive function.

On the next slide, looking at exercise versus medications. And putting it in context, well, exercise helps; but how does it help in terms of the medications we give. Is it better to give medication, or is it better to

prescribe exercise. In this study, they looked at neurogenesis in the hippocampus in animal models, comparing fluoxetine, which is Prozac, and duloxetine, which is Cymbalta, which are very common SSRIs and SNRIs, compared to exercise in female mice.

On the top part of the graph, this is a representative sample of each group. The top left is the control; the top right is the fluoxetine; bottom left is Cymbalta; and the bottom right is the exercise group. Not apparent on the visual graph; but on the bottom bar graph, what's apparent is that the last bar is the highest at the end of each. That's the exercise group. So they had the best results compared to any other treatments and even compared to Cymbalta at different doses and fluoxetine. So exercise had a pretty powerful effect compared to medication alone.

And then on the next study, looking at a human study, is that of the Pittsburgh group looking at neurocognitive performance and activity to look at a retrospective cohort study in athletes and looking at the impact scores. On the next slide, the effective of exertion on recovery, and what we basically see is that the middle bar or the white bar shows low levels of exercise in the early phase, such as lawn mowing or slow walking, had actually the best outcomes cognitively whereas people with a higher level of exercise, running for example on the right side, had more cognitive performance in all areas measured by impact studies.

In terms of mood, TBI, and exercise, a study out of University of Washington and (inaudible) in that lab, they looked at the exercise in chronic TBI over six months to five years. So you can see that it helps to improve mood.

On the next slide, they looked at the data and the pilot endpoint per treatment analysis, whether this helps or not, treatment analysis meaning you check every patient, whether they follow the protocol or not. And there are no differences in the outcomes for anything except for a little bit on the pain side, which are the ones that are bolded.

But on the next slide, when they broke it down to the ones that actually followed the protocol of doing the exercise, as compared to those that did not, there was some improvement in mood in the depression inventory and in the sleep as well. So you can argue that primary endpoint exercise didn't help, but when you looked at it deeper, of those that exercised, it actually did seem to help their sleep and their depression, even for those patients that were chronic, meaning six months to five years out.

In summary, bed rest may or may not be helpful. Cognitive rest is not well studied in terms of not bed rest specifically, but cognitive rest. I know that there's a study recently that came out of the Swanson regarding two days of rest versus five days of rest. I'll discuss that in the Q&A if people have questions. But there is some controversy about that.

Animal studies support aerobic exercise in the late phase, not the early phase. And we do need a little better study of timing and duration of exercise, dose of exercise, and when to introduce exercise for treatment.

The other part of this is the relaxation exercises. That's really specifically to address the stress response. And the reason we want to go into (inaudible) and it says so on the background prevalence, there is a lot of interest around exercise particularly in alternative medicine. Those with symptoms, the ones who are treating symptoms have a high prevalence of use, in the 40% or 50%, of those with those symptoms use some type of alternative medicine. And in the odds ratio, when you account for just the symptom and account for all the other demographics among clinicians, it really does point to the symptom being associated with the increased likelihood of use, 42% to 85% more than those without symptoms.

And then in terms of modality on the next slide, the mind/body medicine is the number one thing used – biological things like herbal medication. Or mind body is things like medication yoga, with a high prevalence in the general population as well as the military population. And so the demand is there. And we wanted to present some of the evidence, and some of the reasons for use on the next slide. We find that conventional treatment is not effective a lot of the time, and it's about 25% of the time for those with

symptoms. And then providers actually recommended almost 40% of the time for those with symptoms. So it's really high in demand, not just by patients but also by providers.

And in the general population, they're spending a lot of money for this. It shows the out-of-pocket expenditures for these categories. If we look at the total, it shows that those with symptoms are spending about \$200 extra out-of-pocket in addition to any other instrument that they're paying for.

And then the biological norm says that they keep buying herbal medication. The mind/body is one of the most prevalent as well. And people are actually paying money instead of just relying on insurance, so it's creating demand.

When we looked at MBSR, mindfulness-based stress reduction, it's a combination of mindfulness and medication and yoga; four weekly sessions for patients and then given a home CD, this was a pilot trial. And the results that we found on this neuroimaging just eight weeks, is there is a 1% increase in the bilateral hippocampi for the patients in the group with the intervention versus those without. There was amygdala increase as well on the left side. And this is counterintuitive, but this is actually seen a lot with mindful studies. The effects of the amygdala increasing are actually counterintuitive to what we would expect in that they are calmer and less fearful and less PTSD symptoms.

And then also the right orbito-frontal white matter, uncinate fasciculus, improved 6% in volume, meaning that patients were more aware of the things that were going on and better able to deal with them. So pretty good pilot evidence; obviously needs a larger sampling size and a bigger study. But it's one of the evidences in patients with TBI.

On the next slide, we have (inaudible) actually changes in cortical thickness in patients that meditate versus those that don't. And on the left screenshot and on the right are different areas, 9 and 10 in the insula. And in those that meditated, those areas had a higher grey matter volume, meaning those areas actually grew in size compared to those that did not meditate, indicating that there is a benefit from meditation in those areas that is very physical and not just psychological.

On the next slide, looking at the function of these areas -- the previous slide was looking at just the structure -- this is looking at the function of those areas, fMRI, in ACC and medial prefrontal cortex ranging from cognitive areas to emotional processing areas also improved in function, not just structure.

On the third slide, we're looking at genetic changes. These are very complex outcomes for genetics. But on the N1 group, what we see on the left side is all of those different genes that are listed out there on the N1 group top to bottom. The red indicates that they're more expressed and more prevalent, and the green means that they're downgraded and less prevalent.

The N1 group is the standard population in the U.S. and is the representative of that sample. And the ones that are expressed in the top, the red ones, are high inflammatory D. The M group, the meditation group on the far right, they're the exact opposite. So those that meditate for a long time have less inflammatory genes, indicated by the green on top, and more anti-inflammatory genes, indicated at the right on the bottom.

So what they said was, well, can we take those that haven't meditated and give them eight weeks of meditation and see what the results are. So that's what the N2 group is in the middle. They started out just like the N1 group in terms of their genetics and the expression. But after eight weeks of meditation, you see that there are changes in the expression in those genes. And they are closer to the meditation group than they were prior to meditation, indicating that even in eight weeks we can have a change.

The next slide, going to sleep, sleep in TBI is a big issue. 97% of people with people have subjective sleep complaints. 55% have objective insomnia. 34% have sleep apnea. So one-third of patients with TBI end up with some type of sleep apnea. So it's important to screen them. 85% have hypersomnia, meaning daytime sleepiness or sleeping too much. Sleep fragmentation, meaning the cycle of sleep, disturbs more than half. And then certain types of injury, like blunt trauma, are more related to sleep

apnea, whereas blast injury is more related to primary insomnia. We looked at things, such as nightmare disorder, which are part of this, but wanted to stick to sleep strictly.

Sleep architecture – the meaning of sleep architecture is that there are four stages of sleep – Stage 1, 2 and 3 and then REM sleep. Stage one is getting into sleep. Stage 2 is light sleep, but sleep. And then Stage 3 is the deep sleep, the delta sleep that people talk about. And then REM sleep is the dream sleep or traditionally thought of as the dream sleep. All stages are important; but particular Stage 3 is important because that's when the highest amount of growth hormones is secreted, which is important for restoration and reparative functions in the body. REM sleep is important for processing thoughts and memories from the prior day or the past in general. And these two are really important stages because they help the brain develop and grow and recover from whatever trauma and other things that they may have experienced. So without these stages and without having the proper sleep, it can lead to a lot of different issues for patients.

The next slide talks about REM sleep and disturbance in patients with TBI. So 14 veterans with TBI were compared in their glucose metabolism during REM and wakefulness. And what we see is across the board in many areas – in the amygdala, hippocampus, parahippocampal gyrus, thalamus, insula – there are a lot of functional changes in metabolic activity in patients with TBI. And all the areas in red are different parts of the brain listed below that were affected and had a different glucose metabolism as a result of TBIs.

And then the role of sleep in terms of symptoms and clinical presentation – they looked at patients with sleep disturbances, (inaudible), and falls longitudinally for about 6 months and 12 months and said, is there a difference in their symptoms. What they found is without sleep, there is a definite difference in their depression scale, their aptitude scale, which was a trend for statistically significant, and their mini mental status at one year compared to those with TBIs but with good sleep. Sleep has a definite effect on long-term health and long-term symptomatology clinically.

Sleep and debris clearance – this is one of the reasons that sleep has an effect similar to the lymphatic system. Now, the brain does not have a lymphatic system to clear debris. But it has glial cells that support this function by clearing debris and sending them to the blood stream to get rid of damage that might have occurred.

So the glymphatic system presented on the left side, in initial injury or initial stage pre-injury, they're working fine to clear the debris. It goes into the lymphatic and out into normal blood flow. The second stage with acute injury, there is a change in polarity. And over chronic time, that change in polarity remains and it really affects their ability to capture the tau and secrete it into the blood stream. That allows the tau proteins to accumulate and cause long-term effects, and this may be one mechanism as a way of causing the long-term effects of TBI that we see. Oftentimes, we talk about symptoms that occur in the immediate phase but they accrue over time. This may be one method or one reason as to why that may happen.

In the pharmacological treatment, these are the common drugs that people use: benzodiazepines, Z drugs, trazadone and melatonin agonists. They all have their issues in terms of side effects, affecting cognition, affecting drowsiness in the morning. I think these are pretty well-known to this audience. And so we look at other methods to improve this sleep situation through some of the mind/body things that we talked about earlier. And so mindfulness and sleep, this is a support group and focus group to see if mindfulness was something that was effective for the patients in subjective reporting.

What they found was that after treatment after eight weeks, the quantity may be unaffected but the quality of sleep improved in subjective reports; and the patients felt better about their sleep. And as a result, they were motivated by the results to do this more often, which is a huge swing in terms of lifestyle measures and compliance. When the motivation increases and the compliance increases, the results get better.

And then looking at neurophysiology, this is looking at Gamma waves, which are considered higher cognitive ways, higher functioning waves of the brain. And what we see on the left side in the red are

those that have been meditating and practicing mindfulness versus on the blue side that have not been and are the general population. And we see a clear difference in the Gamma wave productivity of those that have been meditating for a long time versus those that have not been meditating for a long time. And there is a higher level of Gamma function, which is key for cognition.

And then looking at MBSR compared to medication to put it in a context. MBSR, which is mindfulness and meditation and yoga, had non- (inaudible) effects in terms of results at eight weeks and five months compared to Lunesta. And Lunesta has far more adverse events than yoga and meditation do, so it was a big statement saying that MBSRs may be equivalent to Lunesta.

So just summarizing sleep, it's important for neural healing. Poor sleep may have worse outcomes. The lymphatic system is very important for acute and long-term injury. And the pharmacologic interventions may have negative consequences, so we're looking for better options.

So conclusions for my section overall, exercise has mixed results; but we're looking for better dosing and better understanding of when and where to give exercise and what type. And then sleep is very critical for good recovery in the long term.

And one thing I want to present at the last is traditionally, we've had biowearables. But this is a way to monitor things beyond the subjective report of monitoring patients and what benefits they're actually getting.

I'm going to turn it over to Dr. Lin for the next stage, and thank you for allowing me to present.

Thank you. I echo the disclosures of the previous speakers.

I will be speaking about the topic of nutrition. It is well-known as a fuel for the body and the brain and, like a medication, can be both beneficial or toxic. This is an exciting area of research as nutrition has the potential to play a role in preventing and optimizing recovery in brain injury.

I will be discussing the following topics: sugar, supplements, alcohol, meals ready to eat (MREs) and telomeres. As you can see from the picture, there is a balance between good factors – those being omega 3s and certain supplements – and detrimental factors including sugar, alcohol and substances which are somewhat prevalent in our society and in some of our military populations. The good factors have the potential to balance out and even cancel out the effects of the negative factors, as we will discuss.

Let's talk about sugar. Here we can see from the CDC data that we, as a nation, consume sugar on a daily basis, whether it be from soda or fruit drinks, consistently throughout the years. And this statistic extends internationally, and the world average daily intake is now 70 grams or 17 teaspoons. So let's take a closer look at how the U.S. compares to the rest of the world.

Here is a graph depicting the annual global soda consumption versus GDP per capita. See how most of the other countries follow the trend line. So this shows a general correlation between GDP and soda consumption. So the richer you are, the more soda you can drink. However, look at where the USA is in relation to everyone else. We're well above the trend line. In fact, when they made this graph, they actually had to extend the y axis so that we could fit.

So how could this be? We'll take a look at the typical sugar content in popular drinks. What does it mean when we talk about grams of sugar? It usually means nothing. It means that it's a number. So let's put it into context. Soda usually has the equivalent of about two chocolate bars full of sugar, so think about this the next time you have a can of soda.

Next, coffee or coffee-based beverages can contain up to 8.5 scoops of ice cream. Surprising, right – so think about that the next time you go and order a cappuccino. Next, energy drinks, which are very popular in the population we serve. Often they can contain up to six glazed donuts worth of sugar. And even

healthy drinks, such as Odwalla or sports and health drinks, often contain a lot of sugar in order to make them taste better. Are you surprised?

So sugar is already potentially addictive. And what happens when you add caffeine? Here is a chart with some popular energy drinks. And if you want to take a look at the serving size, the serving size is eight fluid ounces. And a lot of the energy drinks are actually 1.5 to 2.0 serving sizes, so double whatever numbers you see here. So let's say, for example, look at Monster: 8 fluid ounces, 100 calories, 27 grams of sugar, and also 92 grams of caffeine. So in a usual can of Monster, you'll have close to 200, which is almost half of the recommended daily max.

These drinks are important to keep in mind because they are very popular among our military service members, especially when they're in a deployed setting or working 24 hours. So it quickly adds up.

Let's look at how sugar can affect the brain. Is there a connection between diet and cognition or between cell metabolism and neuroplasticity? Gomez-Pinilla and Agrawal conducted a research study on animals. So they had one group of mice who got a fructose solution, and a second group of mice got that which had an addition of omega 3 fatty acids made up of flaxseed oil and DHA, which we'll talk about later. These are essential for synaptic function.

So what did they find? They found that there was a definite different in maze performance. Group 1 was definitely slower. They had decreased synaptic activity, and they had increased influx resistance. So they can see a physiological from the consumption of the plain fructose. And Group 2 performed much faster. So what is the significance of this? A diet high in fructose can slow a brain's function and cause a decrease in memory and learning. And omega 3 fatty acids can help counteract this effect.

Let's take a closer look at the data. So in A, you can see that insulin to resistance is significantly increased in the deficient mice, which is important because this is one of the factors activating the proinflammatory response and other associated negative pathways. In graphs B and C, you can see there is a positive correlation between both serum triglyceride level and IR with latency times. So therefore, the presence of omega 3 can affect cognition in terms of speed and processing speed and visual memory.

So what does this study suggest? Diet indeed can affect energy, metabolism, and synaptic processes, which in turn influences neuronal function, signaling and synaptic plasticity. And oxidative stress activated by the proinflammatory pathway promotes damage to the phospholipids present in the plasma membrane, which includes the omega 3 fatty acid DHA, which in turn disrupts neuronal signaling.

And Dr. Purohit already spoke of [VDNS] earlier. So omega 3s are present in standard foods including almonds, walnuts, salmon and sardines. And so far, we have discussed that they have many potential benefits including neuroplastic effects, supporting synaptic connections, counteracting a high-sugar diet, working on the sedative level to reduce free radicals and inflammation, and maintaining insulin and sugar balance. And they also play a role in the plasma membrane itself, which is important for neuronal signaling.

So let's take a look at how omega 3s can affect recovery. Here is the data from results from an animal study showing full recovery from TBI in the DHA deficient group, which is deficient TBI versus the adequate group, which is adequate TBI. The first graph shows the recovery curves of the adequate mice versus the deficient mice on the rotarod, which is sort of like a treadmill for mice. And it tests how long they are able to endure staying on that treadmill. And you can see that on Days 2 and 4 on the left side, there is a statistically significant difference in endurance from the adequate to the deficient mice.

And on the right side, which looks at the motor function quality, so how well are they really running on this treadmill looking at their percentage of foot slips, you can also see that there is a huge, significant difference in the quality of the foot placement between the two groups. Why is this important? If we extrapolate this to the military population, who may or may not have a good diet or may be out on the frontlines and only eating the MREs, which are low in omega 3s, they already have a potential towards

having a brain injury and many other injuries. And if they sustain a TBI, their recovery may be hindered; and this can place them and their team in danger because their endurance isn't as good, their preciseness of action isn't as good.

So how can these animal studies help us humans? They sound promising as methods to pretreat and treat brain injuries. Unfortunately, research is limited but promising. Here is a case study. This is a case study of a teenager who sustained a severe TBI after a car accident. And with collaboration of his neurosurgeon, he was put on a diet high in omega 3 fatty acids. He did remarkably well, progressing from not responding and needing total assistance to being able to return to school, graduating with his diploma and becoming independent. So this study suggests that omega 3 fatty acids may be beneficial and therapeutic, especially in the acute stage of severe TBI.

Let's talk about supplements. In the interest of time, I will highlight important points and concepts of the study. Creatine is an amino acid that is a common supplement taken purportedly to promote gains in performance, strength and lean body amounts. So it's often taken by athletes of all levels and many of our military service members. Here is a prospective, randomized open-label pilot study where creatine was given for six months. And what they found was a statistically significant difference between the control in the black and the cases in the white in regards to the symptoms of headache on the left, dizziness in the middle and fatigue on the right. These results build a strong case towards a randomized control trial for the possible neuro protective effect of creatine.

Next, BCAAs – these are essential amino acids important in energy metabolism and protein in neuro transmitter synthesis and, therefore, cognitive performance. This animal study found that the consumption of isoleucine and valine for five days after a TBI restored hippocampal BCAA levels to normal. You can see that in the left-hand chart. The differences are not significant from the SHAM, which is the black.

And on the right side, they looked at fear conditioning tests for the prevention of freezing to adverse stimuli. So you can see the SHAM group on the left has a certain percentage of freezing. And on the TBI group has a significant cognitive impairment. You can see, it's much smaller. And this is completely reversed by the consumption of the BCAA treatment, which you see with the green arrow.

Why is this important? The hippocampus is a brain structure implicated in higher learning and memory, and this is often damaged in a brain injury. So in short, BCAA concentration is indeed higher post consumption – Graph 1 – and also has functional effect on the right side, as you can see.

Lastly, I'll talk about curcumin; and this is the principal natural phenom in this size tumor, which is a common ingredient used in Indian cooking. A GFAP is a marker of damage. And in this study, as you can see, SHAM shows 100% of GFAP expression, and you can see that having a TBI more than doubles this GFAP expression. Giving curcumin 30 minutes prior to injury decreases expression below baseline levels, as you can see in the medium grey bar. So this is just a loading of curcumin supports neuroprotection, and it causes less damage by decreasing glial activation in cerebral edema.

Let's talk about alcohol. Even after abstinence, alcohol still has a negative effect on the brain. And in the first study that we'll talk about, Hayes compared abstinent alcoholics to healthy controls and still found that the abstinent alcoholic had reduced whole brain thickness compared to controls and in addition to that had decreased cortical thickness bilaterally in multiple areas of the brain, and most severe in the frontal and temporal regions. And these are areas that are especially vulnerable in TBI to the true (inaudible) injury. So if you have a person who is an abstinent alcoholic and they get a brain injury, they're even more susceptible to further injury and delayed recovery.

Moving on to white matter tracts, yes, alcohol affects them as well. Fortier looked at the effect of alcohol on white matter tracts, which are really important for cognition, brain circuitry, executive functioning and processing. And what they found was there was a widespread bilateral decrease in multiple tracts including frontal, temporal, parietal and cerebellar white matter tracts – so generalized effects. And they also found a dose-specific effect in the inferior frontal gyrus, and this area is important for decision

making and inhibition. So the effects are frontostriatal circuits, which mediate the inhibitory control of the brain. This can lead to a terrible vicious cycle for these populations.

Let's talk about MREs. These are meals ready to eat, high in calories – in fact, one often contains 2,900 calories – and it's lightweight. Unfortunately, it is not very high on nutrition and especially deficient in omega 3. So oftentimes, unfortunately, they are also the only food source on the frontlines. And these military service members are expected to be ready for high-intensity combat operations. We've discussed earlier why it's important to support and brain function in these situations, so research is ongoing.

Finally, telomeres – some of you may remember these from middle school or high school biology. And these are the protective caps on the ends of chromosomes that protect our genetic material. And their length is maintained by a careful balance of shortening and lengthening, and the lengthening is done by telomerase. And shortening of telomeres is associated with the potential loss of our genetic material and with chronological age and is also associated with an increased risk of morbidity and mortality in later years.

So as you can see in this graph, there are several factors that can cause shortening; and the main catalyst is stress, way on the left. And it can cause a cascade of inflammation, cellular aging, oxidative stress, DNA damage and mitochondrial dysfunction. And on the right side, telomere lengthening is encouraged with antioxidant defense, physical activity, healthy diet and stress reduction. As you can see, all things come back to being influenced by the triad of nutrition, sleep and exercise.

So how much can diet really affect telomere length? It turns out that the quality of diet is really important. Crous-Bou, et al, looked at a cohort study and examined the diet of this group of females and grouped them into a prudent diet, which is a cardiac diet similar to the Mediterranean diet – high in vegetables, fruits, legumes, seafood, unsaturated fat – versus a Western diet, which is heavy in bread and processed meats and saturated fats. And they graded diets on an AMD score. And the higher the score, the closer to the Mediterranean diet.

What did they find? They found that telomere length was statistically significantly inversely associated between age and telomere length. So younger women had longer telomeres, which is expected. What else? They found a positive association between adherence to this Mediterranean diet and telomeres, so higher AMD scores associated with higher telomere length, which stayed significant even after adjusting for other factors. They also found a significant trend across AMD groups with telomere length.

So let's look at the relevant graph. At the bottom, you see the AMED score for association with the telomere length, which we talked about earlier, which is statistically significant. And this is closely mirrored by the AHEI score, the alternate healthy eating index score, which is on the left. And that is slightly less significant. There was no statistically significant association for the prudent or Western dietary patterns. So what they found was the difference in telomere length for each one-point change in AMD score corresponded to an average of 1.5 years of aging.

So let's put this in context of other healthy (inaudible) cell factors. A three-point change in AMD score corresponds to 4.5 years of aging. This is actually comparable to the difference between smokers and non-smokers. Most of us would say, oh my diet is terrible; but that's okay because I don't smoke. But guess what? It's just as bad. And to add insult to injury, also physical activity and exercise is the next thing they looked at. Having a sedentary lifestyle can be as deadly as smoking. And also, the last point on this slide, anxiety is even worse, which leads us into the next study and reemphasizes the importance of psychological health. You can see that anxiety can actually correspond to six years of aging. (inaudible) for you to think about this.

Lastly, to tie it all together with what Drs. Chae and Purohit have spoken of earlier, Epel et al examined how mindfulness can influence cognition in aging and in turn can affect the triad of sleep, nutrition and exercise. And the effects of stress are cumulative. So here we can see how mindfulness in cognitive states can go either way.

Stress cognition, on the right, is where one perceives everything as a threat, thus activating the stress arousal response. To tie it into the triad, for example, someone in this state is not thinking clearly and definitely doesn't have the time to plan out a good Mediterranean meal. On the flip side, on the left-hand side, this is a positive cognitive state. This is where one perceives things as a challenge and they're in control and positive arousal state is activated, which leads to better cognition and likely better neuro physiological and psychological health.

Let's take a look next at a real case study, if we have time. This is involving a professional athlete. And much like a military service member, a professional athlete has the optimal – well, actually, let me skip it so I can go to the – this is a fun story that we can talk about later.

Summary and recommendations – we went over a bunch of studies ranging from basic science to animal studies to human studies, and we found a lot of positive results. And we looked at a human study which had a very powerful result that being sedentary and having a bad diet can be as bad as smoking. And so the take home message is lifestyle changes and incorporation of exercise and sleep are important. Of course, we always need more clinical research in terms of extrapolating from animal studies, looking at dosing and duration, looking at preloading, looking at the deployed setting and, of course different populations and performing prospective randomized controlled trials.

Thank you for allowing us to share our thoughts with you.

Thank you, Dr. Purohit, and thank you, Dr. Lin, for wonderful presentations. As you can see, I think we had the challenge to really cram a lot of information in a short period of time. And honestly, we could have talked about each topic for a day. So I just want to apologize to the audience; if we seemed a little bit rushed, it's because of our excitement to share as much information with all of you. I think this is a good time to have you think about questions for the speakers.

And I just want to wrap up by saying that as a clinician, I think we have a tendency to minimize the effect of MTBI, meaning that if we hear that a service member had the injury three or four years ago, we can quickly dismiss it, that the problems they're having now has nothing to do with that event. Or on the flip side, we can pretty much blame all the problems that they have on the TBI and TBI events that happened a couple of years ago, a few years ago. So I think the answer lies somewhere between. I think we have to appreciate the fact that MTBI – anytime we injure a complex organ, there's going to be a complex reaction to it. So we're still learning what that really means.

At the same time, we cannot (inaudible) everything the person has, certainly after a certain time passes after the event because we know that the context of the injury is important, the comorbid factors are important. But as you heard today, the patterns, the habit of sleep, exercise and nutrition can play a huge role in the brain function.

So here at Intrepid Center at Fort Belvoir, we like to emphasize more about brain health, towards treatment concerns and moving forward rather than talking about the TBI, PTSD. We get the diagnosis out of the way and focus on improving brain health, brain function, so that they can have a sense of control, a sense of empowerment that, hey, I can do something. I can (inaudible) something of my sleep, nutrition, exercise so my brain can function better than it currently is.

So with that note, I'll close and turn to the questions from the audience. Thank you.

The questions that we have so far, the first question goes to Dr. Purohit: As far as metabolic and physiological changes, do the images show these changes even years after the injury; or will the imaging change over time? Dr. Purohit?

Thank you for a very good question. Most of the studies have been done more in the acute phase, in the short-term phase. So it's possible these changes may be lasting chronically, but we don't have sufficient evidence or sufficient studies right now to evaluate that. Most patients have focused on the acute population. It's a great question. Unfortunately, we don't know what it looked like a year or two years,

three years out. I believe the (inaudible) Christina (inaudible) was a little bit further out, I think six months out. So those are probably the longest ones that are out there.

But up to two, three, four years, we don't know what that looks like. Hopefully the next few years, we'll have a little bit more information about that. But it's a great question.

Thank you. The second question actually goes to Dr. Purohit too: "What timeframe is considered a long time for stress exposure to cause?"

Another good question. In terms of what is considered a long time, there is not a cutoff in terms of the way we deal with acute and chronic injury in terms of what caused the damage. But the longer the stress exists, the more damage that there is. There is a linear pattern between the exposure to stress and the amount of effects that the stress has on somebody. So if you're exposed for a year of chronic stress, you'll have a year's worth of damage versus, say, five years or ten years. There isn't really a cutoff between acute and chronic, per se, in that sense because it's an ongoing effect.

But certainly the reverse of that is also possible. The more effort is made towards some of the treatment, someone can improve the result of that stress as well.

Thank you. The third question is: "Injured soldiers often cannot run. Is physical therapy sufficient exercise?"

That's a very good point. Here at our Intrepid Spirit Center, our physical therapists actually assess what a service member can and cannot do with their physical activity. It's often (inaudible) as you know. Service members think that cardiac exercise is running. We try to be creative, such as bringing swimming, aqua therapy, such as aqua therapy, water exercises. We even use some equipment that reduces the load to the joints. The whole point is increasing the heart rate, increasing cardiac output, other than just running per se. So I think that's the mission that physical therapists have here at the Intrepid Spirit Center. The next question: "Do you feel DVBIC advocates a culture that encourages and empowers a soldier to develop a mindset that drives him to optimize their own health in order to improve their performance and resiliency?"

Well, that's a good question. I think this is a challenge for the whole healthcare system. I don't think it's just at DVBIC. But I think we as healthcare professionals, we have bad habits. We think that somehow we have to take the responsibility to make the patient better. So instead of empowering our patients, we try to pretty much minimize that and give them pills and tell them that this is what they've got to do or else. Something is wrong with you.

So I think that we as providers have to adopt the mentality that, hey, here is more and more data and knowledge coming out through research studies and clinical experiences. Certainly from our discussion today, sleep, nutrition, exercise, these are things that a patient can actually change his lifestyle to feel empowered. These are some of the things that I can control in order to improve brain health.

So I think more and more, just the whole healthcare system in general will embrace this – not just TBI, but cardiac diseases and diabetes and all the chronic diseases will adopt this model. And certainly DVBIC with owning the path (inaudible) care TBI, will certainly enforce this important factor as well.

The next question is: "Is it true that the sleep deprivation is part of the military culture? What role will the performance triad play in that culture in the Intrepid Centers in the care we are providing?"

Well, I think this is very true. Certainly, service members who've had multiple deployments, and even one deployment, come back sleep deprived. I had actually a marine in infantry tell me this morning that after concussive events, two people – this actually happened in 2006 – but two marines sat next to him and tried to make him stay awake for 48 hours so that they know that something is not wrong with him. So you can see that the individual story varies, and sleep deprivation is certainly, unfortunately, a byproduct, maybe not part of the culture, but byproduct of being in a combat zone in a highly stressful situation.

So I do believe that our Army performance triad will play a role in changing this culture. Everybody knows the importance of this. And I think I believe that the TBI centers, clinics, Intrepid Centers, everywhere that treats TBI soldiers, should emphasize this role.

And the next one is: "Does the Intrepid Center do an assessment to determine if the soldiers are experiencing a sleep problem, and how is it treated in a primary care setting or a specialty clinic?"

The answer is, yes. All the things that triad – including the load of stress – actually that's part of our initial assessment, including sleep studies on those people. Yes, so this is a very important part of our assessment and treatment. And as far as a primary care setting and specialty clinics, we try to encourage our colleagues to move away from just giving medication prescriptions but on helping to understand there are complicated factors involved in sleep disruptions, including high cortisol levels, including bad sleep hygiene.

As you all know, a lot of members are just hooked on cell phones and Internet until they sleep, things like that. A lot of times that sleep hygiene makes a big difference. Everything that we try to do, there are so many different factors affecting sleep.

The next question is for Dr. Lin: "How does diet disparity between income groups affect the population?"

Great question. Diet disparity between income groups has the same affect, and--

Okay. And: "What interventions, other than mindfulness, is the Army triad going to be available to veterans?" I guess that's for Dr. Purohit.

We're in the Department of Defense, so (inaudible). But I think the VA has been actually pretty supportive of this from what I understand. There is some data at a conference recently from the VA side of just prevalence of canned therapies and other things. And I think there is a huge push from the VA as well, for mindfulness, for yoga, for meditation, for tai chi. And all those things that have started to have good evidence behind them, the VA is starting to promote them as much as possible.

I think some of the limitations are just figuring out how to execute and mobilize some of these things. But they are very much about them from what I understand and what the data shows, and I think it will continue to grow as we get more and more evidence.

Okay, I think some of the other questions I will try to go over as much as I can in the allotted time that we have. I think the question is: "Given the high rates of sugar drinks, sugar intake, does it matter what types of sugar are in the drink?"

Obviously this is something that we are continuing to understand and learn. But we do know that for the brain, it's fairly simple in the sense that if they detect the glucose in the blood, that's all they care. So whether the form of complex carb or other things, yes. Basically, the bottom line is does that increase or spike the glucose level in the blood. And as Dr. Purohit mentioned, the reason that we're talking about sugar so much is not just about weight gains or weight-related things, but it really fuels the stress physiology that he described after injuring the brain or being under chronic stressful situations.

So we want to actually really move away from that pattern. So we're trying to turn off or provide less fuel to the fire, and sugar is the perfect fuel to the fire. And also with the fact that chronic stress physiology already increases the insulin resistance, it certainly can make the blood glucose available a lot longer.

The next question is: "How do we know how substitute sugar affects nutrition in TBI recovery?"

I think sugar substitutes, like Equal, I guess that's what it means. Well, actually, the three of us have been having a lot of debates these days. And in light of the literature that's coming out, the effect of substitute sugar, such as aspartame and equal, how much it affects the gut bacteria as well as affecting the mood

and so on. We do know that there is a role to it. I think the important thing is, like any of the studies and findings, I guess what we are hoping from our presentation today is to spur discussion among your own clinics, among your own clinicians, that sleep, nutrition and exercise can play a role in the brain function.

So maybe not so much as going to an extreme case, but even such things as sugar, really empowering the patient to change the diet can reduce the sugar level in the blood stream. That can certainly help not only the immediate affect like energy, mood, but also help other treatments gear towards reducing stress response, make it that much more effective. And it's the role of all these things, different factors, playing together to promote the neuroplasticity or brain healing.

I think we only have time for one more question: "Dr. Purohit, given the ongoing effects, is there a planned discussion change to duration of PDRL for service members (audio difficulty)."

It's a great question. I'm not sure if there is, whether there is a change to that or not. It's sort of our purview. We're more on the clinical side and treating patients, so some of the administrative things are out of our scope. But it's a great question, and definitely evidence should inform the policy decisions. But that's more on the policy side than something that we can address at this time. But I apologize; it's a great question.

Okay, I think we can do more question: "What are the thoughts on implementing sleep, exercise, diet before prescribing medication?"

Actually, that's exactly what we do here at Intrepid Center. And we're hoping that this presentation will spur all of you to think about this. Instead of jumping on medication, perhaps we can really empower our patient population to change their sleep, exercise and diet habits, which can certainly impact the brain function even for patients who do not have any TBI per se.

Okay, so I think we have to wrap up due to time constraints. I just wanted to close by saying that DVBC promotes excellence in clinical care through the development and dissemination of clinical recommendations that give providers the assessment and management of symptoms associated with TBI.

In collaboration with subject matter expert representing the services, Department of Veteran Affairs and academic research (inaudible), DVBC developed the following clinical recommendations to help providers deliver evidence-based treatment: assessment and management of (inaudible) associated with mild TBI; assessment and management of visual dysfunction associated with mild TBI; management of sleep disturbances following concussion, mild TBI; neuroendocrine dysfunction screening post mild TBI; neuroimaging following mild TBI in non-deployed settings; progressive return to activity following acute concussion, mild TBI; guidance for primary care managers in deployed and non-deployed settings; guidance for medication providers in the deployed and non-deployed settings.

In addition to the CR itself, the CR product suite includes the following complementary resources: clinical support tools that offer an algorithmic approach for evaluating, managing and referring mild TBI patients for specialty care; training slides that educate providers regarding how to identify and treat patients with mild TBI symptoms; factsheets or brochures that provide tips to help service members and veterans cope with mild TBI.

We also want your feedback. Please complete the interactive Customer Evaluation, which will open in a new browser window after the webinar or send comments to the link that is listed on this slide.

Thank you so much and have a wonderful afternoon. Thank you for your participation.