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*Dr. Schiehser:* Hello. Good morning and I want to thank everybody for attending this talk. I am excited to be here to talk about the diagnosis, mechanism and management of fatigue in mild traumatic brain injuries, as well as traumatic brain injury as a whole. I will just do a quick disclaimer here. I have no relevant relationship to disclose with any entity associated with this presentation. My research is supported by the VA. My opinions and assertions are not necessarily those of the VA, or the University of California.

I have a quick poll question to see who is out there. What is your primary role in the VA? Are you a student, clinician, researcher, manager, policy maker or other? Okay, great.

*Moderator 1:* Thank you Dawn. It looks like the answers are streaming in. We will give people a few more seconds to respond. Then we will go over the results with you.

*Dr. Schiehser:* There are quite a few clinicians out there. Fantastic.

*Moderator 1:* It looks like a lot of clinicians and about 15% researchers. Thank you to our respondents. We will have a survey at the end of the session, which has a more extensive list of your roles. If you clicked Other, you might have the opportunity to specify that later.

*Dr. Schiehser:* Great. Thanks so much for answering that. I am going to go ahead and talk about the presentation overview. I will provide a brief overview of traumatic brain injury (TBI), as well as post-concussive symptoms (PCS). I am going to define fatigue for you in TBI, as well as the epidemiology and correlates of post-TBA fatigue, as well as talk about assessment and diagnosis of fatigue in TBI. I will talk about the mechanism, as well as management and treatment of fatigue in TBI.

The VA and DoD (Department of Defense), define traumatic brain injury or TBI as a traumatically induced structural injury, and/or physiological disruption of brain function as a result of an external force that is indicated by a new onset or worsening of at least one of the following:

1. Any period of loss of consciousness (LOC).
2. Any loss of memory for events immediately before or after the accident. This is also known as post-traumatic amnesia (PTA).
3. Any alteration in mental state at the time of the accident, also known as alteration of consciousness (AOC), as well as any neurological deficits that may or may not be transient.

The VA and DoD also stratify TBI based on severity, mainly mild, moderate and severe. This can be categorized by looking at loss of consciousness (LOC), AOC, PTA and if available, the Glasgow Coma Scale, as well as imaging. For loss of consciousness between zero and 30 minutes and a PTA of zero to one day, or AOC up to 24 hours, we can characterize this TBI as being mild. In terms of moderate, we are looking at between 30 minutes and 24 hours of LOC, as well as PTA between one and seven days. Anything greater than this can be characterized as severe. We know that the vast majority of individuals who sustain a TBI are characterized as mild, about 80%. The other two categories, moderate and severe, make up about 10% each.

Individuals who sustain a TBI often complain of or have symptoms, what we call post-concussive symptoms. These can be categorized as physical, cognitive, behavioral or emotional. This is just a list of the most common ones that we see in TBI. In terms of physical, we see fatigue, headaches, nausea, dizziness, vision problems, sleep disturbance, noise/light sensitivity and balance problems. in cognition, we see problems with attention, memory, processing speed and executive functioning. In behavioral symptoms, we see depression, anxiety, agitation, irritability, impulsivity and aggression.

For the vast majority of individuals who sustain a mild TBI, they do see a resolution of these symptoms. We see that about 85% to 90% of individuals will actually get better. There are a few people, about 10% to 15%, who will experience these symptoms long term. In other words, they become chronic. We will talk a little bit about what that means. Chronicity does vary between somewhere around four weeks to three months or six months, sometimes even longer.

If symptoms last for a while, individuals may meet the definition of post-concussional disorder. The DSM-IV-TR defines this as a history of head trauma that has caused significant concussion, as well as evidence of memory or attention problems from neuropsychological testing, as well as having three or more of the following symptoms for three months: fatigue, sleep problems, headache, dizziness, irritability, aggression, anxiety, depression, changes in personality or apathy. These symptoms must have followed a head injury and they must cause a significant impairment in function.

For those clinicians out there, you will probably be familiar with the ICD-10 and post-concussional syndrome, which is defined in a fairly similar way. There are some differences. In this case, the symptoms have to have occurred within four weeks – I thought I heard something on the line – A history of head trauma with a loss of consciousness must have preceded the symptoms by a period of up to four weeks. These symptoms must be three of the following, including unpleasant sensations such as pain, excessive fatigue or noise intolerance, as well as emotional changes, subjective complaints of concentration or memory problems, insomnia, reduced tolerance to alcohol and a preoccupation with the above symptoms.

We are going to move into defining fatigue and TBI. I have already mentioned fatigue. What is it, when I am talking about it? Unfortunately, I do not have a straightforward definition for you. There really is no universally accepted definition of fatigue. Surprisingly, little is known about fatigue. We do not really know exactly what it is, what its function is or what causes it. In fact, there is quite a bit of terminology overlap when we talk about fatigue. It is no uncommon for people to define it as being a sense of tiredness, exhaustion, lethargy, listlessness, worn out, petered out or lack of energy. These are just a few.

People also talk about the sense of fatigue as being sleepy or needing sleep. What we do know is that fatigue is not sleepiness. Sleepiness can be defined as being a feeling of being tired, needing or desiring sleep. This is often alleviated or rectified by sleep. Some people say the distinction between sleepiness and fatigue is that fatigue can be alleviated by rest, not necessarily rectified by sleep. We will talk a little bit more about this in the next few slides.

It is important when we are talking about fatigue or how to define it that we make the distinction about whether we are talking about primary fatigue or secondary fatigue. Primary fatigue can be defined as being caused directly by a disease or disorder. In order words, in traumatic brain injury we know there is some type of damage, whether we can see it or not. This can be structural damage or diffuse axonal injury. This, in turn, causes the fatigue. Secondary fatigue results from being exacerbated by a secondary cause, for example, pain, sleep disturbance or psychological distress. Here you can see quite a few sources that can cause fatigue in TBI, such as anxiety, pain, medication, cognitive problems, environmental stress and metabolic issues, just to name a few.

Here we really are getting at how to define fatigue. This is a very important distinction that we often talk about, whether we are describing fatigue as being peripheral or central. Peripheral fatigue has a physical, metabolic or muscular origin. You can think of this as being a feeling of fatigue, exhaustion or tiredness, after you have worked out in the gym for a long time or ran a long marathon. This is muscular fatigue. It is that sense of feeling exhausted from outside of our brain, more or less.

Central fatigue can also be used synonymously with cognitive or mental fatigue. It arises directly from the central nervous system, more or less, the brain. Chaudhuri and Behan did a great definition of central fatigue. They defined it as the failure to initiate and/or sustain attentional, i.e. cognitive or mental tasks and physical activities requiring self-motivation. One thing I want to point out here is that you will note that in this definition, physical is defined as part of central fatigue. That is important to talk about. Here again, we do have some problems in defining fatigue because of terminology overlap. Whereas we know that peripheral fatigue is physical fatigue, that sense of being exhausted after working out in a gym, we also know that people can have central fatigue that may include feeling exhausted or tired, for example, after studying or preparing a talk. It can also result in a decline in physical activity, such as doing household chores or walking to the grocery store. That may actually arise from a more central place.

As I was discussing the central fatigue subtypes, they can include both mental and physical. There are also other subtypes that people will talk about. These are emotional or psychological fatigue, as well as psychosocial fatigue, just to name a few. What we are really talking about here is what type of activity does this fatigue impact. Emotional and psychological, as well as psychosocial, have a lot to do with depression and secondary sources of fatigue. These are just examples, but what we are really going to focus on in this talk are central fatigue, especially mental and cognitive, as well as physical subtypes.

Another distinction to make is between state and trait fatigue. State fatigue is situational at a particular point in time. Trait is a more stable symptom. It is over time. This is an important distinction when we are talking about fatigue. Another one that is important to distinguish is as the stage immediately following injury. Chronic is more persistent and is longer term, after the injury.

What does fatigue look like in TBI? We call this post-traumatic fatigue, or PTF. I will be using these terms throughout, as well post-TBI fatigue or PTBIF. Usually what we are talking about is central or cognitive fatigue, as well as primary fatigue. That is not to say that individuals with TBI do not have peripheral fatigue or do not have secondary fatigue. Of course, I would be completely remiss not to acknowledge the fact that secondary fatigue is quite prevalent in this population, as well as peripheral fatigue. When we are specifically talking about PTF, this is usually what is denoted.

We do talk about PTF as occurring in either an acute stage. It is usually days or weeks. A chronic type of fatigue is greater than three months. For the vast majority of individuals we are seeing at the VA, we are talking about chronic fatigue. Again, these definitions vary. When does an acute fatigue after injury transform into a chronic state of fatigue? That does vary, and sometimes that is what makes it very difficult to talk about the characteristics of fatigue, as well as epidemiology.

That said, I do want to go ahead and talk to you today about the epidemiology and what we do know about it, as well as how prevalent it is and what the correlates of post-TBI fatigue are. It is not surprising that fatigue is ubiquitous. We have all experienced it. This is something that almost every single individual can describe feeling at some point or another. What we do know is that problematic fatigue, meaning fatigue that interferes in our activities or daily function, occurs in about 10% to 20% of the general population. For those with TBI, fatigue is much higher. It usually ranges somewhere between 21% and 77%. I have seen a recent study that actually showed that individuals with TBI may be endorsing fatigue up to 98% of the time. This can be quite high. It is also one of the most common symptoms in TBI. There have been some studies that rank it number one. Others have ranked it number three. It is usually in the top five, depending on the study you are looking at.

While post-TBI fatigue may improve, some studies suggest that fatigue remains problematic or becomes worse over time. This is an important point when we are talking about epidemiology. Fatigue is not a static symptom. Depending on when you are talking to an individual and how far out it has been from the injury, the sense of fatigue or how problematic it is in their life may vary.

That brings me to a couple of studies that I am going to present. This one is by Scholten. They looked at veterans who scored either positive or negative on a VA TBI screen. What they found was that 69% of individuals who scored positive on the TBI screen endorsed having moderate to very severe symptoms in the last 30 days of fatigue. You can see this is compared to individuals who scored negative on the screen. It was about 60%. Both of these groups were fairly high in terms of endorsing moderate to severe symptoms of fatigue. This may not be as surprising as one would think, because we do know and the majority of studies do show that veterans in general have more fatigue. These are veterans without TBI. This could be the nature of the population. These individuals are coming to the VA, usually to seek services for medical or psychological problems. Therefore, they may have that secondary source of fatigue.

I want to present another slide. This is looking at a mixed TBI sample at two years and five years post-injury, by Olver and Group. You will see here that when they assessed fatigue and two years post-injury, 68% were endorsing fatigue. This is the second most common symptom. When they looked at these individuals or a subset of these individuals five years later, there was a higher percentage. in fact, 73% were endorsing fatigue. This became the number one symptom. You can see how fatigue may change over time. It is not static.

What do we know about the associations with fatigue and post-concussive symptoms? Interestingly enough, it is not consistently associated with age, gender, education or TBI severity, even years since injury. What we do see is a very strong association with other post-concussive symptoms like depression, sleep disturbance, anxiety and pain. Of course, this brings a lot of researchers to wonder how primary fatigue is in TBI. Maybe what we are really talking about is secondary fatigue, if it is the case that fatigue is not associated with TBI severity, but is in fact associated with these other factors like depression, anxiety and pain.

The big question is whether fatigue is the chicken or the egg. There really were not too many studies out there that could answer that. Recently, hot off the press, Ponsford and Group – I think this was just published last month or the month before. They used an elegant study of structural equation modeling to try to figure out whether fatigue is a consequence of some other disorders that we see in TBI, or it is a cause. What you can see here from this diagram is that they found it is more causal than a consequence. Fatigue is really the primary symptom and we should be focusing on this.

We conducted a study recently that I think underscores the importance of fatigue in traumatic brain injury, especially in mild traumatic brain injury. What we found is that fatigue is one of the most critical symptoms, out of 22 post-concussive symptoms. It was associated with decreased quality of life in veterans with chronic mild TBI. I do want to underscore the mild. I have been using quite a few examples so far, mixed samples, because that is what is really out there. There has been a recent focus on what this looks like in mild. What we are seeing is that fatigue is critical, especially when it has to do with quality of life. In fact, it is apparently secondary only to depression.

That brings us to the assessment and diagnosis of fatigue and TBI. There is no gold standard measure of fatigue. The most prevalent mechanism of assessing fatigue is by subjective assessment such as interviewing or use of self-reports. There has been a new wave of groups that are trying to measure fatigue objectively. They do this by looking at performance over time, as well as the physiological measures and imaging. I am going to discuss each one of these in the following slides.

The interview is extremely important. I know that most of you out there are clinicians. This becomes, I would venture to say the gold standard, of assessing fatigue. It is asking the right questions. This was adopted from Dr. Zasler. These are some questions that he asks when he is looking at fatigue and TBI. These are the critical questions. You want to know when the fatigue started. You really want to try to see if this is due to a primary source or secondary source. You want to know if the fatigue correlates with any medications or depression. You want to know what aggravates it or triggers it, as well as what helps to make it go away. You want to understand whether or not we are talking about the physical fatigue or the mental fatigue, or both. Is it associated with sleep, mood or pain, trying to assess these secondary sources?

It is also important to rule out other causes of fatigue. For example, individuals with TBI may have seizures. You want to know if we are talking about a seizure related fatigue or hormonal abnormalities like hypothyroidism, as well as nutritional deficiencies like low B12, anemia or renal failure, even hepatitis. There is substance abuse as well, just to name a few. You are also assessing the medications that individuals with TBI may be taking. These individuals are often on several medications. We do know that medications like muscle relaxers, pain medications, blood pressure medications, benzodiazepines, antihistamines, antidepressants and antibiotics all have a side effect of fatigue.

Now I am going to talk about self-report measures. These are very helpful. Clinically, they are helpful in terms of assessing fatigue quickly and efficiently. In terms of research, they are probably one of the most important ways to measure fatigue. Now I am going to talk about when you are picking a measure to use, to know that they are not all created equal. In fact, when we talk about fatigue measures, sometimes they may be assessing different aspects of fatigue or perhaps not even fatigue at all.

The first distinction to make is between state or trait fatigue. For example, state fatigue like the Visual Analog Scale of Fatigue may ask an individual how they are feeling right now. That is really assessing fatigue at a specific point in time. Trait self-report measures are looking at longer or chronic fatigue, such as the Modified Fatigue Impact Scale, which asks individuals how often fatigue has affected them during the past four weeks.

Another distinction that we want to make when looking at self-report measures is whether or not we are using a unidimensional versus multidimensional measure of fatigue. A unidimensional measure will just assess general or overall fatigue, without any distinction between the subtypes that I previously discussed. For example, this Fatigue Severity Scale, which is one of the most prevalently used scales out there, really just arrives at a total or overall fatigue score based on nine items. There is no way to know whether or not this is physical fatigue or cognitive fatigue. A multidimensional scale would not only offer you an overall or total score, but will also allow you to look at certain subtypes, like cognitive or physical. The Modified Fatigue Impact Scale does have two scales that look at this.

I think one of the most critical distinctions you want to make when you are looking at or choosing a self-report measure is whether or not you are looking at fatigue impact versus fatigue quantification. The best way to make this distinction is by giving examples. For example, the Modified Fatigue Impact Scale, which looks at fatigue impact, asks individuals to rate how their fatigue has impacted certain states or certain activities. It says, “Because of my fatigue during the past four weeks, I have been less alert, having difficulty paying attention, etc.”

On the other hand, a fatigue quantification scale, such as the Multidimensional Fatigue Symptom Inventory Short Form, lists a bunch of symptoms or states and asks individuals to rate how problematic they are. In this example, individuals will rate on a scale from zero to four how much trouble they are having remembering things, if their muscles are achy, if they are feeling upset of not cheerful or if their legs are weak. An obvious criticism of the latter version is that we really do not know if these symptoms are in fact fatigue. The scale assumes that if somebody is feeling cheerful or not, or having trouble remembering things, that this is directly indicative of fatigue. As we know in traumatic brain injury, individuals have other problems like sleep disturbance, orthopedic injuries or cognitive problems that might be directly related to fatigue per se.

There are some other things to think about when we are looking at fatigue scales. As you know, there are psychometric properties, as well as the use of cut-off scores. Cut-off scores are particularly important, especially in the clinical sense. We like to have these measures. We like to know what number we can say is the cut-off. If somebody scores below this number or above this number, they are fatigued and they have clinical and relevant fatigue that we want to treat, versus individuals who have not scored at that level and we know they are okay. The important thing in remembering this is that we need to know if these cut-off scores were derived from the right group, to be valid and reliable in TBI. Unfortunately, there are not enough scales out there that have really been validated in TBI, and specifically in mild TBI. This was something that my group looked at. We did validate the Modified Fatigue Impact Scale for mild to moderate TBI, to at least partially address this need.

The advantage of a self-report measure is that it is efficient, it is quick and it can tell us whether or not we are dealing with fatigue that is in need of critical intervention. A lot of people do believe that the assessment of subjective fatigue is really the most relevant. Fatigue is essentially an internal state. However, there are some limitations. We have problems with measurement overlap, between symptoms of depression and sleep disturbance. This has particularly been a problem with the scales that are looking at fatigue as a quantification, as I described before. We also have issues with biases. We do know that sometimes depression or if somebody is in a bad mood, it may influence the way that they answer some questions.

This led a lot of people to think how we can measure fatigue objectively. This is analogous to neuropsychological assessment. We know that individuals sometimes come in and say that they have problems with memory or with attention, but then we notice that on objective assessment that they really do not. That is why some people believe that we need to find an objective measure of fatigue. I am going to discuss that in a little bit. First, I want to know if any of you use self-report measures of fatigue with your patients or research subjects. Look at that. We have a 30/60 split there. About 30% of you do.

I am going to quickly talk about objective measurements. Some people have defined objective fatigue as being a decline in cognitive performance over time. An example of this is the Ashman Study. What they did was look at cognitive performance on the CANTAB. They looked at a double baseline, meaning that they gave the cognitive assessment two times, right in a row. Then they administered individuals with TBI, as well as controls, two hours’ worth of questionnaires and assessed the cognitive performance again at Time Three. What they found was that the control group continued to show an improvement over time, or practice effects from Time One to Time Three. The TBI group, while they showed a practice effect from Time One to Time Two, showed a stark decline from Time Two to Time Three. This was after the two hours of questionnaires. They defined this as being an example of mental fatigue.

We do notice with this that we do have to look at accuracy and reaction time. People may be more accurate at the cost of being slow or having slower reaction time. We know that people will be fast, and unfortunately, that may be at the cost of accuracy. However, there are some problems with this method. We know that objective measurement is not always associated with subjective feelings of fatigue. What we have seen in quite a few studies is that fatigued individuals may achieve adequate performance in accuracy, as well as reaction time.

We do know there has to be another variable in play here. This is what we believe is called effort. The people with TBI increase their effort in order to maintain adequate performance. This equates to increased fatigue. Now we have a push to measure effort of proxy fatigue. One way to do this is by using physiological measures. Ziino and Ponsford looked at TBI and controls on a cognitive task, and they found that they did perform it fine, with no problems. The TBI group had increased blood pressure, which they believe was due to increased effort, which was associated with subjective fatigue. You can see with the advent with neuroimaging that this has allowed us to use this new mechanism as a way to objectively measure fatigue. In this case, we defined fatigue as an increased effort, brain effort, which is evidenced by increased cortical activation.

With this objective measurement, this really brings us nicely into the topic of post-TBI fatigue. A theoretical model of cognitive fatigue in TBI was proposed by van Zomeren in 1984, called the Coping Hypothesis. This states that cognitive fatigue is due to the constant mental effort individuals with TBI need to exert to compensate for cognitive impairment, i.e. attentional problems and processing speed, in order to maintain adequate task performance. In essence, a traumatic brain injury results in cognitive impairment. In order to compensate for this impairment, individuals must increase their mental effort in order to maintain adequate performance. In turn, this causes cognitive fatigue.

In 2000 and 2004, Chaudhuri and Behan proposed a theoretical mechanistic model of fatigue. Here, they described it a disruption in the striatal-thalamic-frontal cortical, or loop, as the primary cause of central fatigue. They use this as a general model for all neurological disorders, not just TBI. It can be highly applicable to that problem. I will talk about that in a few slides. They did identify the basal ganglia as being particularly important in this loop, as well as the connection between the prefrontal cortex and the thalamus. What is interesting is that we do know that there are several groups that have identified a dysregulation in neurotransmitters, specifically in glutamine and dopamine, as being important in central fatigue. We do know that these neurotransmitters are associated with this circuit.

This is not surprising, but individuals and researchers want to know if we can use fMRI to confirm this theoretical model in TBI. This is a really nice study by Kohl and Group. They looked at 11 moderate to severe TBIs, compared to 11 healthy controls, who performed an attentional task in the scanner. What they found was there were no differences in performance between TBI and control. What they did find was a difference in activation patterns in the areas that are proposed in the Chaudhuri and Behan model, such as the basal ganglia, the frontal gyrus and the anterior cingulate. For most of the cases, what they found was that while control activation pattern declined over the trial task, in individuals with TBI the patterns increased. This could be surmised as being due to increased effort and therefore increased fatigue.

A limitation of this study is that they did not look at subjective fatigue. We do not know how well their objective measure maps onto subjective assessment. Of course, research is still needed. We really need to know the neural correlates of subjective and objective cognitive fatigue, as well as how it this specifically maps onto individuals with just mild TBI. What are the other correlates, such as injury type or how it is related to other symptoms like sleep and depression?

What we are doing out here in San Diego is this. We are looking at the neural correlates of cognitive fatigue, specifically looking at subjective measurements as well as objective measurements by using imaging techniques such as fMRI and diffusion tensor imaging (DTI). The fMRI study is still ongoing. We are collecting data as we speak. We did have a chance to look at some of our DTI data, which I am going to show you right now.

We looked at 38 veterans with mild TBI. As a measure of fatigue, we used the Modified Fatigue Impact Scale. We looked at total scores, as well as cognitive and physical subscales. As a measure of white matter integrity, these are tracks to see how well the brain is moving information from one place to another. We used diffusion tensor imaging (DTI) and FA as a measure of integrity.

What we found was that fatigue, and specifically cognitive fatigue but not physical fatigue, was associated with decreased white matter integrity or decreased FA, that is our proxy, our measure of white matter integrity, in the anterior internal capsule (AIC). While we know that the AIC has connections through the caudate and thalamus, this is very consistent with Chaudhuri and Behan’s theoretical model of central fatigue, and does support the role of striatal-thalamic-frontal connections in fatigue and TBI, especially in mild TBI. Of course, more research is needed. We are just beginning to look at this data. I think there are several groups throughout the country that are looking on the [indiscernable] to see if we can really pinpoint exactly where fatigue is occurring.

This brings us to our last section, which is the management and treatment of fatigue in TBI. I have a quick poll question. Do you treat patients with fatigue?

*Moderator 1:* It looks like the audience is a little shier to answer this one. Do not worry. Your responses are anonymous. Go ahead and pick an answer. We will give you some more time to get those in. It looks like the answers have stopped streaming in, if you want to go through them really quickly Dr. Schiehser.

*Dr. Schiehser:* Okay. It looks like the majority of individuals do focus on fatigue as a secondary symptom. Fantastic. We can close this out. Okay, great. Okay. I think since the majority of you do treat fatigue, this will be important, even if you do treat it as a secondary symptom.

One main question that people always ask is if they should treat it or not. Sometimes this answer is not always clear. There is a theory. It is called the Adaptive Theory of Fatigue, in which fatigue is seen as a warning signal to us to stop what we are doing, because we do not want to cause our brain any further damage. Similarly, being able to sleep, how sleepiness is to sleep or needing sleep, fatigue may be a warning signal for us that we need to rest and stop doing what we are doing. We wish it were that easy. That is not the case. We do know that individuals with TBI often complain that this functional fatigue interferes with their activities of daily living. It also causes problems with their quality of life. As you recall from a study that I had presented before by the Ponsford Group, it may actually be a causal symptom of depression and anxiety. This might be something we do not want to just brush off.

Unfortunately, there are no empirically supported treatments for PTF. There are two main approaches, which I will talk about, mainly pharmacological and behavioral, that we can do in order to help individuals with PTF. The big question is what you should treat first, primary or secondary fatigue.

It is commonly thought that you will want to treat what the primary cause of the fatigue is. If we are talking about depression, we are going to want to use antidepressants. If we are talking about the main cause of the fatigue as a sleep disorder, we are going to want to treat that. If we know that medications are causing the fatigue, we are going to want to titrate the medications as much as we can, in order to try to alleviate the fatigue. I bring up the Ponsford Study, in that this fatigue may be an important causal agent. We do want to try to treat this as best we can.

Unfortunately, there is little research support for any medications to treat PTF, but there are common off-label use medications such as neurostimulants like Ritalin, Dexedrine and Cylert. There are dopaminergic medications like Symmetrel. There are herbal medications and caffeine. These are all used to treat PTF. There are only a handful, if that, of studies that have systematically looked at certain medications for post-traumatic fatigue. There are two double blind placebo controlled studies in TBI that looked at Modafinil. Unfortunately, no clinical benefit over placebo was found. Recently, and this is another study hot off the presses, Johansson and Group looked at Ritalin in a double blind crossover study and found that it decreased mental fatigue in 29 mild TBI subjects.

While there seems to be some support for at least Ritalin as a pharmacological agent, it does appear that behavioral treatment, right now, seems to be a first line approach. This mainly involves psychoeducation, talking about sleep, hygiene, nutrition and teaching individuals how to self-pace in terms of breaks throughout the day or resting before they become overwhelmed or are not able to accomplish a task to the degree they would like to. Sometimes what we found was that the psychoeducation might only go so far. Unfortunately, there is really no systematic study that I am aware of that really shows that this is truly effective for those who have some of the worst problems with fatigue. It does seem that some more empirically validated studies or empirically validated treatments may be needed.

We do know that cognitive behavioral therapy improves fatigue in other populations, such as MS and chronic fatigue syndrome. In fact, there was one study in which eight weeks of CBT for post-TBI insomnia improved fatigue in 11 mixed sample TBI patients. It does seem like this may be a treatment that could help. In another randomized control trial of eight weeks of mindfulness-based stress reduction, we found that in a mixed sample of TBI and stroke patients, fatigue improved as well.

Another treatment that might be helpful is physical exercise. We know that physical exercise has been shown to reduce fatigue in other populations. Recently, Chin and Colleagues looked at 12 weeks, 30 minutes three times per week, of aerobic exercise on the treadmill. They found that it reduced subjective fatigue in ten TBI patients, 50% of whom were mild. It appears that there are some behavioral treatments that may be helpful. We do need more research on this, specifically on how these treatments affect post-traumatic fatigue and especially how they affect fatigue in the mild TBI population.

In summary, fatigue is one of the most common and persistent symptoms of TBI. It is associated with poor quality of life. Post-traumatic fatigue is most often defined as central and cognitive mental fatigue. That is not to say that individuals with TBI do not experience peripheral or physical fatigue, because they do. There is no gold standard measure of post-traumatic fatigue; however, it can be assessed with self-report, interviews and objective based methods. While PTF appears to involve a disruption of the striatal-thalamic-frontal cortical system, there are other areas and this type of research is still ongoing as we speak.

There are no empirically supported treatments for PTF, however behavioral treatments such as CBT and MBSR, as well as exercise and some pharmacological treatments like Ritalin, appear to be promising. More research is needed to better ascertain the mechanism, trajectory, treatment and management of post-TBI fatigue.

Here I have listed some references, for those of you who would like to do some further reading on the studies I discussed. I would also like to acknowledge the Department of Veteran’s Affairs and the VA-San Diego, as well as UCSD and the VA Center of Excellence for Stress and Mental Health, and my lab members, Dr. Lisa Delano-Wood, Dr. Scott Sorg, Alexandra Clark, Norman Luc and Russell Kim. I would like to acknowledge my collaborators, Dr. Filoteo, Dr. Jak, Dr. Lang, Dr. Simmons and Dr. Twamley. Thank you very much. Here is my contact information. Feel free to email me if you have any questions. I think there is some time where we do some questions.

*Moderator 1:* Yes. Thank you so much Dr. Schiehser. We do have several great pending questions. We are going to get right to those. I know a lot of people joined us after the top of the hour. To submit your questions or comments, please use the Q&A box in the lower right hand corner. Just type your question or comment into the lowest box and press the Speech bubble. With that, we will jump right into it. The first question that came in is this. How did you define “chronic mTBI in your study?”

*Dr. Schiehser:* Okay. That is a great question. When people talk about chronic mTBI, it is often used synonymously with chronic post-concussive symptoms, meaning that individuals with traumatic brain injury continue to have symptoms over time. There is some debate about using this terminology, because what people say is that you cannot have mTBI that is particularly chronic. In other words, a TBI is not ongoing. It is the post-concussive symptoms that are ongoing. This terminology has been used synonymously, but I have started to steer away from using the term chronic mild TBI and am talking more about chronic PCS in mild TBI.

*Moderator 1:* Thank you for that response. This is the next question. If there is not clear chronological association with the medicine and fatigue, how useful might medication modification be prioritized? How important might it be to change certain more problematic medications?

*Dr. Schiehser:* Okay. Let’s see if I understand this question correctly. What we are talking about here is whether or not we are dealing with a secondary source of fatigue, if I am interpreting this correctly. How important is it going to be to change medications? I think this is definitely going to be done on a clinical basis, maybe even a case-by-case basis. When you are interviewing a patient, you want to see how problematic this fatigue is and prioritize what the symptoms are that are most problematic to that individual. If an individual has fatigue as something they endorse that is not very problematic, and you know they have pain and you need to treat the pain, then this may be something that you are not going to prioritize.

We talk about it being chronological, in terms of a long term effect. Let’s see if I understand that correctly. In terms of looking at chronology and medications, we do not know too much about that. As I mentioned in the pharmacological slide, we really do not even know too much in terms of cross-sectional studies on how important medications are on fatigue. I think looking at long term effects will be an important point in the research. I hope I answered that question the way that the person who asked it requested. If not, I will try to answer it if they want to type it in again.

*Moderator 1:* Not a problem at all. They do have the option to clarify. In fact, he is asking this now. With current therapies and current available diagnostic tools, how important is it for clinicians to answer whether this is primary or secondary fatigue?

*Dr. Schiehser:* This is great. I like this question. We do joke about that a little bit, although it is a very serious question about how much is too much. That is absolutely a balance. In all seriousness, when we are talking about fatigue and TBI, we are also usually looking at people who have a chronic type or trait type of fatigue. While we may be inducing situational fatigue at that time, it might be important in order to really get out how problematic fatigue is in their daily lives.

*Moderator 1:* Thank you for that reply. We do have another question involved reducing mental fatigue. Can we induce mental fatigue by asking too many questions in the assessment and reassessment?

*Dr. Schiehser:* I am sorry. I think I answered that. I am following the questions along and I think I just answered that previous question Molly.

*Moderator 1:* Perfect. I apologize. I am juggling more than one thing. I wanted to read it aloud, just in case. All right. Any tips on treatment efficacy?

*Dr. Schiehser:* Treatment efficacy? Okay. I believe this might be related to some of the slides that I presented at the end about whether or not some of these studies that we have seen might prove to be efficacious in this population. We are not quite sure. There have been a couple that have shown that some of these treatments like CBT and mindfulness may be efficacious in this population. We do not know for sure until we do conduct these systematic studies to look at this.

*Moderator 1:* Thank you for that reply. We do have many more pending questions and a very engaged audience. The next one is this. Using “Coping Hypothesis,” could management goals be expanded to reconsider if the person with mild TBI might have an inappropriately high bar of what is “adequate performance?” Might benefit from mindfulness come in part from reevaluating values and one’s goals?

*Dr. Schiehser:* That is great. This is great. There are very insightful questions here. There is a lot of research that has been done, looking at coping as being particularly influential in fatigue, and being able to modify what people’s expectations are in terms of trying to get them to achieve at a higher bar. This becomes particularly important when we are talking about adaptive fatigue. We should listen to our bodies. Our bodies may be telling us that we are in overdrive. We are doing way too much. In fact, some treatments such as mindfulness or even CBT, may help us to reevaluate these goals or bars that we are setting. I think that is an important comment.

*Moderator 1:* Thank you. What are the sample sizes in those studies of successful behavioral therapies? The Ritalin study seems fairly small and short term.

*Dr. Schiehser:* Yes. That is true. Some of them were small. I know the Chin Study only looked at about 11 or so individuals. That is an important consideration. I have some of the references that you can check for particular sample sizes. I do not know them off the top of my head. I do know that they are fairly small. These definitely need to be replicated in larger ones. We also need to look at this in particular groups. I think even the CBT study that I mentioned only looked at CBT in post-TBI insomnia. It looked at the measure they tacked on. They were not targeting fatigue per se. I think there is a lot that needs to be done in this area of behavioral management and treatment of fatigue.

*Moderator 1:* Thank you for that reply. I am going to take a quick moment to mention that if anybody has any other comments or questions, to get them in now because in just a moment I am going to put up our feedback form and that will make the Q&A box go away. We will continue on for another moment or two. Do patients with mild TBI and fatigue show a different fMRI pattern than patients with no history of mild TBI who complain of fatigue?

*Dr. Schiehser:* This is a question that is close to my heart. This is what we are studying in this lab. In fact, we are seeing this. I do not want to say too much until we actually get all the data in, but we are showing that individuals with TBI and fatigue are showing a different pattern than those who do not have fatigue. We also know from past literature that in fact, individuals who have TBI, as well as do not have TBI, have a different activation pattern as well. Yes, we are seeing different patterns. Stay tuned. We hope we will start having this data coming out pretty soon. We hope to get that out in the literature within the next year or two.

*Moderator 1:* Thank you for that reply. I am going to put up our feedback form now. Do not worry. We still have more Q&A to get through. For our attendees, please do take a moment to fill this out. I will also leave it up after the session is over. Feel free to continue focusing on the Q&A now. You can respond to it later. I just want to put this up. The next question is this. How do you manage the high BP and use of Ritalin?

*Dr. Schiehser:* That sounds like a very important question. It is a little beyond my expertise. I do not know too much about the relationship between those two. I apologize. That is something I will follow up on with a nurse or physician, to find out how the management goes. I would surmise that you would need to find a balance between maintaining adequate blood pressure control, as well as using the Ritalin in order to alleviate the fatigue. It may not be an option for some people.

*Moderator 1:* Thank you for that reply. The next question is this. How much do you think post-TBI hypometabolism is contributing to the fatigue?

*Dr. Schiehser:* Okay. There is some research out there. I did not cover it in my talk here. It looks at metabolic issues being a primary source that could cause fatigue. That is definitely possible. On a related note, we do know that there may be some issues in terms of the neuroendocrine system, particularly the pituitary gland, that may be influential in fatigue. The studies have not been consistent, so we cannot say one thing or another. This is something that people are looking at.

*Moderator 1:* Thank you for that reply. We have about four questions and three minutes before the top of the hour. We are doing pretty well on time. It seems that fatigue could be perceived by people as tiredness or being stressed, even mentally fed up with life situations. This is a perception that changes dynamically with normal life. It could be easily overdiagnosed. When does fatigue cross the threshold from non-clinical fatigue to clinical fatigue that needs a formal intervention? Could all new parents potentially be given fatigue treatment?

*Dr. Schiehser:* Great. This is about the adaptive fatigue, where the fatigue may be important and may not be something that we should look at as being disabling, although it can be, or pathologizing it. The fatigue may in fact be something that is helpful to us. Where do you cross that threshold? I think that at least when we see our patients in TBI; the threshold does seem to crossover when fatigue is significantly interfering with daily activities. People cannot function anymore. They are really having trouble just functioning in their everyday lives. In that case, it does seem as though this adaptive process has now transformed into a pathological process. From a clinical standpoint, it is something that can be ascertained by the interview and really understanding how fatigue is impacting this individual’s life.

*Moderator 1:* I cannot see the questions on my screen anymore.

*Moderator 1:* If you are all right with me reading them aloud, we can proceed that way. Is that okay?

*Dr. Schiehser:* Sure. Absolutely.

*Moderator 1:* This is a comment that came in. The problem with research involving mild TBI is that the definition of mTBI is so broad that you are studying an extremely heterogeneous group. It is hard to imagine that you are going to see clear-cut results. In addition, any apparent effect of mTBI may be attributable to some other factors.

*Dr. Schiehser:* This is a great comment. Absolutely. It talked a lot about the terminology of fatigue and how there is quite a bit of overlap in terms of our definitions of fatigue. We cannot give you a clear definition of fatigue because we do not even agree on it in our field. This is extremely applicable to TBI as well. I really thank that person for making that comment. I guess while we are not only dealing with trying to define fatigue in a population, we are also having trouble defining it in and of itself. I think research is helpful in this mechanism and trying to figure out how we can best define these groups, as well as how we can best define the symptoms within them.

*Moderator 2:* Molly, can I make a comment here?

*Moderator 1:* Yes, absolutely. Go ahead.

*Moderator 2:* There has been a great deal of confusion about mTBI because it is a heterogeneous injury. That heterogeneity and nuance to it does not mean that it does not exist. It does exist. We know it is a very serious problem among our veterans. It becomes challenging to derive evidence based treatments for it. Nonetheless, clinically relating the event as precisely as possible, as Dawn did at the beginning, the event followed by the loss of consciousness of less than 30 minutes and so on, is key to understanding this. That definition is being constantly upgraded by the Department of Defense, so that we are looking at getting more objective definition of the event heuristically followed by the condition. I hope that does not add to the confusion. I feel impelled to make that comment.

*Dr. Schiehser:* Thank you so much for that. I really do want to underscore that as well. Sometimes we get caught up, especially in research, in trying to figure out how to best define it or measure this. Truth be told, this does exist. People are having problems with this. However, we slice or dice it might not be as important as knowing that this does exist and we do need to figure this out, in order to best manage and treat them, so as not to throw up our arms in the air and say, “We are having trouble figuring out exactly how to define it. We might as well give up.” That would be very unfortunate. Veterans definitely have mild traumatic brain injuries. They have these symptoms that persist. We know that fatigue is one of them. It really does need to be looked at very seriously. Thank you so much for saying that.

*Moderator 2:* In addition, heterogeneity is a characteristic of a lot of diseases.

*Moderator 1:* Great. Thank you both for your replies. I know it is just a minute or two past the top of the hour. Are you able to stay on an answer the two remaining questions so we can capture it in our recording?

*Dr. Schiehser:* Sure, absolutely.

*Moderator 1:* Great. Thank you so much. This next one is this. Can this pattern be replicated with EEG versus fMRI?

*Dr. Schiehser:* I think there was one study that did look at EEG, if I recollect that. I know that when it became very important to try to objectively measure fatigue, we were trying to figure out physiological measures. I know there was, after the blood pressure study, a group that did look at EEG as well. I cannot recall that off the top of my head. I think the answer to that question is yes. You can use any of these methods to look at what is considered to be increased brain activity or increased effort, which people are now beginning to believe is indicative of fatigue or is used as a proxy for measuring fatigue.

*Moderator 1:* Thank you for that reply. This is our final question. What recommendations do you make for student veterans with this complaint? Do you consider accommodations for them?

*Dr. Schiehser:* I am sorry Molly. Can you repeat that one more time?

*Moderator 1:* What recommendations do you make for student veterans with this complaint? Do you consider accommodations?

*Dr. Schiehser:* Recommendations in terms of treatment? Was that clarified?

*Moderator 1:* I am not sure if it was in terms of treatment or in terms of recommendations for them as students. If the person is still on the call, they are more than welcome to write in for clarification.

*Dr. Schiehser:* Okay, absolutely. I think I would focus on the fact that the person who asked the question did specify that they want to know about students in particular. I think this is very important, especially when we are talking about mental fatigue in terms of the effort that it takes in order to maintain a focus on a task at hand. Studying becomes very important when you are a student veteran. Some of the recommendations that people have had in terms of psychoeducation become really important. A lot of people, and I am one of them, believe that teaching people how to pace themselves and take breaks, although it does seem somewhat simplistic, seems to really help student veterans who have had mild traumatic brain injuries manage their fatigue quite well.

I think if it becomes very problematic, there are other alternatives you can use. People talk about tape recording classes and going over them again when they are more rested. People talk about getting treated for sleep problems if they think sleep might be inducing the fatigue, as well using some of these other treatments I had talked about, mindfulness and CBT. They might be helpful, in particular.

*Moderator 1:* Thank you very much for taking the time to answer those. At this point, I would like to give you the opportunity to make any concluding comments you would like to.

*Dr. Schiehser:* I thank everybody for coming. I really appreciate those of you who hung in there for this talk. I am really excited about this topic. I really am excited to see how the research will evolve in this space. I do want to underscore what we had talked about before. This is an important consideration, something that I do think we should not brush off and should focus on with our patients, with our research subjects and research, to do what we can in order to better manage it, as well as to further this field if we are researchers in this area. I think the more we understand fatigue and the more we understand about fatigue in traumatic brain injuries, especially mild traumatic brain injuries, I think the more we are going to be able to help veterans. Thank you so much for having me.

*Moderator 1:* Thank you very much for lending your expertise to this field. Of course, thank you to Dr. Ralph De Palma for helping set up this series and these talks. I encourage our audience to come to the next TBI session, which will be the 28th of July, 2:00 PM Eastern. That will be presented by Dr. Martha Shentin. That is diffusion tensor imaging findings in mild TBI. You can go to our online registration catalogue to register for that. I will be leaving this feedback survey up. Feel free to take your time responding to it. Once again, thank you so much to our audience for joining us, to Dawn and to Ralph. This does conclude today’s HSR&D cyber seminar.