



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

**June 12, 2014, 1-2:30 p.m. (EDT)**

### **Why Does Concussion Affect Men Differently Than Women?**

Standing by. At this time, all participants are in a listen-only mode. Today's conference is being recorded. If you have any objections, please disconnect at this time. Now I'd like to turn the meeting over to Dr. Don (Inaudible). You may begin.

Thank you very much. Good afternoon, everyone, and thank you for joining us today for the DCoE Traumatic Brain Injury June webinar entitled Why Do Concussions Affect Men Differently Than Women? Why Oh Why? My name is Dr. Donald Marion, and I am the Clinical Affairs Senior Advisor providing contract support for the Defense and Veterans Brain Injury Center. I will be your moderator for today's webinar.

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There is increasing concern in the military and sports medicine communities that concussive events may affect men differently than women. And so we thought that this topic or this webinar would be a timely webinar. Controversy does exist regarding the risk and prevalence of hypogonadism following concussion or more severe traumatic brain injury. Possible neuroprotective effects of sex hormones such as progesterone or estradiols and the potential benefits of treating men with TBI with female sex hormones progesterone or estrogen. Today's webinar will address the pathophysiologic and neuroendocrine responses to concussion and to more severe brain injuries, recovery patterns for men and the clinical evidence regarding hormone therapy after TBI.

At the webinar's conclusion, participants will be able to describe the different effects of TBI on long-term quality of life depending on gender, articulate the importance of post-traumatic multidisciplinary rehabilitation that is sensitive to gender issues, discuss the prevalence of hypogonadism after TBI and relate the clinical evidence regarding the use of hormone therapy after TBI.

So let's begin with our presenters. Our first presenter is Dr. Amy Wagner. She is an Associate Professor and Endowed Research Chair in the Department of Physical Medicine and Rehabilitation at the University of Pittsburgh – go Panthers – as well as the Associate Director of Rehabilitation Research at the Safford Center for Resuscitation Research. She is the lead investigator in the use of biomarkers in developing and optimizing individualized treatment outcomes. Her research focuses on the neurobiology, neuroplasticity and recovery after TBI and how commonly used therapeutic agents impact neurobiological and neurobehavioral processes associated with neuroplasticity and with recover. Dr. Wagner is incredibly prolific and has published more than 50 original research manuscripts, has more than a dozen review articles on her work, and is a widely-requested speaker for multiple neurotrauma meetings throughout the year. So thank you for joining us today, Amy, and I very much appreciate it.

Great. Thank you for that kind introduction, Don.

So today I'm going to be speaking about sex hormone physiology and hypogonadism after TBI and will be relying heavily on our work that we've done in moderate and severe injury. I'm not seeing the forward slides button on my screen, guys. There we go. Okay.

So just before we get going too deep into the science, I just wanted to say that I don't have any specific disclosures to overview there for you with regard to what's on the screen.

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And then this background slide lists here the funding sources for the research that we are presenting. And just a quick note that the graphs, charts and tables not referenced in this presentation are associated with research study results.

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All right. So to get started I wanted to just touch on, for a moment, the concept of sex and TBI epidemiology. For many of you logging into today's presentation you probably are aware that the overall incidence of traumatic brain injury is about 200 per 100,000 per year, and men tend to have a higher incidence rate. And the increase in incidence in men is likely secondary to their greater prevalence and involvement in higher risk activities and occupations. But as Don mentioned, there is becoming an increasing interest in hormones and hormone physiology and how hormones might be used in the context of treatment for TBI.

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So in order to kind of discuss some of these general topics, I wanted to start off by making a few statements that one might take away from the literature as possibly the phase of the literature and try to help you all understand today, at least based on some of our work, what we think we know and what we don't know about the reproductive hormones and their neuroprotective effects, both endogenously and from a treatment perspective.

So just to go over a couple of statements here, we're going to think about them as we go through the talk today and decide if they are myths or facts. The first statement is ovarian hormones are neuroprotective, so women should be neuroprotected and have better outcomes than men. Another statement to consider is women wouldn't benefit from hormone therapy after TBI since they already have protective hormones as a part of their natural physiology. The next statement is endogenous estradiol for men and testosterone for women are not relevant to our understanding of hormone physiology after a TBI. Another statement is serum hormone physiology is a likely reflection of the CNS system physiology after TBI. And finally, hypogonadism is a transient syndrome and probably does not influence outcome. So we're going to start diving in to the research questions and literature that will help inform whether these statements are myths or fact.

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So, yes, so the first question is how are hormones interrelated and what mechanisms of injury can hormones target? We're going to take a real quick overview of this concept with many of the statements bulleted out for you being generated from the experimental literature.

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To get started I put up this slide that takes you through steroidogenesis, essentially, and the synthesis production of these hormones. As you can see, all of the hormones in question, whether it's progesterone, testosterone, estradiol or cortisol, are derived from cholesterol, and progesterone is a synthetic precursor to other hormones including testosterone, estradiol, and the stress hormone cortisol.

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Now when thinking about the effects of these hormones in the context of TBI, I wanted to put this slide forward to you just to kind of help recognize that secondary injury cascades, even in the context of mild TBI, as well as severe TBI, are really quite complex, and hormones potentially, at least based on experimental literature, may have multiple targets on the secondary injury cascades.

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Estradiol is known in the experimental literature to help maintain cerebral blood flow, prevent apoptosis and excited toxicity and can also facilitate growth factor production. But one of the more recent pieces of information of estradiol that is relevant to today's conversation is that estradiol is also emerging as a biomarker that's associated with increased stress that's linked with critical illness and trauma. And in these particular instances, whether we're talking about critical illness, trauma or other major surgery,

adrenal synthesis and peripheral aromatization of estradiol occurs and this may be an important component to our understanding of endogenous hormone physiology after TBI.

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Other hormones of interest include testosterone and progesterone. Testosterone is a bit of a double-edged sword. The experimental literature suggests that there are some bad things that testosterone can do particularly in the context of cerebral ischemia and reperfusion injury. But testosterone is also a necessary substrate for the synthesis of estradiol, so in certain circumstances it may be a helpful hormone.

Progesterone has had several decades now of experimental research in support of its ability to decrease cerebral edema, influence lipid peroxidation, blood brain barrier disruption and neural inflammation that can accompany TBI.

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Cortisol, again another byproduct that's made from progesterone, is another sort of double-edged sword, if you will. We need cortisol, particularly with our stress response in order to have a health response to major trauma. But too much cortisol can have a negative influence on the CNS in a variety of ways including the perpetuation of inflammation.

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So just a quick stop and check here. Do we have the answer? So on the question of how are hormones interrelated? I think that the quick overview that we did kind of shows you that the stratogenesis (inaudible) pathways include the major reproductive hormones, and these hormones can be generated in the gonad, but also particularly in times of stress, the adrenal gland and also peripheral sites like adipose tissue. We also know that these hormones can impact multiple mechanisms that are relevant to TBI. And that under these circumstances, at least in animal models, they can be neuroprotected. However, most animal studies are not able to and have not looked at how the stress response may play into the innate hormone physiology or perhaps hormone effects as treatments.

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So moving on, in order to really kind of address what does happen to endogenous hormone levels after TBI, some of our work has really focused on tracking and characterizing that process. And specifically we'll look in the next study at how endogenous hormone levels can be linked to outcomes and how aging, in addition to gender, those factors can influence hormone physiology.

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So acute hypogonadism – hypogonadism can occur in conjunction with any range of severity of TBI, including mild TBI. It is more prevalent, though, in patients who have more moderate or severe injuries, with one study suggesting hypogonadism in the acute phase being as high as 80%.

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But there's really very little known, particularly in the acute phase, about the temporal dynamics of hormone profiles over time, so that was the main focus of this initial study that we're going to review. We looked at 117 men and women with severe traumatic brain injury. And in these patients we were able to collect daily serum samples for a week and determine from these serum samples how hormone profiles evolved over time and if they could be linked at all to later outcomes. Also the point of reference, we gathered several control, healthy control subjects, and procured serum samples from them for hormone analysis as well.

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And the next few slides are some data slides just to give you a little bit of an overview of what we found. This first slide here is the pituitary hormone profiles that we observed over the first week. And you can see in this slide that the darker gray are levels that we observed in females and the lighter gray are observed in our male population. And what you can really kind of see here over time is that regardless of whether we are talking about men or women, we see a natural decline in SSH and LH levels over the course of the first week post-injury.

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We also see, for example, with cortisol, too, that cortisol is elevated for both men and women after TBI compared to controls. There's a little bit of a dynamic there for a decrease for both subgroups by days three or four but then still a little bit higher than the control bar by days five and six. No big significant differences, though, with regard to gender.

We also see that for serum progesterone that the levels are quite dynamic. They are a little bit high on day zero for progesterone for men but fall in about the mid range between the types of hormone levels you would see for follicular phase versus luteal phase levels in women. But for both groups there's very few gender differences, and by day six levels in both groups are quite low.

We see also a similar downward trend for testosterone. Men have higher levels than women initially, although the levels seen in women are above their control group. And by day six the levels are fairly similar and quite low for both men and women.

And then finally serum estradiol is a little bit variable in its presentation over time, but again, by day six after injury, we do see that they are relatively on the low side for that hormone as well for both men and women.

And what we conclude, too, with these hormone profiles that we see is that their likely genesis is from adrenal and peripheral hormone synthesis given the reduction in pituitary hormones over the time course that we just looked at.

So what we wanted to do next was to try to identify if there were unique clusters of patients who had unique hormone profiles. And to do that we used a technique, a statistical technique, called group-based trajectory analysis. And you can see here the different groupings of subjects for patients in terms of their cortisol levels and their progesterone levels. And I'm not going to go through them in a lot of detail, but suffice it to say that there was a bit of a gender difference in terms of progesterone. Most of the women were found to be in our higher progesterone group. Interestingly, again, progesterone is elevated early on for women. And there are no gender-exclusive groups for either cortisol or progesterone.

For cortisol, two of our three groups were elevated above controls. And it's also important to note that cortisol group membership was not associated with outcome. However, progesterone groups were. And high progesterone was associated with acute mortality, which is an interesting thought if you are thinking about progesterone as a potential neuroprotectant.

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We also looked at group based trajectory analysis for our testosterone levels as well as our estradiol levels. There were, again, no gender-exclusive groups. Both for testosterone and estradiol, we saw that older subjects were more likely to be in the higher trajectory group compared to lower trajectory groups. And both high estradiol and high testosterone were associated with increased risk for acute mortality and poor long-term outcome as measured by the Glasgow outcome scale at six months post-injury.

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Now, with these findings in mind and the thought that estradiol and progesterone could have potential neuroprotective effects, but also understanding the idea that progesterone is really a synthetic precursor for each of these hormones, we wanted to find a way to physiologically model all four of these hormones in the context of outcome. So we developed a rather simple structural equation model, the cartoon of which you see here on the screen, showing progesterone's interrelationships with each of these other hormones while also taking into account its relationship to outcome. And what we find in this type of multivariate model is that the progesterone does not have a direct influence on global outcome or acute mortality but rather its effects are manifested through its role as a synthetic precursor to these other hormones. And, again, testosterone, and particularly estradiol, were noted for their relationship to poor outcome, again with higher levels being associated with greater risk of mortality and worse outcomes.

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So, just to recap that particular study for us in the context of the myth versus fact here, what happens to endogenous hormone levels after TBI and are they neuroprotected? So basically I think what we see with this study is that endogenous pituitary gonadotropins plummet pretty early over the first few days post-injury and that there are some unique temporal profiles that are emerging for each of our hormone groups. And that peripheral aromatization and also adrenal synthesis is probably responsible for the majority of the testosterone and estradiol levels that we see for men and for women and probably reflects a stress response and that elevated estradiol and testosterone are associated with worse outcomes, particularly for people who are older.

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Okay. So with that set of data in mind, the next research question to kind of take on is how are chronic hormone levels affected by injury? And are chronic hormone levels and hypogonadism related at all to TBI outcomes? And lastly, when should we possibly think about testing for chronic hypogonadism after TBI?

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Chronically hypogonadism affects about a third of patients who have moderate to severe injuries over the first year after their TBI. And studies do indicate that there can be a negative impact on outcome, and this impact can be for women and for men. We know that menstrual cycle dysfunction can be impaired up to several months for women after severe injury. And also some recent work has come out suggesting that chronic hypogonadism is a very relevant complication after blast-induced concussion.

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Now we published a study in 2012, a small cohort study looking just at men with severe TBI who survived their injury. We looked at their average hormone levels beginning 72 hours out from their initial injury out to one week and called that an averaged week one value. From there we sampled these subjects – obtained blood samples every two weeks for the first six months post-injury and then again another sample at one year. And we looked at luteinizing hormone, the pituitary hormone LH, in the context of estradiol and testosterone. And we wanted to try to get a sense of whether or not patients met clinical criteria for hypogonadotropic hypogonadism greater than 50% of their time points which would meet our definition of someone who has a persistent hypogonadism state. If less than 50% of their time points met clinical criteria for hypogonadism, then we labeled them as a resolver and we went on to graph our hormone levels based on that group's stratification.

We also wanted to take a look at group stratification and also hormone profiles in the context of outcomes. And so we looked at functional cognition, some measures of neuropsychological performance, global outcome and a disability measurement.

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And here are the graphs of the hormone profiles over time. And you can see the triangles group is the group that has the persistent hypogonadism status while the squares represent the group that we called early resolvers. And you can see that over the first week post-injury, if you look at Panel A testosterone levels are quite low for everyone. But over the few weeks the profiles begin to diverge, and there's a group that stays low over the entire first year post-injury, another group who's levels returned to what were observed in our healthy control group. LH levels are also lower over time for our persistent hypogonadism group. And interestingly, in these men estradiol was also reduced over this timeframe.

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We were able to show, too, that the persistent hypogonadism status, if you will, was associated with worse global outcomes, higher disability burden, lower abilities on functional cognition metrics, and lower performance on cognitive testing.

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We've since been able to double our population that we've been able to track over the first year and found that we were able to reproduce the results from the initial published report quite nicely. Again, you can see in the upper left-hand corner this time window of about four to eight weeks where the two groups really begin to diverge, and again you can see how LH levels are lower in our persistent hypogonadism group and our estradiol levels are a bit lower, too, over the first-year post-injury.

And so some of our next steps for this work is to really try to look at four-to-eight-weeks after injury as a possible window for clinical testing and look at the ability of that sampling window to help us predict what might be chronic problems with regard to hypogonadism.

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So, when reviewing this paper, again, real quickly. What happens to chronic endogenous hormones after a TBI and how do they relate to outcome? We see that testosterone profiles for male survivors are associated with persistent hypogonadism and that testosterone is associated with outcomes. Low estradiol may also have some implications regarding plasticity and recovery in the chronic phases for the group having persistent hypogonadism. And that hypogonadism could be considered a chronic condition for some, and we really need to try to do a little bit more work understanding what mechanisms might contribute to that finding as well as follow these people out longer to determine if there is a late recovery period at all.

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Great. So the next research question is can hormones be used as pharmacotherapies for nerve protection or to enhance recovery after brain injury.

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And kind of picking up where we left off with the chronic study, there really is not a lot of consensus at this point in terms of the duration, dose and treatment end points that would be helpful to understand how to use testosterone as a therapy. I think the literature is pretty reasonable on the idea that testosterone replacement could help some of the symptoms associated traditionally with hypogonadism including fatigue, cognitive function and other elements of a low androgen state. Our initial data suggests that four to six weeks after injury might be a nice time to test for evidence that there's a possibility of persistent dysfunction, and again, we hope to look at that. But we also note, too, in the literature, that endocrinopathies don't necessarily happen in isolation, and from a clinical standpoint one would need to draw a full neuroendocrine panel and think about hormone replacement under multiple axes in addition to treating any low androgen status that might be apparent on testing.

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So estradiol as a therapy. There's really not a lot of literature out there at this time about estradiol as a clinical therapy. There is a group out of the University of Texas Southwestern that's looking at a single IV dose of Premarin in the Phase 2 clinical trial. The study plan, at least on [clinicaltrials.gov](http://clinicaltrials.gov), was to have concluded in 2013, but I have not seen any results in the literature. But I do think it is important to point out, too, that this study is looking at Premarin, which is not the same as *nastro* estradiol, and some of you may know that within the context of the Women's Health Initiative, Premarin was found to have some detrimental cardiovascular outcomes, so we'll have to keep in mind the particular formulation of estrogen when interpreting the results when they come out.

Clearly our work on serum estradiol as a biomarker for mortality in TBI warrants a word of caution about what the possible effects of additional estradiol might be or other estrogen-like therapies. But some recent work that we've been able to publish and aren't going to spend much time on today does suggest that at least estradiol levels in cerebral spinal fluid seem to be associated with the more traditional neuroprotective attributes that we've observed in the animal literature.

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So, yes, so progesterone therapy. Progesterone, again, has been looked at probably the most out of all of the hormones that we've discussed today. There has been two large Phase 2 clinical trials that showed some initial evidence of efficacy best supporting a Phase 3 multi-site clinical trial. The results of the Phase 3 trial are not yet out there, so it will remain to be seen if and how progesterone therapy might affect folks and affect outcomes, at least for some potential subgroups.

Glucocorticoids, though, have also been looked at, not necessarily recently but about ten years ago there was a paper that came out on the crash trial suggesting that acute methylprednisolone usage increased risk of death after TBI, and so that study was stopped prematurely due to an interim analysis suggesting that to be the case.

Now given that fact, you know, progesterone as a potential neuroprotectant, I think it will be interesting to see what kinds of hormone profiles are associated with it as a therapy and whether or not cortisol levels are at all affected through progesterone treatment. But some of our more recent work, again looking at cortisol in CSF, as opposed to serum, suggests that cortisol levels are quite high after severe TBI, which might be one potential reason why glucocorticoids did not seem to be beneficial, and perhaps even detrimental, in the crash study.

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So just to kind of summarize here about do we have the answers for hormone (inaudible) therapies, supplemental testosterone use could be pursued in a systemic way along with exploration and management of other neuroendocrinologies. I would suggest that there's really no clinical data at this point to support estradiol use for patients with TBI and that we do need to have a word of caution about what the particular estrogen preparation is that we're looking at when evaluating the literature. Seeing as glucocorticoids are elevated after severe TBI which may have some implications in terms of the effectiveness of progesterone as a therapy. And hopefully studies like the Bioprotect study that accompanies the Phase 3 clinical trial will help us sort some of those questions out with regard to how progesterone as a treatment might impact steroidogenesis after significant TBI.

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These are just some acknowledgements for my collaborators and students and staff. And I think next slide.

We have a couple slides here for references if you'd like additional information about the work that was covered today. And I think from there I'll turn it over to our next speaker.

So thanks very much, Amy, that was excellent. I would remind people that the bulk of Amy's work, or actually all of Amy's work, has been in moderate and severe TBI and not so much concussion. But I think that's important because that work has really set the stage for some of the pathophysiology and pathobiology of gender differences and hormonal interactions in TBI.

So if you have any questions for Amy, please submit them on the Q&A box in your monitor now.

So let's continue on with the second presenter. Dr. Janet Niemeier is Professor and Senior Director of Research at the Carolinas Medical Center in Charlotte, North Carolina. She also is an Adjunct Professor in the Department of Psychology at the University of North Carolina at Chapel Hills. Dr. Niemeier's research (inaudible) include interventional trials for participants with acquired TBI and gender differences in post-acquired brain injury and TBI. Janet, thank you for joining us and the floor is yours.

(inaudible) and I'm pleased to be here today talking about this topic. I also want to take this opportunity to say that the content and comments I'm going to be making and discussing are my own, but as you note, I did have external support for some of my research from NICHD and National Institutes of Health.

I do want to touch on the points that I'll be discussing today. I'll give some background and significance from the scientific brain injury literature and kind of drill down toward those articles that deal with gender differences. There's been quite a lot of interest in our field lately. I'll also review three studies in which we explored gender differences from a more social behavioral outcomes point of view, cognitive functioning point of view, and possible hormonal factors in these differences as well as cognitive correlative differences.

I do want to kind of wind up with the impact of traumatic brain injury on the life and health of women. I know Dr. Wagner so eloquently talked about the stress and the impact of worsening some of our physiological symptoms after TBI. And then targeting needs of women after TBI.

I'd like to first talk about the gender differences in the traumatic brain injury literature. And I think the byword or the theme for the next 15 minutes that I'd most like to emphasize is the mixed findings in outcomes after TBI and what the implications of that might be.

So some authors in our field for the last ten to 15 years have found that females are more likely than men to have better outcomes especially after comprehensive rehabilitation. They often raise their quality of life more highly than men, as much as 18 to 24 years after injury. And some authors have found that outcomes are better related to word capacity evaluation.

On the other hand, we have to remember that these, especially for women, are mediated quite a bit by the variables of social support, and that's perceived by women, depressive symptoms, and posttraumatic headache.

Males with traumatic brain injury, some investigators have found are actually more likely to receive vocational rehabilitation services, more likely to be successfully employed after injury, and less likely to have vocational services prematurely terminated than women. Now the reasons for all these differences in findings, which we're going to continue to talk about, are really not clear. With regard to neuropsychological testing and performance cognition after traumatic brain injury, women are often found to outperform men in certain areas such as verbal memory, executive functioning, and with high school athletes, women have been known to obtain better scores on IQ tests especially verbal and full scale IQs, as well as attention and memory subtests than men do.

Here is a table that sort of summarizes pretty dramatically how with all these different studies we certainly can see that the findings are mixed along several different abilities domains as well as at the bottom,

length of stay and mortality in addition. And that kind of brings to mind some of the discussion by Dr. Wagner.

TBI often results in disruptions of the so-called executive functioning domains of planning, initiation, problem solving, self-awareness and control of both cognition and self-regulation of behavior. And these are some of the areas that some authors have found women do better in than men do after traumatic brain injury.

The kind of neurologic region of interest here has been the frontal lobe, particularly prefrontal tracks. But the hallmark, especially in acute rehab with people who have moderate and severe injuries include pretty visible decreased ability to monitor and regulate their behavior and more agitation, in general, and trouble establishing and keeping a mental set, a lot of inflexibility.

Deficits also include major problems with self-awareness, which has very bad prognostic implications for long-term outcomes in resuming community living. Poor problem solving, poor planning, and the ongoing regulation and prospective response to daily life demands.

It's very difficult on caregivers as well when a patient has inability to see their injury-related deficits and how these impact and what that means for their ongoing work or home life.

We see some executive function differences between the genders through our neuro site testing. Prior research shows that though more men have frontal lobe injury, females also have some executive function symptoms. And it doesn't extend to agitation because both genders seem to have this in equal frequency on the inpatient acute as well as post acute settings.

TBI in males seems to more frequently occur when their injury is sustained in a violent incident, and they have more post-injury neurobehavioral problems and adjustment difficulties after a traumatic brain injury are more frequent. Interestingly a recent published study by Dan O'Connor (sp) applying some of the newer hierarchical statistical models suggests that all people that have TBI may have had more pre-morbid difficulty than the average healthy person so that they had some chronic problems before they sustained their injury.

One of the uses that we have for neuropsychological evaluations is to help us develop individualized profiles of neural behavioral and cognitive strengths and weaknesses after TBI, and then we can use these test findings to characterize some of these patients' frontal lobe deficits, executive functioning problems and pave the way for interventions that will improve coping. So that's part of the interest in using neuropsych testing findings and also exploring these gender differences after TBI.

One very often-used measure of executive functions is the Wisconsin card sort test, and in reviewing our studies that we've published over the last five to ten years we have used this measure, it's linked to early investigations back in the forties of abstraction ability. It doesn't seem to be influenced by educational level and it's accepted as one of the best measures of executive function deficits that we have. It's a measure of several features of executive functions including planning and organization. Being able to use environmental feedback to kind of revise your behavior and shift when you need to shift your cognitive set. And ability to modulate impulsive responding. Specifically two of the subscales, categories completed and (inaudible) errors hone in on some of these particular executive domains.

We do need to study further the impact on long-term outcomes on the effect of gender on presentation of executive dysfunction following TBI. We need in particular to kind of look at some of the variables that might impact the course and degree of recovery. And so we undertook in our first study a retrospective analysis of a large TBI model systems database and compared performance of men and women who were recovering from severe or moderate TBI in an inpatient setting across the country. So we enrolled in this study retrospectively 1,331 males and females. The mean Glasgow coma score on the emergency room admission was 8.7. And 67% were white, 73% high school education, and 73% had been employed

at time of injury. And the cause of injury broke out in the usual ways with vehicular crash right up there at the top.

The results indicated that there was an independent effect of gender. Female subjects performed significantly better on the Wisconsin card sort than male subjects. And it was related to an interaction of education, gender and ethnicity in regards to the categories achieved. Ethnicity and gender in relation to (inaudible) responses.

So the conclusions are we're left with a question, and that is are men possibly more at risk for post-TBI executive function deficit and on all negative effects on outcomes that go along with these impairments? Research needed on possible hormonal associations with these findings, so I'm looking forward to brokering a nice collaboration with my co-presenter. Brain injury researchers are beginning to study TBI and hormones and the connection with animal model work and humans. So I think that – and some of the visionaries in our field, Dr. Mallack (sp) for instance, suggest that we're kind of coming to the end of our pathway in more social behavioral and targeted therapeutic rehabilitation research and we need to kind of cross-field collaborate with basic science researchers to get the true answers and work together on this.

So our second research question that led us to a study included a larger question of besides executive functions, are there other cognitive and neurobehavioral (inaudible) of hormonal neuro protection for women after TBI? The hypothesis for this study was based on literature related to progesterone in that the oldest group of women we thought might perform more poorly on neuropsychological tests than other groups of women and the oldest group of men. And already, even though this was published fairly recently, this study started about three years ago, we can see the field is moving along and the question even seems a bit crude and primitive to me at this time. However, we did a mixed model comparison of neuropsychological test performance of men and women, and the age groups that we compared were 18 to 24, 25 to 34, 35 to 44, and 45 to 54, the oldest group was 55 to 64. And this is men and women in the model systems database.

We did these groupings based on the straw System, which came out in 2001, was updated in 2005. And the presumed age of onset of menopause. The ages were 16 and above, and there were 17 traumatic brain injury model system sites involved (inaudible). They received acute inpatient traumatic brain injury rehab and completed neuropsychological testing while an inpatient and were consented. So the study samples, all together, were enrolled in 1989 to 2002. Measures included tests of motor speed, word fluency, verbal learning, attention, mental flexibility, and the Wisconsin card sort again.

Our results of this study indicated that verbal memory with the (inaudible) we produced a significant age-time-gender effect. The oldest males performed worse than females in all age groups. And oldest women performed worse than youngest women. One interesting finding was that oldest women outperformed oldest men in mental flexibility. So we were speculating that it may be that older women retain mental flexibility despite changes in levels of endogenous hormones over time and after TBI. Again, further research is warranted into what underlying contributions there may be.

One limitation that we became aware of is the idea that the cohort was likely to have taken hormone replacement therapy and may have been still under that impact at time of injury. At that period of time, doctors were not advising their patients to reconsider the fact that hormones may be harmful and time to stop those. We did not also measure hormones prior to the study or during the study.

So turning just for a minute to progesterone. The speculation from some of these differences studies was that there might be a neuroprotective effect of progesterone. There were animal studies as well as some human studies suggesting that this may be the case. For example, with the human studies we found that actual functional outcomes occurred up to six months after injury in men and women with severe TBI. Also progesterone for the treatment of TBI was in several studies, the protect and synapse trials.

We began to think to follow the idea that maybe everyone would not respond the same way to injected progesterone, and it wasn't really clear what additional underlying mechanisms could affect these responses. On the basis of the thought that we might be oversimplifying and some investigators more

recently have suggested there was a negative impact. Certainly some of the things Dr. Wagner was talking about suggest that there are many levels of complexity in this.

So we decided to kind of examine the possibility that there are some other biomarkers or some other variables associated with progesterone that is possibly a therapeutic or neuroprotective substance. We decided to pull together a cross-field collaboration which included possibly our most valuable member, a fertility specialist who is an OB-GYN here at Carolinas. Then our brain injury attending physician. An ALS researcher in our (inaudible) basic science lab and hormone researcher, as well as myself and a great lab assistant.

Our pilot that we just completed is a proof of concept study, a nested case control design with repeated measures. And on the advice of our OB-GYN Dr. Hearst (sp), we decided to make the age range between 18 to 35-year-old women. And he advised that this is a relatively stable time in the menstrual cycle for healthy females. And we had 21 women with traumatic brain injury and then also ten healthy controls matched for age. The range in severity was mild to severe.

We did two blood draws, one at 24 hours and then one two days later. The same was true of controls.

And we are currently working out contractual things with labs for not only hormone level assays but RNA as well. Measured mental status, demographics, and menstrual and reproductive history and then outcomes including community reintegration three months later.

This was our pink flier to alert our emergency room and trauma surgery doctors for referrals.

And so I'm not going to try to go into any more detail than has already been eloquently presented on progesterone, but I just wanted to touch on some of the symptoms and this is by way of moving into more of the impact on women's health and life and how we might help women after TBI with some of these issues.

I will say also that the study of women after TBI, that research is behind that of study of men. Part of that is due to what's already been said, that more men have traumatic brain injury, but it may be that the focus needs to increase, and you see a recent announcement by NIH that they are very much in favor and encouraging vendor stratification of research findings.

So some of the symptoms include PMS and perimenopause and menopause can be worsened after traumatic brain injury. And unfortunately there are very few studies looking at this, but it can cause some problems and even risk of further injury (inaudible) some of those symptoms.

As Dr. Wagner mentioned, the menstrual cycle is disrupted most often and some have it for quite a long time. We're not really sure what the impact would be on PMS or perimenopausal or menopausal symptoms for women yet. It's not well studied. But I think what we need to do for women is to think of them as being somewhat at risk for a worsening of symptoms at certain normally healthy reproductive life phases. Think about increased maybe osteoporosis and fracture risks, deep vein thrombosis risk, and possibly a worsening of the situation because of ankle, foot (inaudible) weight-bearing restrictions.

And maybe interventions to minimize discomfort due to reproductive life phases such as menopause including some (inaudible). And assess for mood disorder, watching nutrition and sleep hygiene. Exercise has certainly received a lot of attention as a therapeutic process after TBI and is very much enjoyed by people with traumatic brain injury.

In general we should build on female strengths in executive functions in our rehabilitation therapies. Monitor mood and coping. Women do report more mood and cognitive symptoms, and with their increased likelihood of combat exposure now, this probably needs to be ramped up.

And then monitor and prevent occurrence of intimate partner violence.

Again, I think cross-field collaborative team approach is ideal for addressing all of these complexities and trying to understand the underpinnings of gender differences. I think they are far more complex than we first realized. We think that maybe looking at polytrauma, olfactory receptors, what are some of the mediating and moderating variables here that are going on.

The rewards of this kind of collaboration are worth any challenges. Meeting with my team, with the OB-GYN, the basic scientist, you had to kind of develop a language or a linguistic currency, it was kind of a euro or something so that everybody could understand each other, but it's definitely rewarding. We hope to be engaged in a lot of additional research.

And these are some references. I'm certainly willing to send any others or entertain questions about those.

And I will return to Dr. Marion.

Thank you, Dr. Niemeier. That was outstanding.

So for those online, if you have any questions for either of our presenters, please submit them now via the Question box located in the upper left side of your screen.

As the attendees to this webinar submit their questions to our presenters, I would like to share this month's DCoE product brief entitled Indications and Conditions for Neuroendocrine Dysfunction Screening Post Mild Traumatic Brain Injury Reference Card and Clinical Recommendation Kit. Most patients with mild TBI recover completely within three months or less of injury. However, a small subset experience persistent symptoms and difficulty in rehabilitation particularly when presenting with co-occurring disorders, Neuroendocrine dysfunction, or NED, may be a contributing factor. The onset of NED can occur any time between the initial event and up to 36 months post-injury. It is the result of direct trauma or biochemical response that interferes with the normal production and regulation of interrelated hormonal processes. The anterior pituitary is the most vulnerable and most often affected endocrine structure. Growth hormone and gonadotropin are most frequently affected and deficiency may lead to symptoms such as fatigue, weight gain, low blood pressure, low libido, loss of muscle mass, and amenorrhea.

The diagnosis of NED, Neuroendocrine Dysfunction, may be difficult and sometimes not considered because the symptoms may significantly overlap with post concussion syndrome as well as other co-occurring conditions such as sleep disorders, PTSD or depression. Service members who experience persistent symptoms suggestive of NED for greater than three months or new ones at up to 36 months following the NTBI may benefit from post-injury NED screening. Screening can provide valuable clinical insight leading to prompt treatment and improved overall prognosis for this subset of patients. However, NED screening studies should not be routinely ordered as a screening or diagnostic tool during the early post-injury period.

DCoE developed a clinical recommendation to offer the primary care provider an approach to identify patients with mild TBI or concussion who may benefit from further endocrine evaluation and care. This recommendation is based on a review of published literature as well as the proceedings of a 2010 expert panel convened by DCoE that included clinical subject matter experts representing the military services, the Department of Veterans Affairs, and the civilian sector. It was also reviewed and approved by the Defense Department's TBI Quad Services Cell, which includes TBI representation from the Air Force, Army, Marines and Navy. To complement the clinical recommendation, DCoE developed a reference card and training slides to assist those who have basic knowledge of TBI but who may require additional information on neuroendocrine dysfunction factors. These resources are available at the DVbic website at [dvbic.dcoe.mil](http://dvbic.dcoe.mil) and can be downloaded now from the Files box at the left of your screen.

So just to summarize for your clinicians, if you're seeing someone out there who is three months out from their mild TBI, and they have lethargy or fatigue or sleep dysfunction and you're confused about that or it seems to be getting worse, a neuroendocrine screen may be in order.

So it's now time to answer questions from the audience. If you have not already done so, you may submit questions now via the Question box located on the screen. We will respond to as many questions as time permits. So let's begin with the first question, and that question is for Dr. Wagner. The question is, are there parallels in research, either published or ongoing, that demonstrate similar data for mild adversely severe TBI regarding neuroendocrine dysfunction, either qualitative or quantitatively?

Yeah, I think that that's definitely an interesting question. My sense of the matter is that a little bit more of the work has been done in the moderate to severely injured population, but again you do see some of evidence of neuroendocrine dysfunction, perhaps in five to ten percent of patients with mild TBI. I think, though, you know, it's matter of discussion that there could be some differences and nuances with regard to the frequency of hypogonadism and neuroendocrine dysfunction based on injury type. So, you know, in reading the literature and trying to consider who falls into that mild group, it's very, I think, important to understand are we looking at a blast-related kind of a mechanism, and my understanding with regard to that population is that there is often the case that there is multiple blast exposures. You have this concept of repetition. Sports concussion, you know, can happen via very different mechanisms, although the repetitive component may still be there. And oftentimes our athletes who are getting concussed are quite a bit younger than, say, your average civilian in a traffic accident who sustains a concussion. So, you know, I would like to say that we've got all of these different scenarios for understanding neuroendocrine dysfunction amongst these different subpopulations well worked out, but I don't believe that the real time course and the history and timing of onset and duration of dysfunction is really worked out so well that we can provide very precise guidelines on how to treat. But I think your statement earlier about when you suspect some of these – or you're observing some of these symptoms, to just think about neuroendocrine dysfunction as another potential point to check to try to get to the bottom of things and potentially identify a treatment pathway forward.

I have a follow-up for you, Amy, and that is so we talked about mild versus severe. What about single versus multiple injuries? What can you tell us about that and endocrine dysfunction?

Well, you know, again, a lot of very specific facts I'm not sure I'm going to be able to speak to, but with repetition comes increased risk. And I think, you know, certainly if someone was presenting to my clinic with a history of repetitive concussion or mild traumatic brain injury that I would consider screening I think probably sooner rather than later because you may have sort of a cumulative kind of a scenario here in terms of risk.

Okay. The next question is for Dr. Niemeier. In studies that show differences in outcome between males and females, was severity of the injury controlled for between the groups? I would be very interested to know specifically what severity level these studies were researching and given that there are significant differences between (inaudible) concussion and moderate and severe TBI? So hopefully that was obtuse enough.

That's a nice, meaty question there.

Yeah.

In terms of our studies, we were only looking at moderate and severe. And part of the problem with enrollment of milds right now is that the gold standards for identification of mild traumatic brain injury are being found to have limitations, and some major groups studying mild TBI are finding them – even calling them primitive that – I'm referring to the Glasgow (inaudible) scale and scans. So studies generally speaking are thought to be weakened if they enroll mild TBI without certain parameters. So a lot of your data is going to be about moderate and severe and then hopefully as we progress in our study and identify biomarkers and algorithmic approaches to identifying the mildly injured person able to see some of those same outcomes reflected in the milds. So that's some of an answer to what you're saying. I think

that the language differences, too, in the different domains of study, and Dr. Wagner you can also comment on that, doesn't help us where we have the blast injury and mild TBI, we have concussion study in athletics, and then civilian car crashes, so there's a bit of language mix up there that doesn't help. That's another reason for us all to get together.

Amy, did you want to comment?

Sure. You know, I agree with what you said, Janet. I think that probably one of the shortcomings of where we're at in trying to translate into clinical care is really getting a good handle on these different subgroups and having a systematic evaluation of their risk time course onset severity and potential responses to treatment. And so at this point I think there are some general guidelines keeping neuroendocrine dysfunction in mind as a potential ongoing problem for people. I think you just sort of having that is kind of high on your radar to think about and screen is one of the best take-home messages at this point.

So I'd like both of you to comment on the next question. So I'm sure you're both aware that Dr. Wright's Protect study was halted. And I think most of us online would like to know from you what's the bottom line. Is progesterone protective or not for TBI in men?

Do you have any preference who goes first, Don?

No, I don't.

Go ahead. Go right ahead.

Sure. Yeah, you know, I think it's a really interesting question. The initial set of results has not come out yet but my understanding is the study was stopped prior to the conclusion of enrollment due to futility, so the main effect, again in a moderate to severely injured population, was not significant. That said, I think there is a role for hormones including natural estradiol, natural progesterone, to be specific, that, you know, from the experimental literature that can't necessarily be ignored. So my thought on the matter is that there may be some subgroups that can benefit from a neuroprotective standpoint. But there may be other groups that just weren't good candidates. And so my hope is that through subgroup analysis, and also through careful biomarker characterization, some of you may know that there is a companion study to the Protect trial called Bioprotect where blood was taken pre-randomization as well as post-treatment. And my hope is that through that other complementary arm of the study that we'll be able to get a little bit better sense of what progesterone might be doing to injury-specific markers, what progesterone might be doing in the context of the stress response that we've identified in the severely injured patients that's not TBI-specific. Again, you know, estradiol is considered a mortality marker in major trauma and other forms of critical illness as well. So I don't think that we have the bottom line just yet. And I think that there are some intrinsically good points to what progesterone could do to various secondary injury targets. We just need to see how it shakes out in terms of the heterogeneity of the population and whether there are still some subgroups for which treatment might be warranted.

Janet, did you have anything to add to that?

Yes, I think that, to borrow from an old German proverb, the devil is in the details. And that there may be many moderators and mediators that we don't really understand. And that that may account for some of the interactions that obscure findings or at least make them mixed like they are. And I would say that that's the case. There's two other things in the heterogeneity. The one is that a lot of people who come into the emergency room and when their blood is first drawn are pretty heavily intoxicated. Men and women. And we just found that history of substance abuse has a significantly negative impact on outcomes. So there just are so many factors that could be going on besides gender, and we just don't know how they all, as Dr. Wagner says, shake out.

All right. The next question is for you, Dr. Niemeier. And that is if there is evidence of brain injury rehabilitation tailored to the special needs of women to enhance recovery in concussed women, is there

also evidence that rehab programs tailored to the special needs of men can enhance their recovery, and what are those special needs?

Well, as astonishing as it may seem, we're really, up until now, have not had an emphasis on gender stratification of outcomes. So it's hard to answer that. I think we're going to see a lot more of that with outcomes research though we already have and it might be built into studies. But there are some differences that have been chronicled for a long time in men and women. And the interesting thing is that many of them are the same as those that are being pointed out in the brain injury literature. And that women tend, in school, and all ages really, to have manifest better verbal memory. Men do better with motor and visualizing skills. And that's been going on for a long time. So we just have to, I think, build on strengths that we know about for men and women and work those into the rehabilitation programs. Give them something meaningful for their gender-related interests in some of the rehab activities, for example, it might be more appealing for men to be able to try to put together a motor than to bake an apple pie and things like that. So kind of basic principles of what activity is rewarding and since it is therapeutic, drawing them in more than otherwise would happen if it's kind of a feminized activity and vice versa.

Just saying, I make a mean strawberry-rhubarb pie.

Well, you know, that's all right, too.

But the next question, I guess I'd like to ask you. What are either of your, especially Amy's, feeling about biomarkers for the acute diagnosis of the concussion and maybe the role of estrogen or progesterone levels, or testosterone levels, for more mild injuries such as along the sidelines of a football game or some forth. Amy, you presented some provocative tables that are evidence about testosterone, progesterone and estradiol. And I know they weren't severes, but what do you think about mild?

In terms of using it as a biomarker for a diagnosis of brain injury?

Yeah.

Is that understanding correctly?

Yes.

Yes. You know, my sense of the matter is that as a biomarker for diagnosis, hormones are not going to be really where you're going to find a lot of diagnostic value. I suppose it's possible that early after injury you might see a reduction in pituitary hormones. But I just don't see those as being viable compared to some of the other structural damage markers that have been studied for a while in the context of concussion. So some brain specific markers, you know, whether it's UHCL1, GSAP, or S100, it's my sense that those are better candidates at this point, especially for uncomplicated kind of a concussion picture where you're not getting a lot of extra cerebral injuries to sort of continue and confound things. But, that being said, you know, I think GSAP and S100 are starting to gain some traction as some really kind of viable markers for concussion, but none of them have been really approved for clinical use. And the development of a clinical and clinically rigorous assay platform I think is also a challenge that likely still needs to be dealt with before making these kinds of biomarkers really available prime time for clinical use.

So the next question is for I think Dr. Niemeier. We talked a little bit about fatigue or sleep difficulties in subjects that come back three or four months after their injury. What about some of the other things that we, especially in women, that we think about in terms of female sex hormones, such as hot flashes, or things like sensitivity to hot or cold or profuse night sweats. Do we see that very much in the aftermath of TBI associated with hypogonadism? In men especially?

That I probably will, with the hypogonadism, I'd defer to Dr. Wagner on that. But I will say for women that question is sadly very understudied at this point.

Okay. Amy, do you have any comments?

Sure. I would agree with Janet that there is really not a lot of data out there to help us link these kinds of symptoms to any one potential complication. But my thought would be that when we're thinking about some of these more vague kinds of symptoms, yeah, it may not necessarily just be a manifestation of hypogonadism but other related endocrinopathies. Thyroid function can certainly impact your thermostat regulation so to speak. People who have some kind of thyroid storm might present with some of the symptoms that you're discussing. On the other hand, you know, a low thyroid state, maybe we're looking more at cold intolerance and difficulties with that end of the thermostat regulation. So I think my sense would be, again, worth thinking about hypogonadism, we need to look at all of the different pituitary axes and make sure that we have a complete picture on what's going on there. And perhaps, even, seek out the help of an endocrinologist if you've got a patient who might have presentation of multiple endocrine dysfunction when you're seeing them in clinic.

Okay. And then I think as a final question, one of our participants asked about are there genetic risk factors for hypogonadism or hormonal dysfunction following TBI? And either one of you can take that.

This is Amy. I'll make a couple of comments. To my knowledge I don't know that there's a genetic polymorphism that has placed people at higher risk. I'd certainly have to do just kind of do a review of the literature to see if there's anything new that's popping up. Genetic risk is certainly a burgeoning field for TBI right now as well as many other areas with all of the accessibilities there are with genetic (inaudible) these days. We have looked, though, at the aromatase gene, which is the gene that helps synthesize estradiol from testosterone. And what we found in a larger group, again severely injured subjects, but what we found in our group was that genetic variation within the aromatase gene was associated with hormone levels in the periphery as well as in the CSF during the first week post injury. And also linked to global outcomes. So, again, using something very basic like a GLS kind of a score. We are not at a point yet where we've been able to apply these analysis or an analytic approach to a population of survivors with the particular interest in hypogonadism per se, but we do continue to build our cohort size and that is one question that we would like to explore, you know, is genetic variation within the steroidogenesis pathway any kind of contributor to risk of hypogonadism or duration, persistence, that kind of thing.

Thank you, Amy.

So we're at our conclude mark. First, I really would like to give my heartfelt thanks to both Dr. Wagner and Dr. Niemeier for agreeing to participate in this webinar. You guys did a fantastic job and we know it's an awful lot of work. People on the line probably don't realize that this is several months of preparation and dry runs and so forth. So thank you guys so much for stepping up and helping us out and very much appreciated. Our attendees always want people from outside DVBIC and DCoE who are the real international and national experts, and you guys certainly fit that bill. So thank you.

Honor of being asked. I've had a lot of fun. Thank you.

Same here. Thanks for the opportunity.

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

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The next DCoE psychological health topic is Depression In Men In the Military, and it's scheduled for June 26, 2014, from 1:00 to 2:30 p.m. Eastern Daylight Time.

The next DCoE TBI webinar topic is Do Helmets Prevent Concussion, and it's scheduled for July 10, 2014 from 1:00 to 2:30 p .m. Eastern Daylight Time.

Finally, thank you again for attending, and I hope you have a wonderful day despite all the rain here in the D.C. area. Out here.

This concludes today's conference. Thank you for your participation. You may disconnect at this time.