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

October 22, 2015, 1-2:30 p.m. (ET)

"Using Meta-analysis to Determine the Most Effective Treatments for Posttraumatic Stress Disorder"

Thank you very much and good afternoon. Thank you for joining us today for the DCoE Psychological Health October Webinar. My name is Vladimir Nacev. And, I'm a clinical psychologist and senior program manager for the Deployment Health Clinical Center. I will be your moderator for today's webinar. Before we begin, let us review some webinar details. Live Closed Captioning is available through Federal Relay Conference Captioning. Please see the pod beneath the presentation slides. Should you experience any technical difficulties, please visit dcoe.mil/webinars and click on the troubleshooting link under the monthly webinars heading. There may be an audio delay as we advance the slides in this presentation. Please be patient as the connection catches up with the speaker's comments. Today's presentation and the resources list are available for download from the files pod below.

All right? This continuing education activity is provided through collaboration between DCoE and Professional Education Services Group. All who wish to obtain continuing education credit, or certificate of attendance, and who meet eligibility requirements, must complete the online education, online CE evaluation? After the webinar, please visit DCoE.cds.pgstce.com to complete the online CE evaluation and download or print your CE certificate of certificate of attendance. The evaluation will be open through Thursday, November 5, 2015. Throughout the webinar, you're welcome to submit technical or content related questions via the Q&A pod located on the screen. All questions will be anonymous. Please do submit technical or content related questions via the chat pod. Participants are encouraged to chat among each other during the webinar using the chat pod, but please refrain from marketing or promoting your organization or product in the chat pod. I will now to our, today's webinar topic, using meta-analysis to determine the most effective treatments for Post-Traumatic Stress Disorder. This webinar will review the current guidelines for the treatment of Post-Traumatic Stress Disorder, PTSD, at all points of the treatment, I'll continue.

It will highlight the significant areas where current matrix guidelines, which are the VADOD, World Health Organization, the America Psychological Association, and are not in agreement including medications versus therapy, individual medications and behavioral therapists. Presenter will discuss variances in the evaluation of data that resulted in these differences and will review the evaluation of current studies in the form of four meta-analysis looking at more than seventeen thousand citations for best evidence-based treatment. The participants at this webinar will be able to re-state the current guidelines for the treatment of PTSD, differentiate between the current evidence from medication versus behavioral therapy, excuse me, as evidence-based treatment, identify medications with the best evidence supporting their use for PTSD, and compare behavioral therapies with best evidence supporting their use for PTSD.

I would like now to introduce you to our presenter, Dr. Jonathan Wolf. Dr. Wolf is an attending psychiatrist at the Walter Reed National Medical Military Center, the National Intrepid Center of Excellence. He is one

of two attending psychiatrists that are an integrated out-patient program treating service members with both acute and long-standing core-current neuro-psychiatric issues. He has professional and technical oversight in the direction of licensed and non-licensed health care providers and listed active duty personnel, service reserve officers, nursing staff, psychiatric residents, interns and medical students, as well as leadership of multi-disciplinary treatment team including psychiatry, occupational and physical therapy.

Dr. Wolf is the lead attending on cases involving substance abuse addictions and provides diagnostic evaluation of patients based upon laboratory and clinical findings, referral of patients to appropriate physical specialty clinics. His work includes collaboration with in-patient and out-patient physicians, the other medical specialties and cases involving complicated and multi-faceted problems. Dr. Wolf also provides oversight on research projects involving psycho-pharmacology and exposure treatment for Post-Traumatic Stress Disorder. I would like to also remind the audience that regrettably we were unable to have Dr. Lee, who was the original presenter for this presentation due to medical condition that he attained today. However, we are delighted to have Dr. Wolf. Dr. Wolf, it's yours.

Oh thank you. Can everybody hear me Okay? So, I'm Jonathan Wolf. My relationship to this is Dr. Lee is the lead author for the work that I'm gonna be talking about, but I was Dr. Lee's research supervisor in attending. I'm now collaboration with Dr. Lee in both this research and some on-going research. So, I'm quite familiar with the work here. I would say, I'm, Dr. Lee has a slightly different slide deck than I do when he talks about it and Dr. Lee, you really did miss out. Dr. Lee is really the master of this particular statistical analysis and for people sort of sitting waiting for really, really, complicated, high-order statistical differentiations, Dr. Lee is a better person to answer questions like that. I will do my best, but I may need to acknowledge the limitations of my own abilities when we come to things like that.

So, first of all, you know, neither Dr. Lee or I have any relevant financial relationships. And, then sort of most importantly, what I'm about to talk about is really only his, my and our other co-author's opinions in terms of treatment, and it doesn't reflex the policy of the Navy, the Army, Air Force, the US Government, or any entity thereof including the National Intrepid Center where I'm in attendance. What I'd like to take you folks through really briefly is, first I'd like to go through, sort of, what the current guidelines are and what the current recommendations are for the treatment of Post-Traumatic Stress. And, then I'd like to look at the evidence for medication versus behavioral therapy. Is the evidence there for one of those modalities over another, and then specifically in both of those modalities, among the medications is there really one that's first among equals. Is there any evidence supporting one approach or another, and the same with behavioral therapies. Although, again, I should point out really what I am is a psycho-pharmacologist. I will attempt to talk about behavioral therapies as best as possible but again it's another area we may run into some limitations in terms of my own knowledge base.

So, I think, this is a point that I always try and get out of the way, sort of, early in the presentation and I make it and then I sort of retreat from it in cowardly fashion. The PTSD diagnosis really underwent substantial modification in going from DSM4 to DSM5 and that modification occurred in 2012. When we look at the studies that are cited, and you look at the time periods that we're looking at in that analysis, really what we're looking at were studies that were done using DSM4 criteria, and so what I would say is, I think the information that I'm going to be presenting to you applies most directly to people who meet DSM4 criteria for PTSD as opposed to DSM5. And, having made that point, I'm now gonna retreat from it because it's a somewhat politically charged issue. So, I want to take you, just looking at the outline, I'd like to take you quickly through, sort of, what the state of the art is right now. What the major guidelines are recommending, and then I'd just like to talk to you about meta-analysis and then finally I'd just, sort of, briefly like to talk about how the results, really of Dan's work, have informed what I do clinically, in terms of how I take care of patients.

So, I think the first thing to acknowledge is that this is really a very sizable and growing, you know, service burden, in terms of what mental health providers are gonna be seeing. So, since, you know, the towers came down on September 11th, American troops have deployed about 3.3 million times, and most

specifically what I'd like to draw your attention to is that in addition to just the sheer number of deployments, we have half a million service members who are returning who were deployed three or more times. And, the PTSD rates in patients like that presenting to outpatient clinics has been estimated to be as high as 25%. So, this is really gonna be a very, very, considerable problem in terms of a very, very, considerable patient base as we go forwards from here. And, I think the other thing that's important to look at is right now, most of these folks, have been getting care in the DOD system. And, you know, I want to be very clear with what I'm saying. There are treaters in VA's who see as much PTSD as the active duty folks do, if not more.

By no means, sort of, besmirching them but part of what's happening is, these folks are getting out and they're retiring and they have, sometimes, some degree of service connected disability, or something like that, they're moving to, sort of, less served areas, and in those situations, they're seeing people in smaller hospitals, and sometimes they're not seeing specialists, they're seeing generalists, and so there's gonna be more burden in terms of looking at what the published guidelines are, in terms of informing treatment because they're gonna be moving away from specialists both at the DOD and some of the bigger VA sites, and they're gonna be moving more out to the community. So, I think this is really something where we need to, sort of, get our ducks in a row, in terms of what the guidelines are saying.

So, part of it is with patients moving to these, sort of, smaller sites, I think clinicians who are less experienced to, in terms of expert guidance, choose to look at guidelines, are gonna find themselves somewhat confused if they do a reasonable search, because the current major guidelines really, I think if you could say one thing easily about the current guidelines, it's that they're completely contradictory. They do look at the same pool of studies, but they really don't reach anything resembling a level of consensus. And, I think it's important to recognize that it's not just Dr. Lee and myself picking nits when we say that there isn't consensus. Some of the basic fundamental questions about how we treat PTSD really aren't clear if you look at the major guidelines. And, that goes down to the level of, you know, not only of which medications should we be picking, but should medication even be considered first-line therapy at all for these patients?

So, first of all, very often when I present this material or talk about it, people say, "What are you talking about, you know, we know how to treat PTSD, we have VA guidelines, or we have APA guidelines? And they're very clear." And, I think what's really important is to take a step back and look at what the major organizations are, and then look at what they're saying and the degree to which they agree or disagree. So, this represents Dr. Lee and my own estimation of what are, sort of, the major guidelines out there, not only US, but also Internationally, in terms of who's seeing PTSD and who's treating it. So, there's our own VA DOD guidelines. There's the UK National Guidelines, those are gonna be abbreviated NIC, N - I - C - E. I don't have any idea whether people actually call that NICE when they look at it, but it really is, essentially, the equivalent of the United Kingdom. There's the, you know, my wife's a psychologist, she tells me I should really call the American Psychiatric, the Little APA, and her's is the big APA, but it's what I think of as the big APA. So, the American Psychiatric is probably the largest organization, you know, for psychiatry providers in this country. Then there's the ITSS, that's the largest, sort of, private, what I think of as a private organization putting out Traumatic Stress guidelines they're a specialized organization. There's the World Health Organization, which I assume people are all familiar with, and there's the Australian Center for Post Traumatic Mental Health. We look at their guidelines.

There are probably the most recent, and in some ways, the most modern guidelines that have been put out. They did a really wonderful job, but again, it's another, sort of, International, sort of, voice in terms of how we treat PTSD. So again, if you want to step back and look at it, it', you know, the American guidelines, VA DOD and the American Psychiatric, and then the, sort of, private American, the International Society for Traumatic Stress, and then probably, the three largest International organizations. So, we felt like this really represented a good faith effort to capture, probably, the biggest players in terms of treatment for Post-Traumatic Stress.

Now, the one thing I would say if you look at these guidelines is, there is, you know, again a nine or ten year spread in terms of when they were founded, which may partly explain when you look at the data, kind of why the degree of discord and the current APA guidelines are presently, to my understanding, pending under review. So, I think the first question I ask when I look at guidelines, and I want to talk to you about what I consider the three basic questions in PTSD treatment. The first is really, should we be treating people with medication or should we be using conventional behavioral therapy? And, behavioral therapy, and are those equivalent? So, if you look, it's a pretty even split, so we have the ADA, the APA, and the ISTSS, all recommending medication or behavioral therapy as co-first line treatment, and then we have the NICE, World Health Organization and the Australian organization which recommend therapy as a preferable first line.

The next two slides, I will tell you right now, are really, really terrible slides. They have an enormous, and I can get away with saying that because I think these were actually originally my slides, but they have an enormous amount of information on them and rather than sitting and trying to take it all in, really what i would be trying to take away from this, is that there really isn't anything resembling agreement in terms of what should be first line, when you look at the slides. If you look at the VA DOD, they're recommending all SSRI's, all SNRI's as equal, then you go over to the British guidelines, the NICE, and they only have four agents. They particularly have one that they like and the ones that they don't, the only medication listed in the VA DOD that was first line is Paroxetine, which I'll probably make this point a couple of times but it's actually the only medication that's recommended as first line, if you go across all of the organizations.

And, then again, that's the first line. If you go down to the second line, there's probably even less agreement in terms of what we should be doing, including, you know, the NICE and ITSS, you know, recommendations of benzodiazepines, which is something that some of the other guidelines say are contra-indicated. So, moving ahead a little bit, this is the recommendations for recommended behavioral health treatments. My wife is a psychologist, tells me that there's an equal amount of discord in these and that I just don't have the technical sophistication to be able to differentiate from them, but to my own, sort of, somewhat naive eye, there looks like there's a little bit more agreement than there is with medications. I wouldn't say it's a complete, just in general a little bit more of an emphasis on, you know, Trauma Focus Therapy as sort of being superior to the other ones, and Exposure Based Therapies. But, there really isn't clear guidelines to guessing which behavioral therapies are better than others. Again, this is essentially what I just told you.

So, if you look, and again I apologize, this slides a little out of date, three out of six guidelines recommended behavioral therapy as superior to medications and three out of six said that they are equivalent. And, then when you go and you look at specifically the medication requirements, there really isn't any kind of consensus in terms of what we should be using. So, some guidelines recommended general classes of them, some separated them and wanted to look at individual agents, and some medications that were, as far as recommended as first line under certain guidelines were contra-indicated in others. There really isn't any sort of agreement whatsoever, in terms of medications or recommendations. As I said, I think there's a little bit of greater consensus with behavioral therapy recommendations, but that could be my, sort of, lack of sophistication. So, I think when you step back, I think the first thing that you want to ask yourself is. "Why are these guidelines so different?" I don't think it's just the time that they were constructed. It really goes down to some basic differences in terms of what people were doing when they collected and looked at data.

So, first of all, from most of the guidelines, the data wasn't collected in an organized fashion. It was a little bit, sort of, idiopathic. I'll get into a little more depth before we get to crunching the numbers in terms of what I mean by that but, the data and the individual studies that were reviewed really did vary pretty considerably. And then, once they collected the data, there were basic fundamental differences in terms of how the data was analyzed. So, if you look at the VA DOD, and you look at the International Society for the Treatment of Traumatic Stress, what they were really interested in was mostly just the number of positive trials, regardless of the strength of the findings and regardless of the, sort of, number of patients

enrolled there. We look at the NICE guidelines and then the Australian Center, not only were they, really what they were interested in, was, not only, are the effects positive, but how strongly positive were they. So, they counted anything with less than a .5 effect size to be a negative study, which I would say is not a completely unreasonable standard, it is used somewhat.

So, and then, the ISTSS really valued uncontrolled data a lot more than the VA DOD, you know, when they were weighing the various pieces of data to determine their influence in terms of the guidelines, and the NICE, for example, completely ignored all uncontrolled data, it was only interested in controlled studies. So, I think stepping back, the other thing that you want to look at, and this is, again I apologize, this is really review for anybody with much of a statistical background, and for people like that I apologize. You certainly feel free to tune me out but, when you look at how guidelines in general are constructed, you probably want to look at some of the language, so in the narrative review, which is really how these things are traditionally assembled. Both the collection of the data and then how they look at is a little idiopathic, so really what you do is you go out, get the World experts on the subject, you ask them what do you think of the important studies, they pull these studies, they come together in a room and then they somehow hash it out.

And, this isn't meant to sound pejorative, it's really a majority of how guidelines in medicine are constructed, in general. And, it's usually a pretty good way of going about things. You know, if we were to get the top people from any one of these countries in a room to discuss the data or to [inaudible], so it's not meant to be pejorative, it's just meant to say there's some problems with that and the biggest one is that because data collection is idiopathic, and because how it synthesizes idiopathic, you really, you can't ever replicate these results.

So, it's useful in the moment it's constructed and it's useful for a finite time period afterwards but, you know, then it's a little less clear what you're supposed to do with it. In a systematic review, the literature is collected by a uniform data search, but then how the conclusions are reached from that data is idiopathic, so there's a, essentially you use a search engine or something like that, you pull together the appropriate studies, the same group of experts reads them, and then they produce guidelines from that. But again, there's an element to which it's difficult to replicate because it comes down to how the experts chose to select the data, after they looked at it. In a meta-analysis, which is a sub-type of a systemic, systematic review, not only is the data collected in a uniform fashion, but then there are clear guidelines in terms of how the data was weighed, and how the conclusions were drawn from it. Whoops. I apologize, I'm having some slight technical difficulties.

So, going from the general to the specific, if you look at how the individual guidelines were compiled, the DOD VA, the APA, the ISTSS, and the World Health Organization were all essentially compiled by narrative review. They got a bunch of very, very, bright people with a lot of experience in the field together. They put their studies forward, and that's how they produced their results. The NICE was a little interesting. They collected the data in a uniform fashion, but then the actual evaluation of the data was somewhat standardized, but then in the end, the guidelines were pushed out to individual providers who, sort of, weighed in on it. So, it started out as a meta-analysis and then it evolved slightly when they were, sort of, completing their work. A wonderful study though and, again, it represents an enormous amount of work.

And, then the Australian guidelines which are pretty terrific. There were some idiopathic qualities in terms of how they collected the data. They pulled studies and essentially broke standardization in terms of their collection of data, but then they used a standardized evaluation of data in attempt to produce replicable results. It again, is also a very wonderful block of work. I mean, all of these do represent an enormous amount of work by a lot of generally very bright people. I'm really trying very hard not to be critical. So, I think what's important to look at is that all of these were compiled by very, very, senior experts in the field, and I'm essentially sitting here telling you that you should, to some extent, disregard what they told you in favor of looking at what Dan and I did. And, I think to do that, you need to be sold on a meta-analysis in

this particular situation as being the answer to solving the riddle of how you treat PTSD. So, I think there are a couple of reasons why meta-analysis is important.

One, the minute you provide transparency in collection of data, and evaluation of data, the problem with a narrative review is it is only really useful at that moment in time, you know what those experts thought at that moment. But, you don't know what they would do when a new study comes out, or new information comes out. How they would take it and how they would weigh it versus the work that they'd done previously. So, it's really useful at that moment, but then, the data essentially degrades over time. It becomes less useful over time. And the other thing is, you're not able to look at the nuts and bolts of what they did. You're not able to say, "I agree with these conclusions." or "I disagree with these conclusions." in terms of how they weigh their data, and in meta-analysis, that's all gonna be right there. And, specifically that brings me to why I think a meta-analysis is the answer for PTSD. I think the first thing is, the experts haven't reached a consensus in terms of how we treat things. If we got anything out of looking at the guidelines, it should really be that they just don't agree with each other.

And, I think part of what that's derivative of, and this is gonna become clearer when I actually go through some of the studies, is that the data is still evolving. We probably are still at the point where we're collecting data on how to treat PTSD. I don't think the definitive studies have been done yet. And, for that reason, a meta-analysis where it's easy to plug-in new pieces of data, and you change your conclusions, is probably the way to go. So, to that end, essentially what, when I say this, really, honestly, the lion's share of the work was done by Dr. Lee. His co-author's, of which I'm one, helped, but it really was his work. We performed a set of format analysis, and we attempted to have them be very, very, transparent, and to collect what we felt was, you know, all the data that was out there, and then also to examine it in the most rigorous fashion possible to tell you how we really feel about this data, the evidence.

So, I think in terms of what we did and how we chose the studies that we did, if you're not really a statistics [inaudible], this is probably the slide that you want to pay the most attention to, because this is the one where if you don't agree with our beginning assumptions about what we looked at and what we didn't, this would be a great place to argue. So, if you like to argue and you're not a statistics guy, this is your slide. So, the first thing was, we only wanted to look at randomized control trials that went eight or more weeks. And, that was really because we didn't want to get into the business of attempting to sort through various shades of grey in terms of the studies. We were interested only really in the very best evidence and the very best studies.

And, we felt like we would start there, because anything you start to evaluate shades of grey, involves a lot of people putting their own personal opinions {inaudible]. We just didn't, we didn't want to go there. And, the second criteria that, sort of, reflects that is we were only interested in studies that required what is considered to be, in the field, the absolute gold standard outcome measures. So, we were interested in the caps, we were interested in the spring, we were interested in the PSSI. And, again for the same reason. There were a lot of great studies that had PCLM, a lot of great studies used, sort of, variables that researchers had, sort of, developed to look at PTSD. And, in no way, sort of, besmirching those, but we were only interested in what was felt to be the gold standard outcome measures.

So, again, here are the first few points. Gold standard studies, gold standard outcome measures, following to where you could maybe argue a little that one was, we were interested in looking at effect size. And, part of it is to look at one treatment against another, you need to talk about effect size, and then the other thing is because we're using more than one outcome variable, we needed something like effect size, uh oh, something's popped up, I apologize, because we were, because we were comparing more than one outcome variable, we needed to convert to the standard, sort of, unit of effect size to be able to compare one study versus another.

And, then finally we looked at studies grouped over time because we were interested in looking at trends, whether certain treatments were more effective up front, and certain treatments had more, sort of, lasting effects. Particularly because, and this into a little more of Dan and my experience of PTSD. PTSD is really

a chronic illness, and a lot of the treatments have their best data up front, so we were very interested in, not only what works, but what works over time. So, when we set out for these format analysis, we really were attempting to answer what we considered to be the bedrock questions about PTSD. One, are medications and psychotherapy equivalent, is there one that's better than the other? And then, among individual medications, which ones are the best ones? Which ones are the first line, and among psychotherapy, which ones are the best.

Again, really basic, fundamental questions about the treatment of PTSD. So, this is now taking you a little bit into the nuts and bolts of the meta-analysis, and this is an area where I really do feel like you probably are a little disadvantaged with me talking and not Dr. Lee, because he's really a world-class statistician and, you know, really has complete command of the data, and can probably answer some questions that are more sophisticated than I can. So, we searched the med-line, the M-base, and the Cochran Register Trials, and this was an attempt to capture eventually most of it, the US studies and basics really the International studies. And, then Cochran is not only the published data, but the unpublished data. It represents a good faith effort on our behalf to capture, really, all the data that everybody was looking at. And, that's published and unpublished.

Okay. And, then, you know, we used a combination of use and search terms, you know. And, after we pulled articles, we would then go through the bibliographies and look for any studies that we might have missed. So, what I would take away from that really is we did our best effort to capture every study that it was possible for us to locate that had reasonable evidence that it could be speaking about the treatment of PTSD. So, again, as I mentioned, we included published and unpublished data. We were only interested in gold standard studies, randomized control trials, gold standard outcomes, we required a placebo control, and for psychotherapy, we count as supported treatment, treatment is usual bio-feedback or relaxation, and it's all being the equivalent for the purpose. We didn't look at studies that compared one treatment versus another, which involved us discarding a fair number of studies of very, very, high quality and we'll get to that a little bit later when we talk about the conclusions.

And, then the other thing is, we defined a minimum of eight weeks of medication or eight psychotherapy sessions. This was really an attempt for us to compare apples to apples. So, there were some shorter medication trials, yes that needed to be disregarded. It just eight weeks seemed to be about the minimum, and again, I'm aware of ART therapy, which really we did look at the articles, because we pulled them, but it was really an attempt to be looking at, sort of, apples to apples to have it be a fair comparison in medications versus psychotherapy. And, we felt that if we included much smaller trials, it would be felt to be unfair. So, as I mentioned earlier, we required a diagnosis of PTSD, by DSM4 criteria, and that was because that was, sort of again, the current guidelines at the time that most of the studies were completed.

This next point is one that sometimes people care to argue with, so let me slow down a little bit when I'm explaining it. We did come across some trials that people were allowed to have comorbid conditions and be, studies were allowed to be of people who had comorbid conditions, and were included. And, that included the personality disorder, it included substance abuse, it included a lot of comorbid disorders and anxiety and things like that. That, you mean, if you threw out those studies, you essentially probably had no PTSD studies left whatsoever. The one thing that we did feel, studies that we felt we should exclude were ones that required you to have a second diagnosis, so that everybody was somebody who has a substance abuse problem in addition to PTSD or psychological problem in addition to PTSD. We felt like it was a little unclear exactly what those studies were looking at or what those studies were treating, so we made the decision to exclude those, but again, most of the studies that we looked at had very, very, high comorbid borderline personality, thought disorder, substance abuse. So, again I think it represents a reasonable representative sample of what your average clinician seeing patients like this, is gonna see in terms of walking into their office. And then again, as I've mentioned many times before, we required a gold standard outcome measure. So, for inclusion criteria, this slide is a little bit out of date, and a little bit

inaccurate. We did evaluate Benzodiazepines, we evaluated mood stabilizers, and we evaluated second-generation anti-psychotics.

Both as adjunct and mono-agent, and I will be discussing those. For the most part, I'd say the benzodiazepine data was really terrible. There was some mild evidence of overall harm, and nothing to support use of benzodiazepines in these patients. And, I'll be discussing some of the other data, a little bit later when I come to the conclusions. We looked at basically every anti-depressant we could name or come up with, and then also Paroxetine. And, it's mostly the results of those agents that I'm gonna be discussing with you when I get to the medication section. Then, we also did search, just for various psycho-therapies. We looked at CBT, we looked at cognitive processing, we looked at DBT, eye movement de-sensitization, prolonged exposure, and stress inoculation therapy. Again, we required that it be individualized, face to face, manualized treatments, and that again was for the sake of generalizability and also for the sake of, sort of, uniformity when we were looking at our treatment. Every now and then we came across a study where people were doing one of those therapies.

Well, we're doing something that's a really, kind of, unique, or different wrinkle, to the point where we had a little, sort of, expert guidance from some psychologists, and we felt like it really, considerably, differentiated from standard manualized treatment. We did exclude those studies. Again, for the purpose of generalizability. And, in the psycho-therapy studies, we certainly allowed for people to be on medications, as well. That was just, sort of, you know, there weren't enough studies that were completely clean, and also, I mean, those are the patients that are gonna be walking in to see clinicians, so we felt that was acceptable for the purpose of generalizability.

So, I'm gonna breeze through most of these, they're for people who are really interested in statistical analysis or the nuts and bolts of it, I'll take you through it, but for the most part, we did a lit. search in stage one, one author, who is Dr. Lee, wanna speak about him doing the lion's share of the data, took a look at all the studies and then it would be looked at by a second author, who would, to discuss just whether the paper met inclusion criteria We had very, very high, you know, regular reliability, we were asking pretty basic questions of studies done. So, in terms of statistical analysis, and this is probably important for me to get to the results. We looked at the CAPS, the SPRINT, the PSI, we measured them in terms of effect size, and then we converted them to effect size and then weighed the data equally when we were sorting it. This let us look at multiple different variables and, sort of, pool the data to perform an effective meta-analysis.

The conventions that you're gonna see below are standard in Research, below .5 is considered to be small, eight to .6 is moderate, over eight is considered to be large. That's gonna be referred to when we get to the conclusions, later. Then, we grouped people in terms of time, eight to twelve weeks is a, sort of, short-term period that was mostly by convention because most of the studies, sort of, ran eight to twelve weeks. It seemed to be when most people started to chop their data off, which sometimes can mean that, that's when they get their data started to go sour, the groups after that look a little gerrymandered, but really it was just that nobody had run a study between twelve and fifteen weeks, so most of the stays were, like fifteen to twenty-seven weeks, we pooled those and then we looked at thirty-four weeks, in terms of looking at long-term data. Most of the studies actually, just by convention, seemed to run eight, twelve, twenty-four, thirty-six weeks. So, the other things that we did in terms of trimming our data a little bit, and this is mostly referring to one specific study, is sometimes, some of the researchers had essentially looked at their data at multiple data points and published that data as independent papers. Not that there's anything wrong with that.

But, when we looked at that, we didn't feel that we should be weighing one particular group of patients, who had one particular intervention three times rather than once, so we just looked at the longest term study. We didn't exactly throw out the data, we just didn't give it triple-weighting. Okay. And then the other thing was that as part of our desire to look only at gold standard studies, some studies had they call the cross-over line, which means that they were originally controlled and then went to uncontrolled, and at that point, the minute the studies became uncontrolled, we stopped looking at the data. So, all the data

points that you're looking at, really are, you know, what we considered to be gold standard data. Okay. I've been giving you a great big build-up. Let me take you through what we actually found.

So, initially we had over sixty-thousand hits on our data search, and this is why you can hear me praise Dr. Lee's work many times. Dr. Lee is the man who basically sat and went through sixty-thousand hits. Out of those, after we went through review, we found two-hundred and eighty-five articles that, based upon retrieval, needed to be pulled and taken a look at. With our criteria that we were only looking at gold standard data, two-hundred and twenty-three articles didn't make the cut, resulting in sixty-three articles that met inclusion criteria. Like I mentioned before, there were some articles that were talking about one study or one population base, looked at multiple times. We trimmed those down such that each of those studies only got represented once, in terms of the data, and that left us with fifty-five articles. I would say, part of what I'm gonna talk to you folks about at the end, is probably what we need is more data. That we're ten years into, you know, the longest war in US history, and we got fifty-five gold standard articles looking at PTSD. It's a little unacceptable, but that's just my opinion and we'll get back to that later.

So, I don't want to sit here and read all the numbers to you, but total we had about six-thousand patients. The studies ran for about eighteen weeks. The other number that I would take you down to, I mean again, there's a fair number of veterans, there's a mix of civilian populations, and then if you look at the CAPS, you know, people, the average was like seventy-seven, the average patient was seventeen, and PSSI was thirty-one. These are relatively sick patients. I think these are the patients that tend to come in and tend to seek treatment. And, the other thing that I should have mentioned, one of the things that we're discovering, is oftentimes a lot of these folks, and this is another reason why people looking for guidance are, maybe kind of, sort of, "Well maybe these guys don't report these symptoms until they're out, and then, sort of, come into the community?" But, these are the kind of patients who are, have enough disability that they tend to present for behavioral health follow-up.

And, I think it's a good representative sample of the patient's that people are gonna be seeing. Okay, and again, as I mentioned before, we had a fair number of [inaudible]. This is a really terrible slide, and I can get away with saying that because I think I'm the guy who put it together at one point. I would not, by any means, attempt to pound this slide into your head, but what I would say is these are the studies that we found, that ended up being included in criteria and this is the specific agents, or the specific interventions that were used. I'm gonna blast through this really quickly. I can't imagine that [inaudible]. So, the first thing was we looked at the quality of the studies and what I would say, and this is most important when you get to our conclusions and how you want to weigh them, is for the most part, the psycho-therapy studies were just a lot better than the medication studies.

And, by that I mean, most of the medication studies were industry funded. There was a higher risk of bias in those. And, in general, just the psycho-therapy studies were higher quality. I don't think that explains, tipping my hand a little bit, why psycho-therapy did a lot better than medication, but I think it's a real effect. But, the only where our conclusions came from wasn't because the psycho-therapy people put their thumbs on the scale, they're probably real results. And, then this again is all the studies we looked at, mostly looking at, sort of, what the effect size was over time. This is a great slide if you're really interested in how we got to our conclusions to go back and take a look at, but I'm not gonna waste people's time banging through it. So, this is arranged a little bit differently than my deck is arranged, and I'm gonna stumble through it a little bit. I may fast forward to a later slide. So, this is really the study, this is the slide that really contains what we look at, and I'm gonna go back and click you through the text. So, what I would look at is, on your left as you sit here, are the results in what's called pre and post design. So, that's ones where people aren't completely blinded to their results. There isn't a really established control. On the right are the studies with control.

And, you're gonna notice green represents a large effect size in this study. White represents, sorry, green represents a large effect size, white represents either a moderate or small, I think it's mostly small effect size, and then red amounts to non-statistically significant results. And, I think what's important to realize is if you just are looking at the non-blended, instead of pre and post, because for the most part people get

better and that is attributable to placebo. People in these trials, regardless of the agencies they report on, tend to get better. The problem is a lot of that gets tied up in placebo effect and some other things. And, so really what pre and post is, it's the analysis with the placebo effect and the, kind of, benefit of a positive contact with a mental health provider, and all those things, sort of, left in there. And, if we didn't leave that in there, everybody looks great. We get a little bit more statistically rigorous, or you say you really want to drill down on what's making the difference, like what's the special sauce, and why the patients getting better? That's on the control side, okay? So, I'm gonna take you through these really, really, briefly, as I go back. But mostly what I want to talk to you about is the placebo effect.

Again, I apologize for anyone getting motion sick watching me work the deck and all. So, when you look against placebo, most of the medications didn't do very well, at all, okay? Most other times when we saw an effect size, they were small, okay? And, I think it's reasonable, when you're putting a patient on things, when I say small, you gotta remember the European Guidelines a small effect size means a negative study. So, and that is the standard that is sometimes used in the Pharma Industry.

So, when I say the effect size is small, that's really not good news, and if you're putting a patient on something, a medication that has some side effects, it's reasonable to be able to say that not only is this gonna work, but I think it's gonna work enough, I think it's gonna make a difference in terms of how you do and what's your life's like. So, I think being willing to look at smaller effect sizes with a little bit of a grain of salt, is not completely unreasonable. So, for the most part, in the short-term, the medications that came out on top were Venlafaxine and Paroxetine. Venlafaxine, if you went back and looked at the studies, in the eight to twelve-week period, had the highest effect size of any intervention. Talk therapy, medication, anything, okay? I'm sorry, I apologize, I think in brand names. I've been a psychiatrist long enough. Venlafaxine, which is Prozac, Venlafaxine, which is Paxil, [inaudible]. All had a small effect size. If you then, sort of, step back and you look at what works over time, the data continues to evolve.

So, at fifteen to twenty-four weeks, Paroxetine, and this is Paroxetine adjunct to [inaudible], it's a mono-agent pulled together, suddenly, kind of, comes forward and it has a large effect size in the immediate time frame. There wasn't long-term data on Paroxetine. But, in a medium effect, in a medium time frame there's a large effect size. Okay? In the, in the short-term period, it had a non-significant event. Venlafaxine, which I mentioned to you short-term was actually the most potent intervention, behavioral health, you know, talk therapy, medications, whatever. At fifteen to twenty-four weeks, it is starting to fade, It actually falls to be a small effect size. And, part of that was, we looked at the studies, a lot of the drug companies are chopping the studies off at twelve weeks, and so in general, and don't tell me that chopping their studies off at a certain point means they don't like the way the data's trending.

So, what it may be is, particularly with this particular medication, seems to peak early and then it fades, okay? And, then at thirty-four weeks, interestingly enough, Zoloft, Sertraline progressed to have a large effect size, so Zoloft seems to be the tortoise in the race. It starts off slow, it actually had a very small effect size at eight to twelve weeks, the smallest of any of the medications that I mentioned to you, but it seems to grow over time. And, there's a unique, when you look at Zoloft, you say, "Well, what's different about Zoloft?" It has a little [inaudible]. So, I actually think we're looking at a real effect here, although again, there were a limited number of long-term studies looking at Zoloft and so, with any of these, sort of, take them with a little grain of salt. But, to summarize it, [inaudible], again the fast-acting short-term real-big winners, and then Paroxetine in the immediate time frame, and long-term Zoloft does very well.

So, this is the pre and post. What did I tell you about pre and post again? If you're not accounting for placebo, everybody looks dynamite. Okay? And, then I just want to take you quickly to psycho-therapy versus a control. By way of comparison, psycho-therapy, particular trauma-focused therapies, have large effect sizes. Okay? Non-trauma focused therapy had a small to moderate effect sizes. If you look in terms of trends, prolonged exposure and cognitive processing did pretty darn well, short-term, medium-term, and long-term. The only ones that, sort of, seemed to not sustain their benefits were stress inoculation therapy, sort of, peaked and then faded. And then, interestingly enough EMDR, which did quite well short-term, really didn't seem to have the same life, again this is based upon a limited number of studies. And, I

want to talk to you a little bit about our limitations in terms of looking at some of the psycho-therapy studies, but what I would take away from it is all the trauma-focused therapies did pretty darn well, and by pretty darn well, I mean, a lot better than any but a small-hand-picked group of medications and, it all seemed to have legs. As opposed to the only med that had real legs that we could speak about from my results was Zoloft. If you're looking at the therapies, everybody except stress inoculation in the MDR, seemed to do pretty well and had pretty good legs. Okay?

Again, what I would say, this is something referring to pre and post. What I would take away from it is pre and post almost everybody looks good, okay? And again, this is really the slide if you want to go back here and you want to see how I got where I got, this is the best slide to look at, but if you're looking at it really quickly, green is what you want to be prescribing for your patients. Those are the things that have large effect sizes at that time period. And, the data that I just referred to is in the control group, which is the three columns to your right. Okay? So, we then get a bunch of sub-meta-analysis where we wanted to look, what we were doing here is we were, sort of, looking at various guidelines against each other attempting to determine which ones were most accurate. Again, if you look at pre and post, everybody looks great, okay?

Part of what I would say about this, because every time I present this data, usually it's the most grey-haired psychiatrist in the room, and I apologize to any grey-haired psychologist that's just listening to me out there, but it's usually the psychiatrist in the room with the most clinical experience who particularly had some questions about how we got where we got. Who wants to stand up and, sort of, discuss this, because I think that the large pre and post, what's important to realize about that, is that's what your patients reporting to you. That's what they look like in your office, because you don't have the ability to keep out the placebo effect, the effect of positive, like, transference of the therapist, and just, sort of, the passage of time. So, a lot of times people think, "I should be using this medication forever, I always have good results with it." That's what the pre and post tells you. But, the fact that you don't see it in the control group, means that you're not look at the pharmacologic effects of the medication, you're looking at something else.

Okay. And again, there are a couple of other, little, sort of, small points that I want to go over real quickly. I'm gonna flip back for a second. So, first is very often people will talk about adjunctive treatment, so not only am I gonna put you on an anti-depressant but I'm gonna add something like a second generation psychotic, or a mood stabilizer, or something like that. None of those medications really came through at all, except for Paroxetine, okay?

There's a little, tiny, effect size for [inaudible] on here, in the fourteen to twenty-seven week. All of the other anti-psychotics, all of the other mood stabilizers, had non-significant results. So, what I would say is, the only, there's only never, adding adjunctive medication, based upon our analysis, doesn't seem to be good support for that as an intervention. Okay, unless it's Paroxetine. And, then the other thing, when you're looking at which of the guidelines did well, it turned out that people who were, sort of, fussy, sort of splitters, in terms of exactly which medications they liked, as opposed to those medications they didn't like, and in terms of which therapies they liked as opposed to which therapies they didn't like, did a lot better. So, what I would say is, my take home from this is it pays to be fussy, and it pays to be particular.

Okay? So, again this is mostly what I already told you. Trauma-focused therapy is probably the big winner in our study. Large effect size, pretty much at every data point, and I would say, they did very well despite the fact that they were going up against a lot of drug company studies that had enormous numbers, in terms of the people, and despite the fact that there was probably less evidence of a potential for bias among the psycho-therapy results even compared to the psycho-pharm studies. So, even with those burdens, trauma-focused therapy outperformed the field. Okay? And that suggested to us that there are probably some advantages to use trauma-focused therapy over medications.

This is where I come to talk to you a little bit about the limitations of our study. When we pull all the articles, there were a lot of really wonderful studies, well-designed, well-0constructed, very rigoursly put

together, studies where the problem was they didn't look at a treatment versus placebo, they looked at one treatment versus another treatment considered to be effective. And, we had to disregard those studies because of the way we designed our meta-analysis, but they're still good studies. And, so based upon the number of really excellent studies that we had to, sort of, remove, I'm a little cautious about saying that we're the final work in terms of one treatment focused therapy over another. And, so even our results that showed this, stress inoculation and EMDR don't seem to sustain their results the way the other approaches do, I would take those with a little bit of a grain of salt. And again, these are things I already told you. Stress inoculation and EMDR did very well but seemed to lose their pop. For long exposure did very well at all time periods at a large effect size, seems to sustain its benefits. Kind of, due process in therapy was essentially equivalent and given our limitations in terms of the studies we had to throw out, I probably consider those to be equivalent to what I'd recommend for patients.

Terms and medication, Venlafaxine was, if you think hare and tortoise, it was the hare. Largest effect size of all medications at twelve weeks, actually the largest effect size of any intervention at twelve weeks, but then it seems to fade. This is a little bit of an older study, Sertraline and adjunctive Paroxetine passed the short-term period, past twelve weeks, seemed to do really well, had considerably better benefits than Venlafaxine. And again, Sertraline in particular did gain over time. Mirtazapine, which is also known as Nefazodone, which is currently not off the US market, you just can't get it anymore because there's a black box one against toxicity, so you can actually, it's still manufactured in Canada, and you can get it for patients if you're really stuck.

Did really strongly, the problem was they didn't have long-term data, it did really strongly short-term. They're still worried about hyper-toxicity which would make be very hesitant about recommending it as a first-line medication. I will say that if you really want to be particularly persnicity, the only study ever published in treatment refractory PTSD, did show positive results, it was with Mirtazapine. And, so what I would say to clinicians is if you're back is really, really, really, against the wall, the med is work thinking about. But, I certainly wouldn't recommend it unless you're a specialist, and unless you're really in a pickle. The other thing is Paxil or Paroxetine, which is the only medication that all, it says five here but it was recommended in all six of the guidelines that we looked at recommended it. It really did very poorly in our study. So, it had a little, tiny effect size, short-term and then it, sort of, pooped out going beyond that. And again, this is a point I'm gonna come back to, Given that PTSD, for the most part, is a chronic illness.

So, more than half of the patients end up having systems beyond the three months that these medications worked. If you do decide to go for medications for your patient, our study would seem to suggest that you probably want to be looking at medications that have good legs or that have more sustaining benefits, which leaves Zoloft and Paroxetine as opposed to those where they have, sort of, a diminishing effect, which would be the effects. So, translating this really quickly into clinical factors and then I'll get to questions, and I apologize for the way that I'm talking so much and I'm going through all these slides. I think there really are only a small number of medications that meet what I feel to be, sort of, Gold Standard or best evidence of treatment for PTSD. So, Paroxetine effects are, and then again, if you're really backed, really to a wall, Mirtazapine. Some of these medications don't know the full effect of them until you have somebody on a long trial. Zoloft is a slow-started, it took twelve weeks. It is less effective than five or six medications. There seems to be something about it, it grows over time, so when I'm looking at people's previous trials, if they were on Zoloft, they were only on it for a short-time trial. I asked them if they were willing to try it again.

Okay. And, so the other thing, how this has affected my practice, is because there's only a handful of medications that I think are the best medications, I usually start out with a very critical eye towards people's previous medications, so I don't, sometimes not as simple as others, Zoloft, I don't want to do that again. You might have taken it at a sub-therapeutic dose, you may have only taken it for a short time. Sometimes you need to go back and try a longer trial at a higher dose, even if it's a medication the patient isn't, has, you know, has been on a short or a flawed trial previously.

The other thing is increasingly I think that behavioral treatment is probably indispensable when you're treating PTSD. Prolonged exposure, if you have multiple options, multiple choices, and they're all equally good practitioners, probably there's a little evidence to say that it might be a little bit better, but again I'm gonna take that with a grain of salt. If you know somebody who's terrific and they do EDT, I would probably go with that over an unknown quantity, and unknown treater who uses prolonged exposure or something like that, or if as a practitioner you consider yourself to be very, very competent in Cognitive Processing therapy, I'd probably go with that with Prolonged Exposure. And, then the other thing I would mention is, it seems that even a short course of some of these exposure-based therapies, seems to have lasting benefits, even if the person isn't able to get in for subsequent treatments, so in a situation where you're geographically pinned, where you don't have a treater who can do these practices, there are a lot of really wonderful referral centers. There's a wonderful one in Colorado, there's a couple of wonderful ones in Florida. You can send a patient for a course of treatment and there's evidence that they can make gains and hang on to those gains even if they leave an intensive program. That's pretty much our presentation. And, really again, it's mostly Dr. Lee's work, you're dealing with a sad understudy. Any questions? All right.

Well, thank you very much, Dr. Wolf.

It's my pleasure. I have to tell you I'm very relieved to hear your voice because I didn't know that anybody was actually there or could hear me for the last hour.

We've paid close attention.

Thank you so much again. We've paid close attention. We have a number of questions for you. It is now time to answer the questions from the audience. If you have not already done so, please submit questions via the question pod located on the screen. We will respond to as many questions as time permits. There are no specific order of the questions. And, I'd like to ask the question, one question was asked, can you comment on the impact, and I'm using that work loosely, of the updated definition of PTSD in the DSM5 as to the treatment options, particularly with pharmacology issues?

Oh gosh. That's a question that I'm gonna finesse or decline to answer. Here's what I would say. When I read the DSM5 criteria, I think it broadened the tent a little bit in terms of the patients that were, that were included as having PTSD. And, I think the only reason why it's important to look at that, is I think in some ways the problem that may be, and this is just my opinion, limits PTSD evaluation is that I don't think always we're looking at a homogeneous population base. I think there may be some sub groups, so when the, and you know, part of my own research is precision medicine with some bio-markers or something like that to treatment. I think as we, sort of, broaden the tent a little bit, it's unclear exactly whether we're still treating the same population base. I'm not saying that anybody's trauma is more legitimate than anybody else's. I'm not saying that people aren't suffering. I'm just saying it's not clear to me that it's the same entity, and I think the data that we have right now just speaks slightly better to the DSM4 stuff, but I think it's a political landmine and I'm doing my best to stay away from it.

Sounds good. Let's keep you out of the landmine. And the next, the following question, the next question is, does the meta-analysis account for non-significant findings that are not published?

Well, I mean again, I can't say that there aren't some studies somewhere, shelved somewhere by drug companies that we couldn't get our hands on. But, we did do the best possible effort to get our hands on as many unpublished studies as possible. And, drug companies are required to report those. There were a couple that we tried to get our hands on and I'm trying to, I don't want to name the wrong drug company, because it was really Dr. Lee doing most of it, but we really worked hardest to get our hands on all the unpublished data that we could and I think that it represents as accurate a picture as we're gonna be able to get, in terms of accounting for non-significant findings. But, the other thing is I'm trying to remember the number of negative studies that it would have taken to invalidate our findings and it was a

few thousand, so I think we've functionally accounted for it and we've done our best to get as many studies as possible.

Good, another question was, any thoughts on [inaudible]? It was cited as having the most evidence for efficacy in PTSD in the 2013 Agency for Healthcare Research and Quality Report on PTSD.

Yeah, there are now a couple, little significant studies from Topamax, we did look at it. I'm not sure, there was, kind of, a line there for Topamax. I think the collective weight of the studies right now doesn't push into the area where I would recommend it, but I think it's an interesting medication going forward. So, it's probably the mood stabilizer that I think right now has the best evidence, but I don't think, and again I'm familiar with the study you were citing, I can't remember exactly where it was published, but there was one that showed reasonably low bias numbers, but it was a small study. I think a couple more positive ones came out and the weight of the data moved that direction, I wouldn't have a problem using the [inaudible], but I just don't think we're there right now.

All right, another question is asking, what are your thoughts regarding newer anti-depressant and anti-psychotics? Specifically, they're particularly interested in those with off of one and half of two C blockage.

I think, I think when you look at medications in general, there's a philosophical divide, in terms of the psycho-pharmacologist you're talking to. And, I apologize for this sounds unbelievably pretentious, obnoxious, but I think they're people who look at things and think that theoretically they should be great and go ahead with those, and they're people who are a little, a little more focused on what's been proven to work. I'm a little bit more of a prove-it-to-me-person, because I think, I think our field is full of incredibly brilliant ideas that really should have worked on paper but that just don't seem to work in the real world. So, I don't use a lot of newer anti-depressants or anti-psychotics because there haven't been enough good studies supporting them yet. And, then if that happens, I'm happy to jump on the bandwagon. I think when I sit with a patient, I like to be able to tell them, "I know this is gonna work." not I think this is gonna work. But, you know, everybody has a slightly different style.

Understood, no problem. Excuse me. Another question was, do you recall how many Paroxetine trials were included in the meta-analysis? And, second were those trials looking at Paroxetine as a treatment for PTSD rather than sleep or nightmares?

Yeah, no I mean part of it is, if you look at the outcome variables that we were looking at, ones that were just looking at sleep or nightmares, probably wouldn't have made it because, I mean again, most of the people had really high CAPS and SPRINTS. These are people with significant PTSD trouble. I'm trying to remember how many. We looked at a lot of Paroxetine studies. I think the number that went forward was about four or five, which given that we only found fifty-five really good studies, is a pretty high number. Certainly Murray Rafkin's work was very heavily reflected. I'm trying to remember how many trials he had, and these are different trials looking at Paroxetine. I would say, I mean the other thing I mentioned about Paroxetine is there's maybe, I think it clearly had stronger evidence as an adjunct as opposed to being a mono-therapy agent right now, but again I think we looked at about five, but I'd need to look that up. I don't know that off the top of my head.

All right, no problem. Another question. Any particular reason how come mindfulness therapies were excluded from your analysis?

Any reason that mindfulness studies were excluded from our analysis. You mean like DBT?

That would be good to start with.

We collected studies on DBT, I can't remember how it did off the top of my head. We, I don't know what to tell you. That would be a slightly better question for Dr. Lee. I do know that we looked at DBT treatments, for some reason the closed captioning is putting it down as DBT, but we looked at DBT treatments. I don't

think, for the most part, they're data did as well as exposure-based therapies. And again, from my own personal experience, I found them to be useful, but that's not exactly where I'm going.

That's fine. Another question was, speaking to sub-groups, how do you see these results being impacted or qualified in those with chronic pain and PTSD.

I think chronic pain, like a co-existing mood disorder is another point that I should have made, I think chronic pain led to co-existing mood disorder, like a co-existing substance disorder, makes PTSD more difficult to treat. I didn't see any particular trends that chronic pain made one medication work better than another, in general. There's certainly in some of the medications that we looked at that have an indication for pain, like the TCA's, like Cymbalta, which did not do very well. Effects are, it doesn't have an FDA indication but it has a large number of positive studies looking at it for pain. I can't speak to it directly. In my own clinical practice, sometimes I do move for its effects when a patient has chronic pain, because it's usually working in conjunction with the pain folks that we work with.

Sorry, I just disconnected you. I pushed nine.

Oh whoops.

Are you still there?

I am.

Oh Okay. Because I couldn't hear you. Can you hear me?

Yup.

Pushed the wrong number, seven instead of-- All right, so next question. Can you discuss a little bit, talk about your findings and the relationship between CPT and EMDR? What have you found in relation to meta-analysis? That is as a choice of treatment.

Oh Okay. I would say, and again, I can see the chat when I'm looking at them and answering the questions, and a couple, one of the slides, I would say CPT did very, very, well in our study. You know, across all time periods. It had a moderate effect short-term and then had a larger effect size medium and long-term.

EMDR did quite well up front, but then it seemed to have a little bit of diminishing, and the reason for that question.

Yes, EMDR, for whatever reason, the effect size was large in the short-term, then it seemed to be down-trending into the middle phase. I don't personally, I don't personally think our results would incline me to stop an existing treatment that's working to switch to another modality. All things being equal, I have a slight bias towards CPT over EMDR but I don't want to claim to be an expert in that area.

Okay, another question was, what are your thoughts as to how come there's not as many psycho-therapy models as placebo studies?

Can you clarify that question a tiny bit?

Well, let me read it again, maybe it will make sense. Sorry, I did not write the question. Why do you think there are not any, there are not as many psycho-therapy models versus placebo studies.

I'm gonna maybe define the question I think is being asked.

Sure.

Then I get to answer a slightly different question probably. My, I guess what people are asking is, why were there more studies looking at medications that we were talking about than looking at psycho-

therapy? I think the answer for me would be I think there is more money from the drug companies coming in and driving research, and so I think they're paying for those studies and they're looking at those studies. Again, we organized studies, we just looked at what was out there. In general the psycho-therapy studies, there were fewer of them, they had fewer patients in them, but they were better designed, more tightly controlled studies. Again, I think what it comes down to is I think there's a fair amount more money to be made in pharma than there is in psycho-therapy, and I think that probably influenced the number of studies being produced, but again, we just reviewed studies, we didn't actually fund them or start them, or anything like that.

Sure, okay. Another question, moving right along so to say, was TBI a comorbidity that was considered in this study? And perhaps we can get you to expand a little bit more, can you elaborate some more on other comorbid conditions as well?

Yeah, sure. In terms of TBI, I think certain studies looked at it, and certain studies didn't. I would say I currently work, I'm really a TBI, a psycho-pharmacologist and a TBI doctor is what I really do and I work at, the center that I work at everybody coming there has to have a history of TBI and some sort of psychological condition, so there are a lot of the patients that I see.

So, certainly something that I was interested in. If a study was a hundred percent comorbid TBI with PTSD, we probably would have excluded it the same way if a study had a hundred percent character disorder with TBI or a hundred percent mood disorder, or a hundred percent anything, as a requirement of the study, we probably would have excluded it. I didn't see a lot that had a large number of TBI patients in it, and I think that part of that is TBI is becoming something that's increasingly recognized, as a condition that we should be treating, and a lot of the studies that we were looking at were significantly older. So, if you look at how far back our lit search went, people weren't publishing a lot of things on TBI in, like, 2004. So, that may be some data that's coming forward. I would say, in general, as a psycho-pharmacologist with mild TBI, I don't vary from, I don't think mild TBI would make an experienced clinician deviate significantly from the algorithm with any of his medications.

Okay. Here's another standard question from another psychologist in military service. He's asking, were there limits--

I'm sorry.

In MTF, the Military Treatment Facility, where there is a limited access to psychiatry, do you have any advice for presenting, processing to our PCM, our Primary Care Managers as a viable treatment option for PTSD?

In terms of medication?

Yes sir.

Oh Okay. I think first of all, one thing that came at me, if you look at the International Guidelines, just behavioral therapy is a perfectly reasonable way to go, as for this kind of therapy. Completely, like I don't think that you're not, I don't think your care is inappropriate if you choose to put off starting the medication. What I take away would be among medications, I'm very, very picky. So, I like Zoloft, I like Venlafaxine, and I like Paroxetine, ninety-five percent of the time. And, that would be what I would put forward to a PCM that was working with me, is could we try Zoloft or Venlafaxine, or Paroxetine. And, those are medications that most primary care doctors are quite comfortable with. The Paroxetine one is the one that sometimes we would have a little stumbling block with, and there's a very excellent article, it's Raskin's article from, like 2012 I think which has the dosing regimen I use most of the time. Get them a copy of that article, because brains, the dosing can be a little tricky and more and more I think a primary care doc might have some stumbles.

Okay, last question. Is there any research regarding using a psycho-pharmalogical with pain disease?

What?

CNS effector, for example, in patients with PTSD plus pain symptoms?

Hold on, just peeking at the question. I want to make sure I had it right.

All right, the question is--

I mean, here's what I'd say. "I don't recall looking at that article". I would say, before I started doing this work, as I mentioned in terms of the methods, Dan pulled all articles and read them all, and then his co-workers, and I'm one of four people who was on this study with him. We looked individually at treatments that, for the most part, had interested them. And I was not super-interested in Venlafaxine, which would probably be the one that I'd be most interested in to answer the particular question you're asking. And, I wasn't interested in Cymbalta, which is the other one that would be interesting. So, it's possible that somebody has done that study and it just, sort of, slipped under my radar, but I haven't actually seen it. And, again, if there is a hundred percent comorbid study, it would have been excluded from our meta-analysis.

Oops.

Okay. Very well. Thank you very much, Dr. Wolf. This presentation will be archived in the webinar section of the DCoE website.

Okay.

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