# Multi-Jurisdictional Contractor Advisory Committee (CAC): Evidentiary Discussion Regarding Transcranial Magnetic Stimulation (TMS) for the Treatment of Obsessive-Compulsive Disorder (OCD)

**Date: Wednesday, September 29, 2021**

**Time of Meeting: 2:00 PM CT (3:00 PM ET)**

**Richard Staley:**

Welcome everyone to the multi-jurisdictional CAC. This is Richard Staley and I'm the policy administrative assistant for WPS. I will now turn the meeting over to Dr Barry Whites who will be presenting the meeting event.

**Dr. Leslie Stevens:**

Dr. Whites, are you speaking? This is Dr Stevens I can't hear you through the video conference.

**[Unknown Voice]**

I also cannot hear.

**Morgan Covarrubias:**

Dr. Whites, this is Morgan. When Rich moved you into the live session, I believe it muted your computer as well and only you can unmute that. I know you were using your phone previously, but you'll have to make sure your computer and your phone are both unmuted.

**Dr. Barry Whites:**

Now, um, can you hear me now?

**Morgan Covarrubias:**

Yes, we can hear me now, Dr. Whites.

**Dr. Barry Whites:**

Yeah. Okay. Sorry I will start all over.

The introduction, I just want to give a brief introduction and some opening comments if I could. My name is Barry Whites and I'm the host CMD of this evidentiary carrier advisory committee meeting. I'm one of the contracted medical directors for WPS, an A/B Medicare Administrative Contractor. This CAC, however, involves multiple MACs who have all been involved in the process.

One of the aims of this meeting is to have subject matter experts review publications that are considered acceptable that have been sent to us by the entity requesting a reconsideration in an attempt to/or are requesting that we expand the current coverage of our LCD to include obsessive-compulsive disorder treatment by transcranial, magnetic stimulation.

According to the Internet, only manual, MACs shall use the available evidence of general acceptance by the medical community, such as published original research and peer review medical journals, Systematic reviews, meta-analysis, evidence, based consensus and clinical guidelines, abstracts and poster presentations. Yes. Poster presentations, although they have been submitted are given variable consideration due to the limited information available on such presentations to make a judgment on the quality of the evidence, and therefore to establish a strength of recommendation on this type of information of which we've been charged by Medicare to do.

We, as MACs have been very fortunate to have 7 subject matter experts who volunteered their time and expertise in this field to assist us in the evaluation of information provided by the requester.

Now, we shall proceed to the formal presentation next slide.

MAC contractor medical directors that are part of this work group include Dr Dick Whitten from Noridian. Dr Leslie Stevens from Novitas, Meredith. Loveless of CGS. Dr Stephen Boren of National Government Services, Dr. Jessica Van, CGS and Dr. Carolyn Cunningham from NGS. next slide.

Our Meeting agenda will be to welcome (which we've had) overview of the CAC process that recently, well, recently in 2019 changed, introduction of our CAC panelists, introduction to be discussed, the format for discussion of material from our requestors and a discussion to the questions and what the actual polling questions are, and a final discussion and questions from both the CMDs and the SMEs.

Next slide, please. Yet, all lines are currently muted, except for the CAC panelists and our host contractor, other than listening mode only. The meeting is being recorded for website posting on each of the respective websites per CMS requirements and the transcript, and the recordings will be posted on all the MACs websites that are participants in this work group.

Next slide.

If you are a member on the panel, please be sure your lines are on mute when you're not speaking. For all the subject matter, experts please indicate any Conflict of interest for the meeting record on your 1st time to speak. It does not have to be on the on every time that you speak. CMDs, if you would please announce not only your name, but your respective MACs, would be very helpful. Again every time that you speak, please announce your name, because it is being recorded and transcribed. Next slide please.

The evidentiary CAC is something fairly new. It became effective in January 2019, with the change in the manual. The purpose of this CAC meeting is to discuss evidence, literature of the topic presented by, and requested by, a reconsideration of an existing LCD. In previous times, we could just go ahead, look at the information, make a decision and post it – yes or no. But now, reconsiderations must go through the same process as an LCD. Meetings are not held to discuss the current LCD, but the literature presented for reconsideration of coverage of obsessive-compulsive disorder about transcranial magnetic stimulation.

CAC members role is advisory in nature. Comments, opinions on the evidence and literature to assist us in determining if a proposed indication for an existing LCD should be developed: either full coverage, partial coverage, or non-coverage. The subject matter experts do supplement our internal expertise and our contractors, internal expertise and serve to ensure unbiased contemporary state of the art technology and in particular transparency. Next slide, please.

Our subject matter experts overwhelmed me with their CMEs, uh, not their CMEs but their CVs and their CMEs; but their CVs they had average of 38 pages. They had 128, average, peer review publications and have published in either 33 books or chapters of books. Next slide please

By way of introduction I will briefly go over each of our panelists, so I think you'll get an appreciation of the caliber of individuals that we have. 1st Dr Wayne Goodman, Baylor College of medicine DC and Irene Ellwood Chair in psychiatry and behavioral sciences, professor and chairman of the Department of psychiatry, Co-founded the international obsessive-compulsive disease foundation. He did a fellowship and residency at Yale with his MD from Boston University, and that was preceded by a BS in Columbia in electrical engineering. He's a fellow of the American college of neuropsychopharmacology, distinguished lifetime fellow of the American Psychiatric Association and one of the codevelopers of the standard scale that, if you've done any reading in this subject, of the Yale-Brown obsessive-compulsive scale.

James Ellison (next slide), Swank Memory care center - the endowed chair in memory and Geriatrics in Wilmington, Delaware. He has his medical degree for University of California, San Francisco, psychiatry at mass general hospital; Here, I gave him a PhD and it should be a Master's from Harvard School of public health; He developed the New England Medical Center Emergency Psychiatric Service; He's Professor of Psychiatry and Human Behavior at Thomas Jefferson University; He's editor in chief of the Journal of Psychiatry and Neurology of the - Geriatric Psychiatry and Neurology; Massachusetts Psychiatric Society Advance of the Profession Award; Prolific writer, speaker, educator, and above all a clinician. Next Slide.

Dr. Linda Carpenter: Butler Hospital Providence, Rhode Island; is professor of psychiatry and human behavior Brown University. She's chief of the mood disorder program; Director of the Butler hospital transcranial magnetic stimulation clinics since 2006. she's an extensive lecturer, publication, accomplished educator and a fellow also at the American College of neuropsychopharmacology. Next Slide.

Dr Andrew Winokur, MD, PhD, distinguished chair of psychiatry University of Connecticut health center; did his undergraduate at Yale from Tufts; University of Pennsylvania, the Department of pharmacology where he got his PhD; And he did his residency in psychiatry at the University of Pennsylvania. He served at both Dartmouth, the University of Pennsylvania as professor of psychiatry and pharmacology; He's had numerous peer-review awards from numerous peer

review publications and teaching awards; He again is an educator, a lecturer, very active on many national committees, and a prolific writer.  Next slide please.

Dr. Rachel Davis an associate professor of the Department of psychiatry, University of Denver, Colorado Anschutz medical center; education was University of Colorado undergrad, did medical school internship and residence where she was chief resident members of AOA, Dean Scholar List, and Phi Beta Kappa. She's a medical director of the obsessive-compulsive disorder and neuromodulation programs in school of medicine, there at the University of Denver, Colorado, Denver; Interim vice chair of clinical affairs. She's received excellence in teachers awards, has numerous publications; She's past president of the Colorado psychiatric society and current chair of the ethics committee. She has a distinguish fellow of the American Psychiatric society and a BrainsWay advisory board member.  Next slide,

G. Randolph "Randy" Schrodt is managing partner of integrative psychiatry in Louisville, is educated with the BA, with honors in philosophy; medical school internship and residency at the University of Louisville school of medicine; Is a diplomat and the American Board of medical examiners; diplomat of American Board of psychology neurology; numerous articles, book chapters and presentations; He's associate professor and the Department of psychiatry and behavioral sciences at the University of Louisville school of medicine.  Next slide please.

Dr. Debra Barnett, Birmingham Southern undergraduate: University of South Alabama medical college; University of South Florida residency in psychiatry and behavioral medicine.  She's a diplomat of the National Board of medical examiners in the American Board of psychiatry; She's board in geriatrics, addiction and forensic psychiatry; a Distinguished fellow of the American Psychiatric Association.  Next slide.

These distinguished panel members are going to be discussing approximately 10 different articles, or 10 different items - They are not all articles, and it is for this reason that we did present a couple of these where you could see that -It really - the amount of information that is needed to make decisions, a lot of the time, is not present in posters, letters to the editor, or in abstracts.

Is Dr. Goodman able to join us yet?

**Dr. Wayne Goodman:**

I'm here.

**Dr. Barry Whites:**

Great.  Appreciate it sir.  I have you down as the 1st presenter on the - just to give us a brief summary of the 2 articles about 2 of the 3 articles by Tender that were sent to you for your comment.  If you would not mind, just giving us a brief overview of those 2 articles. I would certainly appreciate it.

**Dr. Wayne Goodman:**

Sure. Let me just get myself organized here.

So, both of these articles appeared in, uh, “Brain Stimulation.” One is on the Rate of seizures from the H-coil during the period of 2010 to 2020. So let me - that was pretty straightforward. They looked at the period from, Like I said, 2010 to October 2020. They identified 55 seizures, of which 14, as they put it, occurred when the instructions for use were followed. And that includes weekly Re-examination of motor threshold, ensuring questioning the patient about substance use, whether they had a good night's sleep, and the number of patients treated during that period was close to 100,000 -let's go with 100,000. They found an overall seizure frequency of 0.00058. That was for all accounts - and let me put that in terms that people can remember: So, for. Overall seizure frequency of 6 per 10,000 patients; And when they made this adjustment for following instructions (I'm not quite sure how they did that, but let's assume they did that right) It was only 2 per 10,000 reported seizures. And in all cases in this report when the seizures occurred, they were time limited, no pharmacological interventions were required, And no injuries were sustained. None of the seizures occurred in the 1st day of treatment. And they say that the potential causes for seizures included: Not re-checking the motor threshold once a week, Medication changes (Yeah, I forgot - may have forgotten to mention that) since the last motor threshold was checked, substance use in the 24 hours before, and poor sleep the night before. I mean, my sense of that, that's a low and very acceptable safety record for seizures.

I want, I don't know what format you want me to go on to the other article, or invite comments or discussion from the other experts at this point?

**Dr. Barry Whites:**

Yeah, I would like to hear if there are any comments from our CMDs first. If none, then we'll go to the other subject matter experts.

Any from the CMDs about this article?

**Dr. Linda Carpenter:**

I would just say that this speaks to when you're using large coils like this, where there is a well-known –

**Dr. Barry Whites:**

Again, excuse me, excuse me, would you please say your name and -?

**Dr. Linda Carpenter:**

Oh, okay. Yeah. This is a Dr. Linda Carpenter and, if you want me to say my conflicts now, I will, or I can say when I'm talking about the article, I guess the only thing I wanted to bring to

your discussion here was that the instructions for use when you're using a large coil like this include this weekly motor threshold, a redetermination procedure, which is currently not covered by any of the LCDs for treatment of depression. So, just have that in the, in the hopper when thinking about how a coverage policy, what some of the stipulations might include, that's all.

**Dr. Barry Whites:**

Thank you so much. Any other comments from subject matter experts or the CMDs?

Dr. Goodman, I did not get your conflict of interest if you could do that?

**Dr. Wayne Goodman:**

Yeah. Happy to. Uh, so I was -I did participate as an investigator in the multi-center trial that will be presented later. This was while I was at Mount Sinai Hospital icon school of medicine. So, I received the research support from them. The only other Conflict of interest or disclosure would be that we do have a TMS program here, and not too long ago acquired a brain sway device which we are using for clinical purposes and plan to use for research.

**Dr. Barry Whites:**

Thank you, sir if you'd like to proceed with - any other questions on this article? Comments?

Okay, so go ahead and proceed with the second one if you wouldn't mind.

**Dr. Wayne Goodman:**

Okay.

The 2nd one is entitled “Deep Repetitive TMS with the H7 Coil is Sufficient to Treat Co-Morbid Major Depressive Disorder and Obsessive-Compulsive Disorder.” They first start off with pointing out, which in, which is true that depression is often co-morbid with OCD, it's probably one of the most common Co-morbidities. They looked at their multi-center trial, which we’ll be hearing about, I guess, shortly, to see whether they can glean from that what the effect - what the benefit or effects were of TMS on co-morbid depression and they, I forget what the sample size was, but it was a very small sample that seemed to meet criteria for depression. I think they identified - I'm trying to look for the number an n of 10, or so, I don’t know why it was so small, but it was and then they, they said that there was a decrease in the Hamilton depression scores in that trial compared to baseline, but there were no significant, no statistically significant differences between the 2 groups: the active TMS and the sham TMS, with respect to improvement in depression as measured by the Hamilton depression rating scale.

So, then what they went on to do is say, can we learn more about that by looking at some post marketing surveillance studies. And here they report, and that’s a, in this publication on 59 OCD patients who were treated in a open label, clinical fashion. They were all individuals had at least moderate major depression at baseline. Uh, and they looked at several time points after

- during the course of treatment, and after 30 sessions YBOCS scores decreased by an average of 30% in this cohort, And MDD scores, major depressive scores, decreased by 38%. And they conclude that that demonstrate benefit of TMS for both OCD and depression. A point out that generally speaking, when we look at response rates and depression, generally look at a 50% or greater decrease or reduction in Hamilton depression scores. I'm trying to see whether they - I think, at some point in this paper, I'm having a hard time putting my finger on it - They, it may be in one of the figures; they also look at what percentage of patients show to 50% a greater reduction in depression as well. But I'll try to see if I can locate that and add that in.

So, what I would say about this study is it's got some limitations. I mean, this is not a sham control study. This is open label, so subject to various biases. And it still is a small sample size of 59 patients. They go on to point out that the improvement could be just an indirect, the improvement in depression, could be just an indirect benefit of improvement in OCD, which, actually, I think, is the most likely case. But they go on to hypothesize that it could also be that a direct effect on depression as well. So and there really isn't data to make the case one way or the other. But it wouldn't surprise me at all. I mean, based on my experience with a variety of different modalities of treatment. That, if you have patients that present with a primary diagnosis of OCD, and they also have secondary diagnosis of co-morbid depression that if you treat OCD the effectively, depression generally also improves to some degree. So, I, I'll turn that over for to others for, for comments.

**Dr. Barry Whites:**

This is Barry. Question on, uh, this, this study. In general, is "Brain Stimulation" a peer reviewed publication?

**Dr. Wayne Goodman:**

Yeah, it's quite good. Yeah, I think I said it's a high impact factor.

**Dr. Barry Whites**

And as we look at this, we see on both of visit Dr. Tendler serves the chief medical officer and financial interest in BrainsWay as well as commercial research center, and that others also have financial interest in the company. How does that rate? How do you rate that as far as increasing or decreasing the - your consideration for the evidence? Do you decrease? Or does it make any difference to you?

**Dr. Wayne Goodman:**

In this case, it doesn't make any difference to me. I think it would have been a better strategy to include others who are not associated with the, the company as authors, but it doesn't lead me to question the integrity of the of the data as presented. Again, my, my concerns are more

about how the, you know, the data was ascertained and the sample size. But I don't in any way question the validity of the data as presented.

And I did find the graph, so that there is a graph it's the 2nd, part of the, the figure, uh, they, they have one panel - a top panel where they showed the change in YBOCS and the other one where they showed the change in depression scores and full response, which is defined as a 50% increase is also shown. But, so, I'd have to add up the number of bars to tell you how many that was, but you can see it If you have a copy of the paper, It shows it in green.

**Dr. Barry Whites:**

Yes, sir, got it Thank you. Any other comments from subject matter experts or our CMDs?.

**Dr. Linda Carpenter:**

This is Dr Carpenter again, I just wanted to point out that. Um, one of the reasons - one of the things that's very interesting about this particular study in this paper is, and maybe you all already know this, is that the coil that's been FDA approved and shown by this company to treat depression targets the stimulation to a different area of the brain than the one for OCD. So, this was able to demonstrate that, uh, from this kind of naturalistic database, that it would hit the same - enough at the same - targets in the brain. This was just pointed out to be able to treat both sets of symptoms: depressive symptoms and OCD symptoms.

**Dr. Barry Whites:**

Thank you. Any other comments?

Okay, next we will go with Dr. Ellison. Yes, two to present: one from Carmi and the other one from Tendler.

**Dr. James Ellison:**

So, I believe I'm un-muted now, this is Dr James Ellison. And -

**Dr. Barry Whites:**

Yes, sir, you are Un-muted.

**Dr. James Ellison:**

Am I unmuted?

**Dr. Barry Whites:**

You're fine.

You're un-muted, you sound fine.

**Dr. James Ellison:**

Okay, great. So, I have no conflicts of interest. It's Dr. James Ellison. I am a clinician: a geriatric psychiatrist. I certainly refer people for TMS, and I have treated a number with pharmacotherapy and psychotherapy, but I am not involved with the TMS service, although we have one at our hospital. And I was asked to look in depth at two articles by Dr Carmi and colleagues, and it's already been mentioned that they have connections with BrainsWay and with the H7 coil.

The first paper was in "Brain Stimulation," and it was published in 2017. And it's a preliminary study that asks a question about whether deep transcranial magnetic stimulation done with high frequency or versus low frequency has benefits for the treatment of OCD. It's motivated, because the World Health Organization considers OCD one of the most disabling disorders. And although CBT psychotherapy and SRI pharmacotherapy are first line treatment in many systems, there are a number of patients who are treatment resistant, so, the value of TMS is worth exploring.

There's observed hyper activation of the cortico-striato-thalamo-cortical circuit in OCD, and transcranial magnetic stimulation targets can be designed to target this area: the medial prefrontal cortex and anterior cingulate cortex. In this study, there were 41 patients who met criteria for OCD and had failed 2 or more trials of serotonin reuptake inhibitors plus, or CBT. They were from age 18 into the sixties diagnosed, according to DSM-IV, had YBOCS scores of 20 or greater, and some of them were on stable medications or psychotherapy when they went into the study. They were not depressed at the time of this study. So, during the course of the study - which was well designed and randomized, Controlled – it, the patients were followed for 5 weeks with treatments 4 times a week and measured from pre to post looking for an outcome of 30% or more reduction in symptoms, with a CGI less than or equal to two - a clinical global impression. And what was found was that the groups at baseline were comparable, the adverse effects were minimal. Side effects in 3 of the high frequency patients were (inaudible) fatigue and one in the sham group.

Now, the interesting - one interesting - aspect of this study was that after interim analysis, the low frequency group was found not to be responding, and that arm of the study was stopped. And the high frequency was continued. Which is why you'll see in the subsequent study they did, they just used high frequency stimulation. The results of the study were positive. There was a significant change in the YBOCS score. 30% reduction was achieved by 43.75% versus 7.14%. and the difference was seen as early as one week. After one month the numbers of improvement were 55.55% versus 33.33%. So, this was a well-designed positive study, showing that the H Coil at a high frequency was better than sham treatment and seemingly better than low frequency therapy as well,

would you like me to move on to the 2019 study or other comments first, about this study?

**Dr. Barry Whites:**

Let's see if there are any comments from on this study, by any of our experts, or our CMDs.

**Dr. Denise Nachodsky**

Good afternoon, This is Dr. Nachodsky with CMD – I mean with WPS - I'm sorry I'm a CMD. A couple of questions. First of all, one of my questions is the short duration for follow up of this study. As I think you stated, Dr. Ellison, was 5 weeks, to see if it was - my question is, is 5 weeks for a follow up a sufficient amount of time? That seems relatively short.

Number two is, you said with the low frequency, you know, the one study had low frequency and then, and the high frequency, the low frequency arm was discontinued and then it was just the high frequency. What would be the more associated side effects or morbidities that might be associated when you have a high frequency? And then, in your clinical practice or your experience, or any of the panelists, how long should follow up be? What are some of the other morbidities we should be watching for to see if this is successful therapy?

**Dr. James Ellison:**

Well, thank you for those questions. Let me address first (inaudible) follow up time. And I think I must have miscommunicated with you.

The study itself treated four times per week for five weeks. And then after that 5 weeks, there was a follow up one month later. I certainly am in agreement that one month is a very short period of time. OCD is a disorder that lasts for decades, and longer term follow up is certainly something that would help assess the value of any treatment for OCD.

Next, let me address your question about the side effects of high frequency treatment, which are the side effects I mentioned: Headache and fatigue in the 3 individuals who were treated with high frequency deep TMS. As to the, uh, other question, how long follow up should be maybe the other experts who have a lot of experience with TMS may be able to (inaudible).

**Dr. Barry Whites:**

Thank you sir, any other questions?

If not would you please proceed with the next article?

**Dr. James Ellison:**

Yes, of course.

The next article, also by Carmi, and a similar group of overlapping colleagues was published in the “American Journal of Psychiatry,” which is a very reputable journal, in 2019. And it’s entitled

“Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial.” So, what the authors did here was expand upon their earlier work with multi center, double blind sham, controlled study of high frequency, deep transcranial, magnetic stimulation, done at 11 centers with 99 patients on high frequency for a longer period of time - six weeks, rather than five weeks - but still followed up only one month after cessation of treatment. Their outcome measures were similar to the earlier study. 89% of the treatment group versus 96% of the sham treatment group completed the study. The reduction in the YBOCS score was greater among the active treatment subjects - 6 points versus 3.3 points - with a difference in response rates of 38.1% versus 11.1%. After one month, the follow up at one month also showed a significant difference of 45.2% versus 17.8%. The authors support their idea that TMS – deep TMS - would be effective for individuals resistant to pharmacologic and psychological treatments. The subjects who were enrolled were significantly ill, with a YBOCS 20 or more, and resistant. They had all been through at least one past serotonin reuptake trial - Serotonin reuptake inhibitors - and in maintenance CBT or on the maintenance serotonin reuptake inhibitors for two months or more. And they were excluded for another axis-1 disorder; seizure risk, neurological impairment and randomly divided 1-to-1 treatment versus sham. And, as you've heard the H coil penetrates deeper and reaches areas of the brain that are not reached by the standard coil. So, they target the medial prefrontal cortex and anterior cingulate cortex. And then, the duration of six weeks was chosen, because in the pilot study, the response had not plateaued after five weeks of treatment. So, in the results, as I mentioned, the YBOCS decreased significantly in both groups, but more in the treatment group. The - at one month - there was a numerical difference in the a treatment groups on the CGI, and adverse events were 37.5% headaches in the treatment group, but 35.3% in the sham treatment group. So that's not a significant difference. Headaches are very common. And the drop out was similar for both groups. So, that summarizes this second study, and the result is, we have a pilot study, a preliminary study, and a larger study, both supporting the use in treatment, resistant patients of this H7 Coil.

**Dr. Barry Whites:**

One question I gather in looking at this information that we have, everything seems so far, it seems to be a short follow up 4 to 6 week’s time interval. And they were done in 2018 is when this study is listed as being published. And I just question now, three, at least two years later, are you aware of follow up studies that have shown this persistent improvement of any duration longer than this?

**Dr. James Ellison**

I am not.

**Dr. Barry Whites:**

Any other questions from our subject matter experts are our medical directors.

**Dr. Linda Carpenter:**

I didn't have a - this is Dr. Carpenter again. I don't have a question, but I'd be happy to take a stab at the questions about long term follow up. So, one of the issues here is that a few things: that patient's stay in other therapies when they finish this treatment. So, when they finished their course of TMS, they continue on medications and they continue in psychotherapy, similar to how it's delivered for depression. And what we've learned from over a decade of doing TMS with depression is that, after you finish the course of treatment, follow people out for about a year. About a third of them are going to slip and need some maintenance treatment or some booster treatment or have some relapse. And the other two-thirds generally remain okay. And because there isn't coverage right now for people to get maintenance treatment with TMS, the standard of care has evolved that you wait until they're sick and in a very severe state of illness again before they qualify for coverage to re-treat. And so, the same assumptions are generally made for OCD that, after you finished treatment, they'll continue with their maintenance medications and continue with their psychotherapy, and that there will be a range of durability for that positive response; where some people go years, some people are becoming symptomatic again within the year after they finish the course of TMS.

**Dr. Barry Whites:**

Thank you very much. Are there any studies on this that are available? That You're aware of?

**Dr. Linda Carpenter:**

At this point, just naturalistic data for OCD, but for depression, there are a number of longer-term studies.

**Dr. Barry Whites:**

Yeah, yes. Okay. Thank you. Very much. Any other questions? comments?

**Dr. Wayne Goodman:**

This is Wayne Goodman.

**Dr. Barry Whites:**

Yes, go ahead. All right.

**Dr. Wayne Goodman:**

Yeah, the other comment I would make about would be about the magnitude of the response rate, and the difference between groups. You know, at first blush, you know, it doesn't look like,

you know, that's a huge difference of three - about 3 points - in the Y, box. But in many studies, including pharmacotherapy, that often does translate into clinically meaningful differences. Moreover, you really see the magnitude of the effect when you look at the differences in the response rates between the active and sham groups. At the end of the study was 38% versus 11% active versus sham respectively. And then at the one month, follow up, it actually there was further improvement and response rates of. 45% in the active group and 18% in the sham group. And, what I often look for is a relatively low response to sham and I think I would consider this a relatively low response to sham. So, I think the magnitude of the effect, and the difference between the two groups is clinically significant.

**Dr. James Ellison:**

I would second that.

**Dr. Barry Whites:**

Who is, who is this the speaking? First we need you to identify yourself. I'm sorry.

**Dr. James Ellison:**

Yeah, it's Dr. Ellison, Oh, sorry. Dr. Goodman -

**Dr. Barry Whites:**

Dr. Goodman, I thought so. Okay. And then now Dr Ellison, Go ahead.

**Dr. James Ellison:**

Yeah, it's Dr Ellison and I would just second what Dr Goodman says that the low sham rate is consistent with this being a treatment resistant group. And a small change in treatment resistant OCD patients can be significant.

**Dr. Barry Whites:**

Thank you so much. Any other comments? or questions?

Okay, Dr. Winokur, you're next, please sir.

**Dr. Andrew Winokur:**

Hey, I think I'm now un-muted, so, um, Andy Winokur, and I have no conflicts. I'm sorry, my phone is going off. I have no way to turn that off. I Apologize for that. So I have no conflicts to declare, and, um, It's distracting. I apologize for that.

So, just a little brief background and overview. I have no active involvement with our TMS treatment. I certainly review - I'll refer some patients for treatment that I'm not, uh, directly involved with our TMS myself, and I suppose the part of my background that is most relevant to This discussion is that I have done a good bit of work in treatment refractory conditions, but primarily depression. Um, but kind of echoing some of the previous comments, I think an important perspective on the studies and the data being discussed and that will apply to the study that I'm reporting on relates to the fact that we are talking about treatment response findings in a group selected to be treatment refractory, and I think we've learned in our field over the years that the condition of being treatment refractory has a significant impact on the likelihood of a favorable treatment response to a subsequent treatment. And to me, the most salient data to have a perspective on that is the STAR*D study, which provided our field with so much systematic Information and experience about what to expect with patients, in this case, depressed patients who were treated and after an unsuccessful first, thorough treatment trial, what happens at the next stage, and then the next stage. And as everyone in this field is familiar, that study clearly underscored the significant reduction in likelihood of positive treatment response following unsuccessful prior treatments. So I think that's to me a very important perspective for looking at the studies and the data that we were asked to review and for the study that I'm asked to comment about I think it's a particularly important perspective, and makes the findings Interesting, although I have some limitations as I'll talk about. So, I have, in order to prompt my memory, written out comments, which I'll go through. My comments are probably a little too long, so I'll skip over some of it, but try to capture the essence of this study.

Um, the title of the article I was asked to discuss is "Deep Transcranial Magnetic Stimulation for Obsessive Compulsive Disorder is Efficacious Even in Patients Who Fail Multiple Medications and CBT." So, again, that's getting to the point of looking at what about patients who are particularly treatment refractory in terms of their past history of treatments that failed to produce a satisfactory response. The author is Roth and colleagues, it was published in the "Journal Psychiatry Research" in 2020. That's a very reputable research Journal. So, the authors give a little background to the motivation for this study and point out that 40 to 60% of patients with OCD show no or inadequate response to treatment by means of either pharmacotherapy, which, of course, is most often SSRIs or CBT, or alternatively, the poor response is due to intolerable adverse effects. So that sets up the rationale for the analysis that they carried out in in this report.

I'm skipping over some of what I have that I don't think is necessary.

So they point out as we've been hearing that recent reports indicate that six weeks of deep transcranial magnetic stimulation represents a safe and effective treatment for OCD patients who have had inadequate response to drugs and or CBT. And in the present study, they chose to investigate the efficacy of deep TMS In OCD patients who had varying degrees of inadequate response to medication and or CBT trials. And this was, in a sense, a report of convenience where they analyzed data from the previous trial. A double blind, placebo controlled study and

in this case, they focused specifically on. either the number of prior medication trials, obviously unsuccessful, and/or Prior CBT trials. So they were specifically looking at in the context of the deep treatment and a response or lack thereof, how that was affected by previous treatment history, whether with medications, CBT or the combination. So, again, it was the secondary analysis carried out using data from 11 sites, and, as I mentioned employed a randomized double line design. It was carried out in three phases. There was a three week screening phase, a six week, treating phase as we've already heard. And not that involved the total of 29 treatment days, and then a four week follow up phase. So, those were the components of the study that was used for the retrospective analysis to look at effect of prior treatment. The subjects in the study were aged between 22 and 68. Obviously with the diagnosis of OCD, and they were selected for having responded - having fail - I'm sorry, having failed to respond to at least one test trial with a SSRI And were on current maintenance therapy with an SSRI, and may have also been receiving. CBT. So, uh, the subjects in the study. Had at least 1 previous failed trial and we're on a current trial but still were showing significant symptoms. And, a baseline they were required to demonstrate a YBOCS score 20 or greater. And I think it's been mentioned before, but just to reiterate: a feature of this design was that prior to the deep transcranial magnetic stimulation, each subject received an individually targeted or tailored brief provocation of OCD to sort of prime the neural circuits to be responsive to the treatment. And I think I'll skip over some of the additional details about the study design, we've heard them before.

So, I have a detailed listing of the results, but I don't think in this kind of - listening to somebody read them, I'm going to read them, and it'll be - there are too many numbers. I think what I'm going to do is go right to my discussion of the results, which sort of summarize the findings. And then if anyone wants to, I can go back and we can parse out the individual findings, but I think the discussion will most effectively capture the nature of what seems to be the key findings and the significance.

So, the majority of subjects in this trial had three or more medication trials, and had had prior treatment with CBT so they weren't primarily subjects who just met the minimal threshold for being treatment refractory. They were the higher end of the treatment refractory in the majority of the cases. So, in subjects who had one or two medication trials and had no CBT treatments; It was a small group and really compromised comparison to the larger group that had had a number of failed trials. So that analysis was compromised by the fact that a pretty limited number had receive the, uh. Limited had previously had a limited number of failed trials. But, so, the main comparison, the data analysis was really between patients who had the active deep TMS versus sham treatment, and had a large number of medication and/or CBT trials. And, um, in the patients who had either a high number of failed. Medication trials with SSRIs and/or a high number of CBT failed trials, there was a significantly greater treatment response initially at the end of the six week treatment period. And then at one month follow up, he sham group somewhat caught up.

So the basic finding that I thought was of greatest interest was a prominent response, whether with respect to the patients who had a high number of failed treatment trials with medication, or treatment trials with CBT, or both; that that particularly was associated with a favorable response to deep TMS which was seen right at the time of the end of the six week treatment trial. And in the discussion, the authors suggested the idea that seem premature and tenuous, but might be interesting to follow up: that there was something about a history of failed

treatment trials that altered the relevant neuro-circuits that are responsive on the TMS that then lent to a more rapid, significant clinical response. I think a lot more data are needed to support that idea, but I think it's a provocative and interesting suggestion. But I think more importantly, from the perspective of this discussion, by parsing out the patient population and really focusing on a, particularly treatment resistant group, the robustness of response to the TMS seems to come out with particular clarity. And going back to my initial point that our field has learned about; how challenging it is, in a number of conditions, certainly depression and also OCD, to get a favorable response in the face of a history of failed responses, I thought these findings, even with a secondary analysis were quite intriguing and potentially promising. So, I think those are the comments that I have, and I will stop and answer any questions

**Dr. Barry Whites:**

Thank you. Sir questions? Comments?

Uh, Dr. Carpenter, you're next.

**Dr. Linda Carpenter:**

Okay. So, um, I'll just really quickly talk about my conflicts. I'm a psychiatrist and a researcher at Brown University in Providence, and I was doing research and TMS before, uh, more than a decade now before the 1st FDA approval for devices to treat depression. So, I, I run a TMS clinic. We do not treat patients with OCD. We don't have an OCD-FDA approved device in our clinic. We have 4 other manufacturer's types of devices. I've consulted to a number of companies that make TMS devices and other neuro-modulatory devices that are not TMS devices. I've been a researcher in vagus nerve stimulation studies and deep brain stimulation studies as well. And so, I've consulted for Neuronetix, which makes a TMS device, uh, for a company called Nexstim, for a company called Neuronix, they never got FDA approval, and I also do a Janson-sponsored clinical trials for eskatamine, which is a treatment for treatment resistant depression. So, my expertise is in treatment resistant depression, I treat patients, I'm a clinician and I do research.

And I have had, uh, some experience with BrainsWay who sponsored all these studies, but I've never worked for them as a consultant nor been investigator in any of these trials. However, at one point, I was interested in some of their data from a prior clinical trial and depression and to my shock and surprise and great delight, they turned over their entire database to me with incredible transparency. I've never seen any other company do that. So that's all I can say about BrainsWay

**Dr. Barry Whites:**

Thank you.

**Dr. Linda Carpenter**

So the paper that I've been asked to review is Predictors, Moderators and Predictors of Response to this Deep TMS for OCD, and basically, this is an analysis, secondary analysis, of the data from the clinical trial that you heard about from Dr Ellison with 100 patients with OCD, and I want to point out that the treatment for OCD as described in these papers um, and, involves a routine wherein the patient 1st test, OCD comes in different flavors; some people are perfectionist, some people are hoarders, some people have contamination fears, but they, they put a routine together. There's a neural psychological testing, and before each individual treatment, before you stimulate the patient's brain, each time they come in 5 days a week for all the weeks of their course of therapy, There's an induction of symptoms - a symptom provocation. So, if you're a person who's got contamination obsessions, I might take your pocketbook and rub it on the ground for a few minutes. And I have to induce a state of anxiety and obsessions. Um, that is at least moderately severe on a scale of 1 to 10 using a special scale. So, I want to point that out because, as we think about the sham response, and the active response, all these patients in addition to having failed trials of SSRI or being on one. or being in cognitive behavior therapy, which is an incredibly effective treatment for many patients. Um, they were getting this exposure therapy every day. So just keep that in mind, as we think about these outcomes that they're seeing clinicians every day, they're getting exposure every day, and then they're getting on top of all that, and the medicine they're taking, and they're ongoing psychotherapy, they're getting either active or sham stimulation.

So this is a secondary analysis, and they looked at a predictors of outcome and then they looked at various variables such as whether the patient's age or gender, the age that they were when their OCD started, whether they had a family history of OCD, their baseline YBOCS score, which is how severe their symptoms are, their baseline depression severity and baseline hoarding systems – er - hoarding symptoms, uh, they had some predictions about that being related to outcomes and they, they evaluated those to see what predicted, um, better or worse outcomes or more rapid outcomes. And when you look at all patients together, all participants in the study, whether they got active or sham, the only thing that they found was that age was a predictor at the follow up; and it was only a trend level finding and that's in both people with active and Sham. So, we're, we're trying to evaluate the strength of the evidence for efficacy, um, we really want to hone-in on the findings that that separate active. And sham. And when they looked at all those things and really nothing was a predictor in many of those categories. Now, they did find that baseline OCD severity moderated the treatment outcomes at all of their endpoints; at the end of the course of treatment and at the one month follow up. And the general gist of this finding is that the stimulation had a stronger efficacy compared to sham for people who were had more severe symptoms to begin with, right. So, there was already a finding in there that, for everybody put together that if your baseline severity was lower and that you'd have a different level of symptom reduction at the end, um, such as people who had lower disability and lower, less severe symptoms, they had faster recovery, whether they got active or sham. But the main finding that emerges from this, and Dr Goodman, who's the senior author on this paper should jump in and elaborate if there's other points to make, um, was this one: and it's, it's, it's about the fact that people who had the most severe symptoms, had the greatest benefit when you're comparing active and sham. Right? So, they split people into kind of a low severity group and a high severity group. They just did a median split on those baseline YBOCS scores. And the people who started off with, that were sicker with more severe symptoms, they had larger improvements. They improved more slowly, but they had a larger improvement. That

might be because there's just more room for change. Right? They had higher scores, So, there's more space to come down and in the scale, the outcome measure. And it's also could be the case that the less severe patients, the patients with the more mild to moderate levels of symptoms coming in, had a bigger placebo effect. They, they had more response to Sham for people who have less severe illness just coming to the clinic every single day, talking to the clinician, having this exposure, may have been useful and therapeutic, uh, to impact their placebo effect.

So, I mean, as thinking about the evidence in, in terms of, um, where the greatest signal of robust efficacy is, certainly it's patients who start off with a YBOCS score of 28 or greater. And that is the main take home point of this. They did not find that those other things, family, history, gender, age, level of depression had anything to do with the outcomes. They were not statistical predictors.

Happy to turn it over to you, now.

**Dr. Barry Whites:**

Thank you very much. What was the percentage of patients who were - do we have a - I see an age range that goes up to 68, but I don't see a percentage of patients that may be in the Medicare range. I mean, were there. Do we know how many – Dr Goodman, do you have any idea how many patients were over age 65 in this group?

**Dr. Wayne Goodman:**

Um, no, I don't remember.

**Dr. Rachel Davis:**

And this is, uh, Rachel Davis, I just wanted to comment that a number of our patients with OCD are disabled, so would also have Medicare possibly at a younger age.

**Dr. Linda Carpenter:**

Yes, I was going to make that same point.  In our TMS clinic where we treat depression, a very significant portion have, SSDI and Medicare, Medicaid and they're much younger than, um, our retired Medicare population.

**Dr. Barry Whites:**

Very good point. Thank you.

Is there any, any information available on that data? The dual coverage, Medicare, Medicaid, or just Medicare only in the population? Is there anybody that has that information, that you are aware of?

**Dr. Linda Carpenter:**

Well, right now, for OCD, Medicaid would never pay for this, so there wouldn't be any patients with Medicaid who've, Who, Medicaid-eligible, who would have received it. Right now the people who are getting treatment with TMS for OCD, either got it in a clinical trial, or they're paying out of pocket, or they're one of a few very small pockets of insurers. I know of no large commercial insurers that are yet covering systematically. It's just starting to happen so I think that there are no Medicaid data available unless people are treating off label and, um. Yeah, nothing published at least.

**Dr. Barry Whites:**

Questions for Dr Carpenter?

**Dr. Wayne Goodman:**

This is Dr Goodman. I did want to make a comment. Dr carpenter mentioned, and others have mentioned that the design of these trials included, uh, an exposure to, that was tailored to, the patient's particular typology of OCD. I would not, though, characterize that as treatment at all. So, in fact, I, I recall when I was being introduced to the study design, I had concerns that the exposure might make patients feel worse. When you're doing exposure as part of exposure and response prevention treatment, which is a form of cognitive behavioral therapy, you not only expose them to something that triggers mild to moderate symptoms; you provide them with instructions and tools of how to manage that anxiety without giving in to compulsions and the goal is, at the end of that, for them to learn that their anxiety abates over time; say, 30 minutes, in the absence of performing compulsions. None of those additional measures took place during the provocation or induction of symptoms. So, uh, I would not characterize the exposure as treatment in the way these studies were designed.

**Dr. Barry Whites:**

The question would come in in the opposite direction, has the provocative testing versus non-provocative testing, matched cases difference in response?

**Dr. Wayne Goodman:**

So maybe others are, but I'm not aware of any studies that have tried to follow the same, you know, the same schedule, the, the same number of treatments in the absence of provocation, uh, I, I'm not aware of it.

**Dr. Barry Whites:**

Thank you sir.

**Dr. Wayne Goodman:**

Thank you.

**Dr. Linda Carpenter:**

Well, so I, if we – This is Dr. Carpenter, if I can comment on that too?

So, there is a meta-analysis that's not, um, it's summarized in one of the summary documents here, but it's not presented in the literature that we're reviewing today, and it looks at a lot of different clinical trials, sham control, clinical trials of TMS for OCD, targeting for different sites with different coils. Uh, it didn't break it down by provocation or not. But there are some studies that have been done where they targeted different areas of the brain with different types of coils, and that they didn't do this symptom provocation. So, we have a direct comparison in the same study.

**Dr. Barry Whites:**

Thank you.

Other questions, comments?

**Dr. James Ellison:**

This is Dr. Ellison. I was wondering whether any of my colleagues here know of a comparison for OCD between the H7 coil, and the standard coil for our TMS.

**Dr. Linda Carpenter**

I don't think they've been compared - this is Dr. Carpenter - head to head, but some of the work that they've been doing, um, and one of the previously presented papers to Dr. Goodman were trying to address that question of whether you're getting to the same areas of the brain, you know, covering both kind of the depression target and the OCD target with the H7 coil, which it looks like we would certainly hit some depression circuits as well as the OCD circuits. But, the other type of data, which are naturalistic data, come from clinics where people have co-morbid depression and OCD and they're using a depression coil, and maybe they're getting reimbursed because they're treating depression and maybe also just tracking the symptoms. So, again, not the highest, uh, the most rigorous type of evaluation.

**Dr. James Ellison:**

Thanks, it's Dr. Ellison again. I understand the theoretical reason why the H7 coil would be better in terms of reaching areas of the brain. I just wondered if there was any actual data of clinical trials, and I couldn't find in the either. Thanks.

**Dr. Denise Nachodsky:**

This is Dr. Nachodsky, and I think this is to all the panelists, but Dr Carpenter you we have a very nice in-depth knowledge with the research, So this may be more directed towards you; if you could just educate me in regards to: some of the panelists also had made comments into the hyperactivity in certain parts of the brain, depending if it's depression versus OCD, and as a cardiologist, this is like, all new to me. I feel like I'm a medical student again so -Is there ways after you use this therapy that you - in follow up - you could measure the hyperactivity in those areas of the brain to see if TMS has helped, or to see if it's at least that hyperactivity is decreased? And then, if there's a failure to check that level again, I don't know, I'm just wondering if that would be a way, because I'm just a little curious or concerned that there's only one month follow up with this type of therapy for these patients, um, so maybe you could speak to that?

**Dr. Linda Carpenter:**

Yeah, so what we, the, the first thing you have to know is that we don't actually know, um, it's, it's not as straightforward as it is in cardiology with regard to, um, what's hyperactive and what's hypoactive. We have, you know, decades of studies where we compare patients with a certain disorder to a healthy controls; and we say oh gee, this side of their brain is hypoactive or hyperactive, and then more recently, there have been studies where you can evaluate patients with, either, say for example depression, who are getting TMS and you can look at functional connectivity of different networks in the brain before, when their sick, and then when their better and you can start to see what changes when they get better with TMS. And we can start to parse out some of the circuits and try to figure out, okay how do we reach those with the stimulation coil sitting on the scalp? Where are the hubs?

And it's starting to look like different symptoms may have different circuits. And so some of the circuitry from OCD, we understand has to do with – comes from - these different types of imaging studies and pre- and post-treatment studies. If you follow, if somebody's better, you can do a brain imaging study after and say, okay, see what changed; we think this is critical circuitry and that provide rationale for the target where they design this coil. They want to get to the medial, uh, dorsomedial prefrontal cortex and to singulate cortex. But then after you finished treating somebody, it's not that we would sort of check like, you would check a blood pressure, or you would check out, you know, um, whatever, uh, some other metric of cardiac function. If the patient's symptoms are returned, that's really more important than what's happening in the circuit. And it's expensive to evaluate with these functional. Right so, so that it ends up not being used as a metric to sort of gauge. Long term outcome. Does that help?

**Dr. Denise Nachodsky:**

Yeah, that that does. Thank you for explaining.

**Dr. Barry Whites:**

If no other questions, we will go on to Dr Schrodt.

Dr. Schrodt, are you there?

This had…One of the more in depth studies, um, meta-analysis so let's go ahead. Dr. Barnett?

**Dr. Randy Schrodt:**

Sorry. Can you hear me now?

**Dr. Barry Whites:**

This doctor Schrodt?

**Dr. Randy Schrodt:**

Yes, sir. This is Dr. Schrodt. I'm sorry. I was just trying to find the, uh, unmute button. Um, uh, thank you.

Um, the article that - first, off Dr. Randy Schrodt, I'm an associate clinical professor at the University of Louisville. I am in a private practice. We have a TMS practice that we've done since, uh, 2010, but we do not have a deep coil and don't treat OCD, and I don't have any connection with BrainsWay.

The article that I reviewed, is entitled "Real World Efficacy of Deep TMS for Obsessive-Compulsive disorder, Post Marketing Data From 22 Clinical Sites." Um, the authors of this article are, as are a number of the others, Roth and Tendler. But what they did was, they reached out to the centers that incorporated the deep coil and retreating TMS in the immediate post marketing period, following the FDA approval in 2018. And they, there are pros and cons of this as you get with any multi-center study. Certainly, it was not as clean, but that's kind of the idea that it says: sort of, what does it look like, in the, in the real world. They, initially, enrolled 219 patients. They had evalu- data that could be evaluated on 167 patients so it's one of the larger studies. and their particular points of interest are overall first response and then a sustained response, again, using the metric of the 30% reduction in the YBOCS scores. This was a [inaudible] that was, quite clinically ill. 66% of the patients had comorbidity in addition to the OCD. They did not detail that in the article, but I suspect it was predominantly depressive disorders. Their lifetime number of failed SSRI antidepressants was just about 6, and notably in this study, compared to the randomized sham control studies a little more than 72% were also

taking concurrent SSRI medications. Average mean age was 37, but with a fairly broad range of symptoms. As I said, and it's been commented on a couple of times before, uh, this was generated from people that were in clinical settings. So, unlike many of the clinical studies, the patients were [inaudible] for their time or anything other than that, other than, uh, the clinics themselves got basically a modicum of money for providing the data, the YBOCS data, things of this sort. Um, but it is noteworthy that this was during a period of time as, I think Dr Carpenter had mentioned before, even today, where, uh, this is not covered by insurance. So, these patients were seeking treatment on their own and, um. Generally paying out of pocket, I would suspect. Most of the patients in this clinical trial followed the research protocol that was prior, uh, previously discussed, but it was noted that 7% of this sample, the clinicians were going off script, including, using, theta burst, and or sequential theta burst and high frequency, H7 coil. Additionally, as I mentioned, a number were taking medications and we're doing concurrent therapy and the authors noted that, certain aspects such as the dose of if you will a provocation prior and between, and after, uh, treatments may have been many of these centers been higher. So that may have been a somewhat mitigating factor. No seizures were reported in any of these patients and adverse events were generally felt to be either unrelated to the device, or typical to what we see in a TMS practice, which is either transient headaches or discomfort at the application site where the, where the coil is placed.

As I said, the 2 primary outcomes that they were looking at was, uh, so called first response. So, how many treatments did it take to achieve the 30% reduction in the YBOCS scale, and then the 1 month follow up, or what they call sustained remission. But again, as was mentioned earlier, they noted it as at least 1 month, but it did not appear to be, you know, notably longer than a than a 1 month follow up following the completion of the, the treatment. Basically, what they ended up finding out was, is that the overall first response rate was 72.6%. And the sustained response was, uh, 52.4%. They did note that there was a variability in the number of treatments and again, as to be expected, for people that were paying out of pocket, they suggested that a number of people may have discontinued treatment once they noted they were better. But there was definitely a trend toward better response rates with increased treatments. And they concluded that 29 treatments, which is more of a 6 week treatment protocol, they had an overall sustained response rate of nearly 60%. And again they went on to talk about why this particular response rate is higher than the standard response rate of 38%, which was reported in the active arm of the sham controlled, multi-center study that was reported earlier in the American Journal of Psychiatry. And again, they talked about concurrent medications, variations and concurrent psychotherapies and provocations. But they suggested that, you know, essentially the clinicians on the ground could make modifications of the concurrent therapies as indicated.

I think the main takeaway from this particular article is that it does look like there is at least equal efficacy and perhaps some enhanced efficacy, because of the reasons I mentioned, in the translation from a research setting to the real world.

**Dr. Barry Whites:**

Taking any questions?

I have one comment: in looking at this study, as I was looking at the numbers, this was supposedly real-world data on 219 individuals. No coast YBOCS was on 37, which took you down to 167. If you then looked at 46 did not have any scores after 29, which left you down to

121.  70 of those 121 had a response and they're talking about that being the significance - and 51 did not, but in, quote, real world, we started 219 and had 70 respond. We did a 31% and not the 58% that they started off with them at 38% in the sham. So, I wonder about those calculations in that you only count those who went through. Then it, it's a little bit hard to get that data together.

**Dr. Randy Schrodt:**

Yeah, I think that that said, um, and, you know, the few studies that have been done in TMS, in terms of real-world outcome data, I think there's going to be these gaps. It was interesting; the, in the discussion, in the article they talked about that, dropout rate. Of course, they interestingly concluded that if anything, it may have diminished.  That some of the people again, considering that they were paying for it, dropped out when they were some better, it doesn't look like there were many dropout rates because of intolerance of the of the treatment. But I certainly concur that compared to the more closely controlled clinical trials, this data has some pretty big gaps in it.  But even, I guess my sense is given that the response rates, even if it was slanted toward the responders, you know, it was significant enough.  So, it would appear from my reading of this, that translating it from a research setting to the real world is at least comparable outcomes.

**Dr. Linda Carpenter**

If I - This is Dr. Carpenter - if I can add to I wanted to speak to your observation of patients not having a post treatment measure with a YBOCS, and unlike depression where we can hand people these, you know, self-report scales and they can check them off in 5 minutes, the assessment of somebody with OCD with the YBOCS, it involves - it's a much more, elaborate and time consuming thing. And you have to think about this in the context of what's billable is there now real-world data and not where you've got hired research assistants, clinicians, coordinators, and psychologists at each site that are paid to do assessments. If you notice in the clinical trial, instead of having a treatment 5 days a week, the very last week, they stopped and had a day for assessment. And I think, well, when I looked at this interpreted, okay, some, some of these guys don't have post treatment, a YBOCS 1. well, they're not participating in a clinical trial. They may not have a person that they can, or a way to bill for somebody coming back the next day and doing a YBOCS assessment. So that may contribute to the, um, diminished, uh, availability of all the outcome data.

**Dr. Barry Whites:**

Thank you. Any other comments?

Dr. Barnett, you're up next.

**Dr. Debra Barnett:**

Hi, good afternoon. So I'm based out of Tampa, Florida. I am also primarily a clinician – clinical psychiatry, although that does include some teaching and, medical director of a treatment program for addiction, but in my clinical practice I do perform TMS, but not using BrainsWay, not treating OCD. So, in terms of my conflict of interest, I'm going to state none.

I was asked to review an article entitled "Modifications of Cognitive Performance in the Stroop Task Following Deep, Repetitive TMS Treatment Course in OCD Patients." In this, there's actually a letter to the editor in the journal Brain Stimulation in 2021. The authors are out of Ben-Gurion University, and I may mispronounce her names. I'll do my best: Alygon. Barnea, Carmi, Zangen. And so, this was actually a post-hoc analysis of a prior study which also was published in brain stimulation and, uh, in which there was a comparison of the efficacy of 5 weeks of active versus sham treatment with deep TMS over the prefrontal cortex for OCD, and in that study, they included a stroop and electro physiological recordings before the first treatment and after the last treatment, um, or, uh, upon the last treatment. So, they had data available for the stroop test in 12 subjects that were in the active arm and in 10 subjects in a sham arm. As a background, since this is a different premise, obviously, than the other studies we've discussed. There - it had been previously observed that in persons with OCD, that there is an abnormal error monitoring, as evidence by performance on different, or psychological tests, like the stroop. Um, so there is a longer reaction time after an error compared to the reaction time after a correct response on the stroop. In addition, reaction time after a correct response is longer compared to persons without OCD. So, we have already a baseline to increase latencies in response times. So anyway, the initial effect I talked about is referred to as post-error slowing. And there had been a study, another study, prior to this, that also showed that data, trans-cranial alternative stimulation over the medial prefrontal cortex of healthy volunteers induce short term reductions of post error responding without compromising accuracy. So that's the backdrop to all of this.

So, the post-hoc analysis showed that only active -the active arm - the active deep TMS significantly reduced the response times in the 95th percentile response times. In other words, reduction of the slowest response times, regardless of the condition, whether it was post-correct response or post-erroneous response. And that the post-error slowing that has been observed was reduced in the active arm more so even of the sham condition.

Um, so obviously, this, this study has limitations and very, obviously, there's a very limited sample size. Uh, there's, also it's a post-hoc analysis. It's not, uh, where there's an a priori declaration of what your primary end points are. I thought it was interesting because this measurement of the response times in the stroop, in a way, could be a proxy to measure the effect in, of treatments of OCD, especially as it is an objective measure, as opposed to a more subjective measure as we would see on the YBOCS. In addition. It's interesting is because it gets to maybe a kind of cognitive dysfunction that occurs in people with OCD. And then, uh, I had some additional observations, not necessarily directly related to this study, but, uh, at this point, I'll go ahead and pause, so that we can discuss this particular study.

**Dr. Barry Whites:**

Hi this is Barry; I would point out editorials for the most part are not something that we would be considering since having peer reviewed and able to analyze the data, certainly, is not as if it was in a clinical trial or any formal to systematic review, et cetera. Uh, and I'll just like to get those comments on how much significance, number 1, does this have any bearing on OCD, other than the fact that get better? Does it improve their OCD because they have a better score? Is it anything that lasts? And all of these, and again, you had only 12 patients in the active or 12 patients so the active group, seven females and ten patients in the sham, seven female, so we're looking at 22 patients. Totally. Again, is that something you would consider to be a, uh, any study that you would base a major decision on?

**Dr. Debra Barnett:**

As it stands by itself, I, I certainly would not, um, I think it suggest, um, a lot of very interesting information and interesting targets. If for any, uh, anybody performing research in this space. But by itself, as opposed to talk analysis with such a small sample size, I would not, and with this indirect measure, without any correlation - direct correlation to, for example, the YBOCS or any, even subjective, assessment in the patient population about whether or not they experienced improvement, I would I would not draw a lot of conclusions from it.

**Dr. Barry Whites:**

Yeah, I think that's the other issue that we're looking at here is not general information, but the information that was provided to us to make a decision on and reconsideration. And that's something that I wouldn't want to everybody to keep in mind is that what we're looking at is the information that was supplied to us to form a decision on non-coverage, coverage, or limited coverage, and when we see things like this, I don't think it's probably going to help us make a decision one way or the other. But, but just as envision as an educational item to bring to our, our MACs and to our listeners that this is not a type of study that we would be looking to make a decision with.

**Dr. Debra Barnett:**

Correct and of course, the other limitation with this particular article, and this particular post-hoc analysis is that it doesn't report again, any kind of follow up. In other words, even, even the changes, uh, on the stroop that they measured are those preserved a month later or two months later three months later. And that would be of great interest to me.

**Dr. Barry Whites:**

Oh, yes, I think it has a lot of possibilities but again, thank you so much for your opinion, any other comments on this task before we go to the next presenter?

Thank you, uh, Dr Davis uh, if you will do the ECRI, the last one, please and do the handbook next. If you don't mind.

**Dr. Rachel Davis:**

Sure. So this is Dr Rachel Davis. In terms of conflicts of interests. I served on a one time BrainsWay advisory board in 2019, and I'm the service director for our psychiatric neuromodulation services. We don't yet do TMS, either for depression or OCD, but we have purchased both the BrainsWay, and a MagVenture device and plan to in the future.

Um, so the, the paper I was assigned was the, um - Actually, Dr, Goodman already covered most of this in his 2021 Tendler Brain Stimulation article, because that article was an extension of this. So, I'll just give a 1 sentence summary. Basically, this was, uh, title of the article was, "Do Co-Morbid OCD Major Depressive Disorder Patients Need Two Separate Deep TMS Protocols." This was a post-hoc analysis of the 2019 American Journal of Psychiatry Carmi trial. They looked at the subset of patients with OCD and Co-morbid major depression with an n of 10. And they did find a significant, uh, a statistically significant reduction in MDD, including at 1 month, follow up however, it didn't statistically significantly separate from sham likely due to being under powered to detect that. And then Dr Goodman summarized, um, everything else already.

**Dr. Barry Whites:**

Any questions on that? Thank you very much again. These are items that were presented to us to evaluate and I appreciate you looking at it.

If you will go on, the ECRI was not one of those items that, that we usually try to look at to get some information from an outside source, and they're usually considered to be unbiased. And if you would just give us a, your, your appraisal of their appraisal, that would be very good. I would appreciate it.

**Dr. Rachel Davis:**

Sure, so we'll give a – I'll summarize briefly – so this was collected in May of 2021. They noted that the FDA has cleared two systems, the BrainsWay and the MagVenture coils. And I'll start with the conclusion: they concluded that the evidence is inconclusive to feed data on outcomes of interest. And so, the evidence that they considered were gathered from January 1st of 2016, through April 19th of 2021, for a total n of 874 subjects. They included four papers. One was 2021 meta-analysis by Perera which had an n of 781 and included 26 studies. Now, I think it's important to note that they didn't look at just FDA approved devices. They looked at different rTMS treatment parameters; they looked at different numbers of treatments; length of treatments; they looked at different anatomical stimulation sites; they looked at - some of them included theta bursts – so, very heterogeneous. This ECRI also included a small, randomized control trial with an n of 30, looking at rTMS of the left dorsolateral pre frontal cortex versus sham, total of 15 sessions. They also included a study in 2021, with an n of 33, which looks at continuous theta burst stimulation to the orbital frontal cortex versus sham, and they reported on

change in symptoms two weeks post treatment. And then a study by Abdel, 2020, within an n of 30. They looked at low frequency rTMS over the right dorsolateral prefrontal cortex, high frequency rTMS over the right dorsolateral prefrontal cortex versus sham and they reported on change up to three months post treatment.

So, what were the findings? In the systematic review with meta-analysis by Perera, they showed a modest effect on reducing YBOCS with the largest significant effect size when clinicians applied left dorsolateral prefrontal cortex. Actually, it says bilateral left; I think it means bilateral dorsolateral prefrontal cortex stimulation. And they found that affects were better than sham up to four weeks treatment. Even though these studies looked - some of them went out as far as three months - they did not find that it separated from sham beyond four weeks post treatment. In the 2021 – I'm going to butcher this name - but Jahanbakhsh, uh, 2021 study, YBOCS was significantly lower in a group that received low frequency stimulation over the left dorsolateral prefrontal cortex. In the Dutta study, they found significant improvements in HAM-A and CGI two weeks post treatment with theta bursts. And then in the Abdel trial, they found no statistically significant difference in YBOCS reduction in low or high frequency over the right dorsolateral prefrontal cortex versus sham.

So, they concluded that the evidence limitations were that there were no medium or long term outcomes. Again, really only able to show us statistically significant maintenance and treatment up to 4 weeks post treatment. Beyond that, there were too few patients and able to assess, um, basically not powered enough to assess further lasting of effects. They point out, uh, what is somewhat obvious, that the systematic review was unable to be conclusive and optimal treatment regimen because they included a whole cadre of different treatment regimens. They did say, had a good methodological quality and low risk of bias. However, they felt that the, the smaller, randomized controlled trials were at medium risk of bias, due to small study size. And then one of these, the, Jahanbakhsh paper, was an unreferred preprint. And so, um, I think. In terms - this is interesting. I'm not sure how useful it is to our particular question, given that it looked at many different parameters with many different devices at many different anatomical locations of the brain. Interestingly though they did still find efficacy, but the main problem is similar to what we found with the other papers, is that we just don't have enough data about outcomes beyond four weeks post treatment.

**Dr. Barry Whites:**

Thank you so much for your time and your expertise again, any questions or comments on either one of these two articles?

**Dr. Linda Carpenter:**

This is Dr Carpenter again I just want to underscore the comment that was made. I think the fatal flaws with this evidence assessment is that they excluded studies that were not in a meta-analysis, and the meta-analysis took all different kinds of treatment with inpatients with OCD that involved TMS and put them all together in one analysis. So it's like, if you were to say, okay, we're going to cover certain scalpel you wouldn't say all right. What's the efficacy when you use a butter knife? Right? So, I think what we have to keep in mind is, I think the decision - I

hope the decision you're making - relates to the FDA-approved protocol and device that reaches a certain area of the brain and works a certain way.

**Dr. Barry Whites:**

Thank you so much. Other comments?

Well, I – personal note – I really do, I mean, I'm almost at a loss for words to thank you for how much expertise you've shown and thank you so much for your contributions, which has been amazing and thank you so much.

The product this meeting answers to various questions had been received by experts, and they've now been received that are being tabulated. These questions of which we really, um. I'll briefly go over these questions to give you an idea of the polling question that we did ask these experts and they were:

Number 1. Do you believe the sufficient evidence to make a recommendation for unconditional, non-coverage, or no limited coverage. And, you know, the strength of the evidence and the - and your confidence of your vote. Your confidence was very - It was a 1 if it was low evidence, stop it with high confidence. Excuse me. Not evidence but high confidence. So, if you said. Yes, to unconditional coverage, how confident were you in that decision? And it could have been a low or yes. It could either have been a low or up to a 5. and that's the sequence: that's how we ran these questions because your opinion. Is certainly very valuable, and that's what we need, but we also need to know how assured you are of your of your - based on the data that was presented by the requester - How confident you and your answer may not change or may not be the same as more data would come in.

Our second question had to do with treatment for TMS with should be reserved for treatment resistant. Do you feel there's evidence to support that? If the answer was positive for coverage should it be limited to psychiatrists? How confident are you in that?

Do you believe that there's evidence of specified deep over repetitive again? How confident are you? and that answer does the evidence indicate the frequency of the number of treatments?

Is there evidence to support a particular standard of managing severity? and the level of change during the treatment, either positive, negative, or no significant change. I think everybody that I've seen so far has felt that the Brown yield score was significant and most, everybody gave it a 5.

Does it present a significant number of Medicare population? Does it represent our population? Because coverage is totally based for us - one of the things that we have to consider - does it affect the Medicare population and that's one of the things that we look at; is there significant data that it was presented by the respond - by the requester - showing that it did represent our Medicare population, realizing that our Medicare population is not just confined to 65 year olds.

Last question was the risk of bias and conflict of interest, was it such that to downgrade the level of evidence? Or was it not acceptable enough to downgrade the evidence?

These questions are going to be compiled, they're being compiled now, the answers to the questions are being compiled. The information that we get from this will be sent to the various

CMDs. The CMDs will get a copy of this. We'll be meeting in a couple of weeks and then discussing coverage, non-coverage, coverage with limitations, we'll see which - where we need to go.

Our next step, next slide. please, again, if you'll go through those key polling questions for me, and let's get to the, uh, go ahead, they have 9 of them.

Our next step is that work group again we'll meet in the next 2 to 3 weeks to discuss the responses. Hopefully come to a consensus on the 3 options before us, as mentioned, unrestricted, limited, or non-coverage, before we have any other next steps, we must decide that issue. The subject matter experts, as I said, I think are to be commended on their hard work, their expertise, and show why they are subject matter experts in this area, and I would certainly would like to entertain any comments that you might have on this process and specifically how we may improve your experience with this and would open it up to our subject matter experts to comment on this process and would more than more than liking it, I would certainly appreciate any comments that you may have that we made how we may improve this.

**Dr. Linda Carpenter:**

Well, this is Dr Carpenter I'm not the quiet one.  I guess it's been a little hard for me to, um, coming into this to know how much, uh, not the, the subject matter experts, but the others, um, in the meeting know about OCD and TMS, and how much the nuances of this population - how difficult it is to get any of them better. What's a typical response rate for any good successful treatment for these types of patients? And I really don't know what everybody's background is. So, I feel that's the piece that was kind of missing and I, I think maybe others spoke to it a little bit.  Maybe Andy Winokur did.  But OCD, you know, a good treatment for OCD, and the best treatments we have don't get people very much better. And so, putting these things in context, I thought it was difficult and I didn't know how much background people had.

**Dr. Barry Whites:**

But I do appreciate it, I think what we're primarily interested in, I've said on more than one occasion, is that the evidence presented for us to evaluate: was it significant enough for us to make a decision?  The overall opinion on whether X Y, or Z therapy should be done, and personal opinions and personal – this - what we're looking at is the evaluation of the data and that's our emphasis; that's what we were charged to do by CMS. Is that we look at the data. We see based on certain instances, such as grade is what most of us use. We look at the quality of the evidence, it is graded. And then we look at the decision, whether or not the strength of recommendation is strong or weak.  And that's where we look at the studies. Because we -  and I say, we - we as contracting medical directors, MDs, as Dr. Nachodsky pointed out, she was a cardiologist. I'm pulmonary critical care. I am no expert in this field, and I've been asked to make a decision and I depend on those to evaluate the data. To if it, if it may be the best thing since sliced bread, but if the data's not there, it's hard to make a decision. And so, the common factor, we have in making our decisions as far as policy is concerned is how good is the data on it? And so that that's what we're looking for. And that's the reason that we had experts in the field of

psychiatry. We had experts in looking at psychiatric data, and hope that that was certainly better than a bunch of pulmonary doctors looking at it. I can assure you.

**Dr. Linda Carpenter:**

Yeah, that's very helpful, and I assumed all those things too. The data, where the point, uh, the evidence, to the point, I just didn't know like, when I went to go present my article, I didn't know, you know, or maybe for the others, how much to share about what is a, a reasonable or a usual, you know, is this definition of response an appropriate - so that you could interpret the data in context that's all I meant.

**Dr. Barry Whites:**

Yeah, I think again, pointing out that the study that was, let's say, study X, we're saying that a 10% response would be acceptable. Now, if that is not something that is uniformly accepted, that is something that you should be commenting on and making a decision on. Is that what is reported in the study is correct or not correct? Is it a standard? It is common medical practice. That's what we need to know from you, and why, and in addition to the data itself, but assumptions made in the presentation in the items that are being considered are those assumptions, correct? Is it a correct assumption that a 30% improvement is a good improvement in OCD? I know in certain diseases, it is, it is good. It's written appears to be probably here and those are the kind of decisions and information that you all provided today, that, I think was certainly very, very helpful to me personally. I'm sure it was to the CMDs and I'm going to thank you.

**Dr. Linda Carpenter:**

Great thanks

**Dr. Barry Whites:**

Are there other comments?

Before closing, um -

**Dr. Deborah Barnett:**

If I could again, I'm sorry for second unmute. Deborah Barnett -

**Dr. Barry Whites:**

Yes,

**Dr. Deborah Barnett:**

from Florida. Um, so as I was reviewing this, I just happened to flip through another Journal, uh, and saw an article that was more recent. It was in Journal of Clinical Psychiatry last year, that had a systemic and meta-analysis and I just what I wanted to just comment about that was that of the different studies, they reported a range and follow ups anywhere from 0.3 months, which is nothing up, though, to – oh jeez - on that, uh, 171 months. So, an average of 33 months. So, I suspect there is some data out there. It's not in the studies that, unfortunately, it's not actually, uh. the longer follow ups are not represented in the studies that we reviewed for this panel. Um, which is unfortunate.

**Dr. Barry Whites:**

Yeah, I think that's to your point, that's why we have a reconsideration process and it is an open process that if there are new articles that should be brought to our attention, that's why we have a reconsideration and they can be added if we choose to do a non-coverage or coverage, if someone does not think is appropriate, then there's another - always a reconsideration avenues open with presenting that type of information.

You say that's a year old. I'm surprised it was not presented, but again, I don't choose what comes to us. We just evaluate comes to - what does come to us - and make a decision based on that. Is there additional information provided to us that would warrant addition of OCD to the transcranial magnetic LCD: that's our question to answer, and it is of the information that was provided to us.  So, reconsideration is out there for that reason. If there's a study that comes out tomorrow that says, you know, it’s the best thing since sliced bread, or it's the worst thing, then, you know, that's, that's for reconsideration and it's open.

I’d like to thank, certainly the CMD colleagues who have been active on this process and here on the meeting today and lastly, but certainly not least, our WPS staff that put all this together for our sharing and learning and transparency that's important to our beneficiaries and providers.

Special thanks again to our Subject Matter Experts, certainly first and foremost want to, thank you for all your help. It wouldn't have been possible to get this much information, I think, from any other group. So, thank you if there is no further comments and I'll wait a second, and otherwise we’ll stand adjourned. Any other comments?

Thanks everybody so much with a meeting will be adjourned and thank you.

**[Unknown Voice]**

Thank you

**[Unknown Voice]**

Thank you. Good afternoon.