

TITLE: Efficacy and Clinical Implementation of TMS, ECT and Ketamine

DATE: November 3, 2023

Moderator: Everyone, and welcome to today's webinar, Efficacy and Clinical Implementation of TMS, ECT and Ketamine. This webinar is paid for by McLean Hospital, a top-ranked freestanding psychiatric hospital, a leader in psychiatric care, research, and education, and the largest psychiatric teaching hospital of Harvard Medical School. Some important points before we get started. Dr. Steve Seiner and Dr. Josh Brown, the presenters for today's webinar, have working relationships with McLean Hospital. As such, they have both a financial and intellectual interest in the webinar content.

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A recording of the presentation will be emailed to everyone in about two weeks' time. That email will also include a copy of the presentation slide. During our time together, you will be on mute. You can communicate with us using the Q&A box located on your webinar screen. If you have questions for our presenters, we encourage you to type them in using that Q&A box on your webinar screen. A link to the presentation slides will be posted in the chat box, and if you miss them, we will email them to you in about two weeks' time, along with the recording.

With that, I would like to introduce today's presenters. We have Dr. Steve Seiner, the director of McLean's Psychiatric Neurotherapeutics program, which includes Electroconvulsive Therapy, Transcranial Magnetic Stimulation, both superficial and deep, and ketamine infusions. McLean's ECT Service now performs over 10,000 treatments a year, making it one of the largest ECT centers in the country. He is also a board-certified geriatric psychiatrist. Our second presenter today, Dr. Josh Brown, is a psychiatrist and neurologist. He is Medical Director of the Transcranial Magnetic Stimulation, TMS, Service, and Director of TMS Research in the Division of Depression and Anxiety Disorders at McLean Hospital.

Dr. Brown is also the Director of the Brain Stimulation Mechanisms Laboratory at McLean. Welcome to both of you.

Dr. Joshua Brown: Thank you so much. It's really a pleasure to be here and I appreciate McLean and APA for putting this on. Just a quick disclaimer is that I do receive research support for TMS-related research, though I have no conflicts, I don't make any money off of that or have any industry-sponsored research. Also, get some money from philanthropy. I'll be starting with talking about the TMS side of this before handing over to Dr. Seiner. This is really in the context of treatment-resistant

depression or TRD. This is something that's I'm sure very well known to the group, and so I won't belabor it too much.

Roughly, about 30% of people that don't respond to medications or psychotherapy get this designation of treatment-resistant depression. It's a large problem with about 90 million or about one-third of the 280 million total with depression worldwide. This is something with a lot of room to improve and a lot of people to be reached. One of the things that I think is so fascinating about the brain is that there's multiple approaches to treat it. Something that this group is, of course, quite familiar with is talk therapy from a biologic standpoint. I have a bit of a bias towards thinking of things at this level and based on my background setting synaptic plasticity.

I look at this as really very precisely changing and modulating synaptic connections between neurons. Then we, of course, have medications which globally modulate, or tune up and down that plasticity. Then we have brain stimulation techniques, which more focally but hit large areas of tissue, but are very robust in their effects. This is what we'll be focusing on today. One of the reasons that we can treat in this way and can focus on this, is that the brain is an electrochemical organ. Just as a refresher of Neuroscience 101, electrical signals propagate down the neuron.

Then in connections between neurons or synapses, chemical mediators for this essentially, if sufficient, will lead to another propagation down the subsequent neuron. The brain is an electrochemical organ. The important thing is that as electricity is the currency of the brain, this is, I think one of the reasons that brain stimulation modalities are so robust in their effects and all of the pharmacology back in the '80s called it a chemical imbalance, and things of this nature. All of that really just serves to support the transmission of these propagations, these electrical signals from one neuron to the next.

This is just an overall context for brain stimulation. We're not going to talk about invasive modalities today. Although, they have very robust effects as well. I'll leave the electroconvulsive therapy to Steve, and I'll be focusing on the TMS side of things, and particularly the treatment-resistant depression. As a brief background on TMS, this statue here is of Michael Faraday, he's holding zoomed in on an electric coil. He's really considered to be the father indirectly of TMS because he discovered the law of electromagnetic induction. This is the principle that if you turn on a current within a coil, it evokes a magnetic field, and then a magnetic field can in turn, as it's delivered to neurons, initiate electrical current there and directly cause an action potential. Tony Barker was the first to show that this could be applied to the brain. 1985. This is published in The Lancet. I apologize, by the way, in the reformatting of my slides, which we're using in a dark background. Some of the references were lost, but this was a '85 Lancet study, and essentially showed that we could change brain activity with magnetic waves.

Mark George, who was my former mentor in a fellowship in England where Tony Barker's from, saw this technology, and then subsequently at the NIH noticing brain activity patterns, differences between depressed and healthy patients, posited he might go to apply this if repetitively given over time to modulate the activity. This had been shown just before this from Alvaro Pascual-Leone in neurologic disorders. This is from the first patient treated with TMS for depression. I show this for two reasons. One is, with all the different things that he could have done, the different parameters

that he could have selected, he was able to get it so that the patient went into remission.

The other part of it is, you can see the treatment sessions, the TMS sessions in the top in black, Phase 1, Phase 2, Phase 3, it was really completely unknown how many sessions would be needed, how many pulses would be needed, et cetera. All of this was really just open for exploration, and as I've heard him say a number of times, modestly, that he got lucky, and the field got lucky because it led to these trials with treatment-resistant depression folks that had failed at least one medication. This was an industry-sponsored trial, and it was really a pivotal trial that led to FDA clearance which happened in 2008.

This was published in '07. The thing that I would point out from this is that, one, the effect was significantly different from Sham, but it wasn't a huge effect, and this same, very similar protocol was given in an NIH-sponsored trial, and really had very- - they don't have a figure, but very similar effects as this one. In clinical trials, of course, we're trying to do everything we can to reduce placebo effect, and so what happens in the real world, and this is what we usually will tell patients when we're describing how effective TMS is. Linda Carpenter led a 40-site study looking at naturalistic TMS responses from the clinic.

This is the canonical thing that we'll tell folks, about 50% to 60% of people will have a response, meaning 50% improvement in symptoms, and about half of those will experience remission. Then this was from a large database registry from a company, and the point of this is that we really haven't come super far in terms of what our standard of care treatment is, in the sense that we're still right around those same levels. **[unintelligible 00:10:12]** as the pulse number increases, as you can see on the X-axis, it does start to go up. I'm going to touch base on that in a little bit down the road on these slides. Then also can't really see the reference here. This is essentially adapted from the STAR*D trial, this shows with each subsequent medication attempt, 1, 2, 3, 4 there's less likelihood of response. By the time you get to five or more, that's where we're talking about our treatment-resistant depression, and the chance of getting better is really quite small.

By comparison, looking at these percent improvements across the board, TMS really does have, even current day, very robust effects, and I'll talk a little bit at the end about some of the promising things right around the corner. In addition to the benefits that I just talked about that come from TMS, I think one of the main reasons to think about TMS is that it has really a favorable side effect profile. As opposed to drugs which circulate throughout the entire body and affect receptors all over the place, TMS is really just localized and focal on the site of stimulation. Most people have some scalp pain or discomfort. This is due to-- and these other adverse effects listed here are due to activation of peripheral nerves as the magnetic waves pass through.

This is something that the brain tends to adapt to pretty quickly in terms of the discomfort side of things. The major risk that people-- we tell people about and people are aware of is seizure. Seizure is quite rare. It's less than 0.03%. It is-- keep in mind that it's about 10 to 100 times less than the risk of antidepressants, and the important thing, I think, is that there's never been seizures reported outside of the chair. It's while people are getting stimulation, every clinic it's required that people

are there with them monitoring them, and so it's really quite safe and no one's had to get medications to get out of that seizure. TMS is considered quite safe, and that's one of the advantages of it. Who is TMS for? These are the different psychiatric indications for TMS, and I'll focus in on the depression side of this.

The original clinical trials were based on unipolar depression, non-psychotic patients at moderate to severe. From these trials, this is why insurance companies focus on this particular population. I've seen a little bit of a loosening as we're seeing more and more benefits outside of this scope, but that's the reason that we focus in on these folks, and that's where we saw-- the reason, of course is to try to have a population that we can see an effect from most likely. The thing that we probably spend the most time of any one particular topic discussing with patients is how many medication trials they've had.

Some insurances also require trials of psychotherapy that haven't worked sufficiently for them. Whether it's inadequate or intolerable response, it's been four or more for many insurance companies, it's now getting close-- It's now two or more for an increasing number of insurance companies. That's the thing that, probably more than anything else, holds this in the diagnosis would keep someone from getting TMS. This is for insurance covered TMS, mind you. Plenty of people will get TMS at private pay clinics, either like as a first line which it is very effective for, but the trials haven't been there and the reason for that is to reduce placebo.

If you have someone that hasn't had any treatment before, they have a higher likelihood of that. The one complete contraindication for TMS is metal or devices that are in the neck or head area. This is because if it's ferromagnetic, it can shift or heat these. That's dental is not included in that, and there are increasing number of like cardiac devices and so forth where there's a battery pack in the chest that are being used, but that's done with plenty of caution. Other things I have as possible exclusions really should just say with caution is seizure history, neurologic problems that would predispose to seizure, and then basically other causes for depression besides primary depression itself would be reasons to approach with some caution.

This is a slide that I would show patients to give them a sense of what we do with TMS. We, of course, start with a consultation. Takes about a week to get insurance approval. We have research that we'll invite folks to participate in. The first day people get a motor threshold where we gauge or determine how much intensity is needed to activate their neurons to elicit a motor response.

Then the traditional process, people get daily treatments for six weeks. Used to last 40 minutes, now pretty much always 20 minutes or less, and many clinics use intermittent theta-burst protocols that are only three minutes long. It's followed by a taper. We'll discharge and meet with them, and then we'll hopefully get them feeling good and hopefully staying good, so up to a year. Studies that have looked out to about a year, over half of patients remain well, and we get from experience that people that stay on medications tend to do better. A quick shift and to wrap up with a couple slides on the future.

The immediate future, I'd say, of TMS is really mechanism-guided TMS, and so focusing in on the synapse, which underlies network changes that we see and behavioral changes from TMS. We use motor evoked potentials to test if we could

change plasticity by adding an NMDA receptor agonist D-Cycloserine and saw that we could increase that after a TMS session. Alex [unintelligible 00:16:28] and the reference is not on this, it's in JAMA psychiatry from last year, about the same time of year, showed effects that really have not been seen before in psychiatry. He's comparing to standard of care, intermittent theta-burst stimulation, and double or triples the response. He's out of Calgary.

Then parameter space is a huge area and a thing that is both a problem because we don't know how to navigate it, but also shows a lot of potential. Another friend and colleague, Nolan Williams and his group focused in on several of these, and had what is very well known now as the same protocol, and also showed very robust effects with active stimulation. Just as a comparison, this was from the original trial from [unintelligible 00:17:24], they do use the same scale and we can actually compare what the magnitude of effect was. This just shows how huge that was.

This is where TMS is going. It's been a quick whirlwind tour of TMS, and there's a lot of indications that are under investigation now, and I think that we'll rapidly see some changes over the coming years. With that, I thank you for your time and turn it over to my friend and colleague, Steve Seiner, who's a luminary, a scholar, fantastic educator, and a great boss and also dresses really well.

Dr. Stephen Seiner: Right. Thank you very much. There we are. Thank you for having me here today. It's a pleasure and a privilege to be talking about two things that are really important to me, which is ECT and TMS. I'm going to start off with ECT. As I was putting this together, especially the ECT portion, I was trying to think, "What would be most useful to all of you as therapists to know about ECT?" This is what I came up with. This is what I'm going to focus on in my very limited time to talk about this really important topic. One is I want you to be able to recognize patients who are not responding to traditional treatments who may be good ECT candidate. I'll go through what makes a good ECT candidate. Then I want you to be able to talk knowledgeably with your patients about this.

I think particularly for ECT that's important, because there's so much misinformation and fear and stigma out there already that it's really important to be knowledgeable about this. Three, I want you to be able to support your patients through the process of going through ECT. That means really understanding the side effects and what's normal and what's not normal. I'm going to spend a fair amount of time talking about the side effects ECT.

Then finally, this is just a point that one place a therapist is really important in this process, is at the end of the course when we get patients either in partial or complete remission, to help them put their lives back together. So many of our patients have had their lives decimated by depression. If they don't get help putting their life back together and getting back on track, then they'll end up relapsing a few months later and we'll have to start all over.

All right, so let's start from the beginning. What is ECT? It stands for Electroconvulsive Therapy, which is really a misnomer because patients don't really convulse anymore, and that's because it's done under a general anesthetic and a full muscle relaxant, so patients are asleep and relaxed. When they are, I give them a brief electrical stimulus, usually about eight seconds, either on one side, which is

called unilateral, or both sides, which is called bilateral. That induces a seizure that lasts about a little under a minute, typically. It's very quick, they get a little more anesthetic, but if they're inpatients, they're back up on the unit eating breakfast, usually in about 45 minutes. If they're outpatients, they stay for about two hours. I meet with them, or one of us meets with them before they go home, at about an hour and a half. At that point, usually they're totally clear, communicating, eating, drinking, talking, walking.

An acute course is usually between 8 to 15 treatments. It can be shorter than that, or it can be longer than that, depending on how long it takes us to find the right treatment for you. It's done two to three times a week. If it's successful, we recommend a continuation taper, and that just means we taper off the ECT, much like you do with the medication that had worked. We start with weekly, and then we taper it to every other week, and then once a month, and then six weeks, and if you get out to six weeks without needing a booster, then we usually stop at that point.

The idea there is to prolong the benefit of the ECT, and also to prevent relapse. For some patients, every time we get to the end and we stop, they end up relapsing. For those patients, we recommend ongoing maintenance ECT, which is just basically indefinitely, every two to eight weeks, we do a treatment indefinitely but that doesn't mean forever. It just means we just give them enough time to really stabilize before we then try and taper again.

All right, so this is a case example. It's a real gentleman in his 70s with a history of depression, who was admitted for worsening depression, and he tried to kill himself in the setting of worsening financial concerns around a real estate deal. He had severe rumination, agitation, poor concentration, poor sleep, anhedonia, and he became paranoid that other people were talking about him. They'd been trying multiple medications, nothing had worked, and he felt that no treatment would help because the situation was hopeless. This is a classic case of psychotic depression, a geriatric psychotic depression.

This responded beautifully to ECT, went into full remission, did well for a year, and then returned, relapsed, under the-- in almost the same circumstances, another real estate deal that went bad. He was, again, psychotically depressed. We treated him again, got him better and then counseled him that maybe real estate in his retirement was not his bag. He ended up going on to write a book, and I know he's still doing it. It's been about 10 years since we treated him, but he sends me an e-Christmas card every year. He's the only 80-year-old that sends me an email Christmas card. I just adore this guy.

I always use a case like that when I'm talking about indications for ECT, and the reason being that for illnesses, that's a case of psychotic depression. For cases like psychotic depression or catatonia, these are two illnesses where I think you should think about ECT first line. You don't have to do it first, but it should pop into your head, "This is a patient who may need ECT." There's three reasons for that. The first is these are horrible illnesses. Many of the patients that we see who have these will have lost 30 or 40 pounds before they get to us. Some of them are in renal failure. Some of them make very serious suicide attempts. It's a horrible, horrible condition.

The second is they're really hard to treat. Psychotic depression is really challenging. There's a lot of trial and error, and it can be really difficult. Sometimes you get lucky early on, but as patients get worse, you feel like you're sinking in quicksand. It's harder and harder to get them out of it. Catatonia, sometimes it will respond to IV benzodiazepines, and that's great, but when it doesn't, you're really not left with a lot of choices besides ECT.

Then the third reason to think about ECT early in the course of these is that it almost always works. The response rates for psychotic depression and catatonia are in the 80% to 95% rate. We don't have much in psychiatry with 80% to 95% responses. The printer in my office here doesn't work a full 95% of the time. This is really very, very effective. If it doesn't work, we're starting to look for, "Do we do imaging, do we check a thyroid, is there something else going on?" Very, very effective.

Now, what about garden variety treatment-resistant major depression? This is our bread and butter. This is what we treat all day long. No treatment has ever been shown to be superior to ECT in this regard. The response range is, it says 50% to 90%, I would say more like 40% to 80% for this group. It's less than with psychotic depression. The range is really depending on how treatment-resistant somebody is and also how much comorbidity there is. Is there a personality disorder or substance abuse, things like that.

I will give you one clinical pearl. I think that people always ask us, "When you're doing a ECT consultation for depression, what are you looking for?" One of the key things any of us are looking for is what is this person's baseline? How far are they from it? The reason for that is that ECT is really kind of like hitting a reset button in the brain. It's just rebooting things. We bring people back to their baseline, for better or for worse.

Somebody who was doing really, really well for a long time and now is doing horribly, is very likely to respond. That's usually the case with psychotic depression, for instance. You do terribly and then we get you back to your baseline. Now, the patient who says, "I've been depressed for the last 20 years and nothing has worked and I want to try ECT." We're a little less optimistic in those cases. We might be a little helpful but it's not going to be a magic bullet. It's got to be part of a major treatment intervention, multidisciplinary treatment intervention.

Bipolar depression. We see a disproportionate amount of bipolar depression and that's for a couple of reasons. One is that they can be very long and they can also be very disabling. Secondly, they're hard to treat. Again, you have to be really careful with antidepressants and some of these patients can really linger, so they find their way to us. The good news is, again, ECT has been shown to be effective in bipolar depression. Multiple studies, but the one I want to talk about is one that came out in 2015 in the Green Journal. Excellent study, randomized, controlled. They randomized patients to either get ECT or the Goodwin and Jamison medication algorithm, so medications or ECT. What they found is the remission rates were similar. 35% for ECT, 30% for meds, so ECT did a little better.

When it came to response rates, the response is a 50% improvement or better. ECT did over twice as well as the medication. In fact, almost three quarters of patients responded to ECT. The reason I like this study so much is that's what we see

clinically with bipolar depressions, is that some patients just get fully better right away, but a big chunk get better. They're now getting out of bed again, they're going to work, they're no longer suicidal. Those are all really important things, right? Those are big wins. When you talk to them, when you talk to their spouse, they say, "They just don't have a lot of interest. They're not that interactive. They still aren't themselves." They have a lot of residual symptoms.

My experience with this is if you stay with those patients in maintenance ECT to keep them from backsliding and you have a good therapy team, family support, people who really just keep working with these patients, eventually they do come out of it and they do go into remission. I don't know if it's because they've been depressed for so long or you're fighting against the natural cycle of bipolar disorder, but we do see this. It sometimes can be a long slog but we do usually get there. There are other uses for ECT. These are more specialized and I don't have time, unfortunately, to go into them but they can be helpful in certain circumstances with these other illnesses.

I will mention with mania, ECT works very well for mania. It's a very good anti-manic device but we don't use it very often because we have other good medications and treatments for mania. When we do end up using it, it's usually in dramatic cases where patients are deliriously manic or they're violent or psychotic or punching nursing students, stuff like that, often in restraints. It's pretty dramatic when we see these. It's a very small percentage and they're usually court-ordered. I will tell you, ECT almost always works for these patients, works great. The majority of the times, patients, even when they're court-ordered, are actually very grateful to have received the treatment.

All right, so I've talked about all the good things about ECT, now I have to talk about the side effects. Unfortunately, nothing's for free. I really want to spend a little bit of time talking about this just because I think it's poorly understood. Even by a lot of people who do ECT, I think it's poorly understood. I think part of the reason for that is just, there's such variation between patients that it's sometimes hard to get a grasp on it. I want to talk about two. There's two types of memory loss that we see with patients. The first is anterograde memory, the second is retrograde memory.

The retrograde memory is the bigger problem and so I'm saving that for last. I'm going to start by talking about anterograde memory. This is the ability to form new memories. I'll throw cognitive functioning there in general. The good thing about anterograde memory is that it's easy to study. We have really good, well-validated, very thorough objective neuropsych testing that we can use with patients. I will tell you, there's been more than 80 studies looking at objective neuropsych testing and ECT. It's overwhelming when you try and read the literature on this.

Fortunately, in 2010 a really famous memory researcher, Semkovska, did a meta analysis and a systematic review in biological psychiatry of all these studies. It's very useful, and what she said was a couple of things. One, yes, ECT does cause anterograde memory. We all know that, anterograde memory loss, and it can be significant. Two, the good news is it's subsequently recovered usually within two to four weeks after the ECT is done. So that's good.

Then she found, no, and in fact, many studies show that many patients actually do much better if you go a month or more out from the ECT, they do better than they did before the ECT on cognitive testing. That's not that we're making them smarter, it's just that when you let the side effect go away from the ECT, you're now comparing a non-depressed person to their depressed self. Of course, they're going to do much better. Actually, it's pretty striking when you see that data on how much depression affects your cognition. They didn't find any evidence of the long-term effect of ECT on anterograde memory.

How do we talk to patients about this? We tell them, look your short-term memory is going to be impacted during the acute course of ECT. You're going to be forgetful, you're going for-- Directions is one of the most common things people forget, a conversation you had, things like that. You're not going to be on the top of your game. It's really not a great time to do your estate planning, to go on a first date, to give a big presentation at work. People still do these things, and it drives us crazy. A lot of times they get away with it, but we do not recommend that.

This reliably improves usually over about, we usually say over the month after ECT. Again, if we are successful in treating your depression, a month or two after the ECT you may actually be thinking and remembering better than you are right now, if the depression is lifted. Anterograde memory. When people come and complain six months after ECT about memory issues this is typically what they're complaining about.

This is what people post online and are concerned about that they've lost big chunks of memory or things from the past and that those memories don't come back and there's been a lot of disagreement about this in the field for a long time. I think part of the problem with retrograde memory is two. One thing is there's so many things that affect retrograde memory, and two, it's really hard to test. We don't have as good a test as we do with the anterograde memory.

When someone says to me, I forgot a trip I took to Aruba in 2007, how do I know if that has anything to do with the ECT? How do I know if they remembered it before the ECT, and how do I test for it? How do I know that when somebody's not going to show them a picture of them parasailing and they'll say, oh, that's right, we were at the Mexican restaurant, we stayed at the Marriott.

It's really complicated. The good news is, over the last couple of decades, there've been a couple of really good autobiographical memory indices developed. One is the Columbia and the other is Pelman, that's a little bit older. Some really good researchers over the last couple of decades have started really using these.

[unintelligible 00:33:25], Sackheim, McClintock, these are people who really spent a lot of time designing studies to really try and figure out what's going on with the ECT and retrograde memory. I will say there's a lot of inconsistent results with these studies but there's a few patterns that have emerged that I think are true.

The first is it does happen. It's a small percentage, hard to put a number on it, but some patients do lose a significant chunk of retrograde memory. Two, it tends to happen more often with bilateral ECT than with unilateral ECT. Three, it tends to happen much less often with this newer type of ECT called ultrabrief pulse, which I'll

talk about in a second. Taken as a whole, what it really means is technique matters. How you do the ECT actually does matter when it comes to retrograde memory.

How do we explain this to patients? We say, look you may experience some gaps in your memory for the period during the ECT and for some period before that. Sometimes the memories will return with prompting or with time, but some memories may be lost permanently. The events closer to the ECT in time, usually 3, 6, 9 months before the ECT, are most at risk.

That makes sense because those memories are still being encoded in the brain when we do ECT. It also correlates with when, by definition, people are the most depressed and they're not storing memories great to begin with. That combination leads to sometimes memories just not making it into the hard drive of the brain or the hypothalamus. My experience is, most commonly the memories that are lost are usually things you did once and then didn't think about again. You're not never going to forget who your daughter is, but you might forget a piano recital you went to three months ago. Weekend getaways are things that people forget quite a bit.

We tell the patients, look, we're going to start off, generally, we're going to start very conservatively, and before we change to less conservative treatments, we're going to talk to you about the risks of that. That's because technique does matter. We do our best to try to really limit this as much as we can. One of the ways we can do that is, as I mentioned, this newer thing called ultra-brief pulse.

Now, this came about it's been about 15 years that this has been around. To understand the ultra-brief pulse, you have to understand what we do with ECT, which is when we're giving the stimulus it's not like cardioversion where we say, I'm clear, you're clear, and then there's a [poof] It's not like that at all. We're touching the patient, we're giving these little tiny pulses spread out over eight seconds.

What people at Columbia said is, why are we using these wide pulses, of one millisecond, when the optimal depolarization time in the brain is about 0.1 to 0.2 milliseconds? That's about five to 10 times wider than we need it to be. What if we shrink it down into these tiny pulses, or ultra-brief pulses, won't that be more efficient, and probably more importantly, more physiologic? As Dr. Brown said, the brain is an electrical organ, it's used to the little tiny pulses. If we deliver pulses much like the brain does, will it tolerate it better?

They did this big study in 2008, probably the most important study in my lifetime in ECT, which, it was by Sackheim, and they did a randomized control trial and they showed, using this Columbia autobiographical memory index, that really the ultra-brief pulse tended to cause very little, if any, retrograde memory loss. Which was much less, notably less, than all the other types of ECT.

It was quite striking. That led to us all sending in our machines to get retrofitted. We probably, because we're so big, we've probably done more ultra-brief than just about anybody in the country. I will say there is definitely a significant cognitive advantage. There's definitely, especially when it comes to retrograde memory, it's very rare to have somebody come back and complain about retrograde memory months after ECT when they got only ultra-brief.

However, it is probably a milder form of ECT and it doesn't work for everybody. We looked at our data a few years ago and we found that about 60% of the time we get away with just ultrabrief, then the rest of the time we have to go to more conventional types of ECT. It's a great option for patients who are really worried about their memory. We treat a lot of doctors, lawyers, teachers, nurses, therapists, we treat a lot of people like that, that are really concerned and this is a good option. I think this indicates where the research is going in ECT right now. We're really focusing on how can we do this in a way that's safer and with less side effect.

I'm going to switch gears and talk about Ketamine. Now, if you're talking about IV ketamine, that is an FDA-approved drug as an anesthetic. If you're using it to treat depression, you're using it off-label or experimental, so I have to say that. Esketamine, which is an intranasal FDA-approved version of ketamine, is FDA-approved for depression and for acute suicidality. I'll talk about both of those.

How does Esketamine work? Well, everybody, including the drug companies, are mostly focusing on this action. It's an NMDA glutamate receptor antagonist. Now, it's a brave new world. We've been decades of serotonin, norepinephrine, dopamine, now we're talking about glutamate. The thing that's missed, and I think part of the reason why all the drug companies are trying all these other glutamate antagonists, is that ketamine is a little bit dirty of a drug. It does all these other things and all these other things can also affect depression, and improve depression. It may be multiple mechanisms of action for ketamine.

Esketamine is simply the S in the enantiomer. If you remember, racemic mixtures, like ketamine is a racemic mixture, have an R and an S in the enantiomer. They just literally took the S in the enantiomer because it is three to four times higher affinity for this NMDA receptor. That's why it's called Esketamine, it's the S enantiomer. I'm going to talk about IV ketamine first.

When IV ketamine first was being studied, I have to admit, I was really skeptical. Really skeptical. And not anxious to start using it, a controlled substance, for depression. As we started to get into the teens, in the mid-2000s, you started to see these, meta-analysis like this, and again to the left here is a positive result.

These were all really good big-name researchers and all these studies were positive, all these studies were good. So it led us to say, hey, maybe we need to think about offering this to our patients, especially those that aren't responding to anything else. Just to understand IV ketamin, I want to take you into the weeds for a second on one of these studies. This is, I think, the best study done out of those, which was done in the American Journal of Psychiatry 2013. Again, the Green Journal.

They used a 40-minute IV infusion at 0.5 mgs per kg, which is a sub-anesthetic dose of Ketamine. You get a little loopy but you don't go to sleep. I want to be clear, almost all the initial studies, and most studies even now, are done with a 40-minute IV infusion and 0.5 mgs per kg. This is a very treatment-resistant group. They used Midazolam as a control, because anybody who's ever given or gotten Ketamine knows that you're going to feel you got something. You need something better than saline as a control. Midazolam, it's a Benzo, it'll give you a little bit of a buzz. That was, I think, one of the first studies to do that, which I thought was great.

The most common adverse effects were dizziness, blurred vision, headache, nausea, vomiting, dry mouth, poor coordination, poor concentration, restlessness. 17% had associative symptoms which can be very distressing. I want you to remember that number, the 17% because it'll come up again in a second. All these side effects go away very quickly. These are not long-term side effects. They go away, and usually within an hour, hour and a half when patients go home, this is all better. They did have two patients that had to be discontinued for blood pressure elevation. That does happen. You do have to watch blood pressure for these patients.

This was the results of that study and I want to point out two things of import. One is, a 60% response rate in a treatment-resistant population is very good, but this was right away. This is day one. It works immediately. We don't have anything in psychiatry that works for depression that fast. Then the effect holds, and then eventually, by about day seven, actually, you lose significance here if you **[unintelligible 00:42:16]** but the effect does fade. It fades in, of course, a week. That has led to people who are doing Ketamine clinics, including ourselves, to do an acute series of Ketamine spread out over a few weeks to try to really solidify that improvement and prolong that improvement.

All right. I want to talk about Esketamine. Now I understand Esketamine, I think the best way to do this is to go through the study that led to Esketamine's approval. Esketamine is given intranasally in these little devices. They're 28 milligrams each and they're delivered by the patient themselves but it has to be done in a clinic setting. It has to be supervised and you have to watch patients for two hours afterwards. Otherwise, you can't prescribe Esketamine.

The way this works is there's 28 milligrams each. You give one, you wait five minutes, you give another, that's 56 milligrams, that's the low dose. If you want to give the high dose, you wait another five minutes and then you give the third one. In the study, it was given twice a week for four weeks. Here's the important part of this study to know about. This was done as an add-on.

This study, you had to have failed a couple of antidepressants, and then they put you on a new antidepressant. It's a switch study. They put you on a new antidepressant, open-label, and then you either got Esketamine or a placebo on top of that. Esketamine is approved as an add-on. That's really important to know because a lot of insurance companies won't pay for it unless you are also on an antidepressant, or you can make a really good case for why you're not.

All right, so here's the responses. You can see good response and remission rates but you see this placebo rate was really high, 30% remission placebo. How can that be? Remember, this is not placebo, this is a switch effect. You've got a new antidepressant and that new antidepressant is clearly picking up some people. So that's baked into these results. This made it hard for them to get FDA approval.

They had to go back and do it again and you can see after enough of these the FDA said, okay, that's significant enough that we're going to grant approval. If I settle a little down on that, maybe I'm a little bit, here's something I'm going to be much more positive about. Janssen did something really smart, is they took the patients who responded and remitted and they put them in a maintenance trial.

These patients were offered Esketamine every one to two weeks for up to two years after their acute course. This is impressive. This is the response rate. You can see all these people in between here stayed well. That impresses me because this is what I do for a living and I know how hard it is to keep some of these treatment-resistant patients well. This is very impressive.

Just as importantly, they collected safety data for repetitive use. That's something we don't have with IV Ketamine. We don't have good long-term maintenance safety data or efficacy data. It would suggest that if you had a patient that you knew was going to need long-term maintenance, that you might think about Esketamine simply because you have the data to really support you.

Sorry, this graph got a little thrown off, but you get the point here. The side effects, very similar to what we see with the IV Ketamine. The difference is dissociation, 28.6%. This is more than the 17%, remember I told you to remember that number with IV Ketamine? To me, that kind of makes sense because one, the Esketamine, as I mentioned, is more potent on the NMD receptor. Two, when you're giving these inhaled squirts, you're getting peaks and troughs. Whereas with IV Ketamine, you're getting a steady state, so you're more likely to see some side effect. Practically speaking, I don't think it's a huge difference, but it does make sense that you see a little more side effect with the Esketamine.

In our clinic, how we're set up, we have IV Ketamine and Esketamine. Both we offer twice a week for up to eight weeks. With the IV Ketamine, we do it, if after four treatments you're really not responding at all or you're deteriorating, we will often recommend pivoting to something else like ECT or TM. Because usually after four, if you don't not seeing anything, it's unlikely. Some patients want us to keep going, we'll try some additional dose adjustments. Sometimes you do catch people a little bit later.

If they are responding, we finish the series of eight and then we stop and we watch. We try and use that to optimize medications, get them in maybe an intensive therapy, day program, really try and kick off a multidisciplinary treatment plan. Then down the road, if they start to relapse, we will do a rescue series which is usually three treatments to get the better. It's not exactly maintenance but it's kind of maintenance.

Esketamine, we do it just like the study and after you finish, we put you in maintenance and then taper it off as we can, just like we would with DCT. Now you may say, how do you decide between IV Ketamine and Esketamine? You can make the argument for doing acute IV Ketamine and then Esketamine for maintenance. Unfortunately, in the real world what ends up happening is the insurance company usually covers one or the other. That's usually what decides what we do because patients that don't want to pay for these. If you have no coverage, most people do IV Ketamine because it's significantly cheaper.

All right. In my last slide or two here, I just want to try and fit it all together. Patients who are referred to us, people often ask, how do you decide between ECT, TMS, and Ketamine? What's your thinking? I think for, even since Ketamine's come around, the patients I talked about at the beginning of this talk, patients with psychotic depression, catatonia, delirious mania, those patients all still go to ECT.

They're not really appropriate for TMS or for Ketamine and they almost always respond to ECT. Those are pretty easy.

Before we had Ketamine, when we're talking about just the run-of-the-mill severe treatment-resistant depression, before we had Ketamine we got pretty good at deciding between TMS and ECT. Basically, it came down to a couple of things. One, the severity of the illness. If this is somebody who's going down really rapidly, and time is important. They're acutely suicidal, they're going downhill fast, they're not functioning, those would go to ECT.

People who were muddling along and trying to work, trying to stay functional, really **[unintelligible 00:49:04]** worried about side effects, would go to TMS. Then if you didn't respond to TMS, you could go over to ECT. If you don't like the ECT, you go to TMS. We got, like I said, pretty good at this. Then Ketamine came along, I will say, it is really confusing. Who's going to respond to Ketamine? I really don't know. The response rates are excellent but it's really hard to predict.

We've had many patients who just did not respond at all to ECT, who then went on to respond to Ketamine. We've had a number of patients who did not respond to Ketamine or deteriorated during Ketamine, who came to ECT and did great. There's a lot of studies out there now trying to figure this out. In fact, we're working with people at Mass General, some computer science AI guys to really try to use computer modeling to take a deep dive into our data and see if we can really find really specific characteristics about patients who responded beautifully to Ketamine, those really rapid responders.

See if there's something we're missing that might help us to guide those patients right to ketamine, who would respond best. For now, when it comes to ketamine, still a little bit of trial and error in patient choice. All right.

In summary, treatment-resistant depression is common. When therapy and medications are not enough, other neurotherapeutic options can be helpful. TMS can be very helpful with very few side effects. It's one of its big advantages, and it continues to evolve rapidly, as Dr. Brown showed you, and the response rates just get more impressive. ECT can be lifesaving, particularly for patients with psychotic depression, catatonia, or intense suicidal thinking.

However, now that there's an improved side effect profile, it doesn't have to be used only for as a treatment last resort. The role of ketamine and Esketamine are yet to be fully determined, but they're very effective in many cases for severe treatment-resistant depression, even when ECT is not. I think it opens up a whole new exciting area of research. Thank you, and I'm open for questions.

Moderator: Awesome. Thank you both so much for your wonderful presentations. Dr. Brown has been in the Q&A answering some of your questions that way, which has been fantastic. Thank you, Dr. Brown. A question that we've gotten a few times worded a few different ways, can ECT be used with folks who have had a traumatic brain injury, a tumor, or surgery in some way, or should it be avoided in those patients?

Dr. Seiner: Yes, absolutely. We treat a number of people with traumatic brain injury, we treat people sometimes with dementia. The things that you have to be really careful about is when people have had brain surgery, for a variety of reasons, most commonly for subdural or for a tumor or for some kind of aneurysm repair, you really want to stay away from the skull defects. That throws off what you're trying to do.

Sometimes we have to get creative depending on where the skull defects are. It can be a little more challenging, and I think those patients, anybody with significant brain injury or trauma are going to be a little more sensitive to some of the confusion effects of ECT. We have to be careful with it, but absolutely you can do it and some of those patients respond really well.

Moderator: Thank you. Another question we've gotten pretty frequently is the use of all of these treatments in both youth and patients with autism. If both of you could speak to that?

Dr. Seiner: You want to go first, Jeff?

Dr. Brown: Yes, sure. TMS, there's been a fair number of trials with adolescents on TMS. The effects are good but the placebo rates are very high and so they haven't been able to pull out a difference. For that reason, it's still not FDA-cleared for adolescents. It's fairly commonly done, and on a case-by-case basis, insurance companies do prove that for us and others. I would say the effects are probably roughly on par with adults.

It had been asked like, "How young would you treat?" 16 is pretty commonly done without much thought. 14, I haven't done myself, but been around studies that have focused on 14 and above and they've done quite well. 12 is about the youngest that I've heard of people doing. I'm not fully in that space adolescents but it is something that I think all of us expect will eventually get to the point of FDA clearance at some point. Maybe with some of these more robust protocols like [unintelligible 00:54:03] augmentation or something like that.

Dr. Seiner: I'll talk about ketamine and ECT. With ECT, here at McLean we don't do anybody under 16. There's a lot of work that goes into treating people under 16, but also we're not really child psychiatrists or nurses or anything like that. So we don't do that but there are places who do. There are several places, Michigan and MGH actually are big places that we'll do under 16.

Typically, when patients are under 16 usually it's reserved for catatonia or a really severe psychotic episode. Really very, very severe, situations, but it has been used for many, many years in that regard. I actually wrote, along with one of our residents, a review in the Harvard View on this, and the data's actually pretty good. I think everybody's careful and you want to be careful about doing anything to a developing brain.

On the other hand, when a kid falls off the normal trajectory of development, it's a psychiatric emergency, and you've got to get them back on that trajectory. You got to get them back as quickly as you can. There's also the appeal of ECT being able to do that quickly. We treat a number of 16 to 18-year-olds and you get mixed results.

Kids are kids, so they're tough, but most of the time they tolerate it pretty well, and usually they do get better.

Ketamine, this is one of the most controversial areas, in ketamine. There's a big debate going on in this and there's actually some big studies going on in this right now. We just had grand rounds about this. There's a lot of concern that ketamine is a neurogenerative agent but it's also a neurotoxic agent, and so there's a lot of, at least, theoretical concern about using an agent like that in children.

Now, ketamine is used all the time as an anesthetic in children, but we're talking about repeated doses, repeated uses of it. I could tell you that some of the most dramatic responses, some of them that we've had, have been in young people in the 1920 range, but right now we're really reluctant to treat kids with ketamine until the data gets a little bit better.

Moderator: Wonderful. Thank you. I think we have time for one more set of questions. Another one we've gotten frequently in various wordings is, how do these treatments work in tandem with talk therapy and medication after they have been done? Do people tend to continue those treatments or do they spend medication? I'm sure it's very patient by patient, but typically what do you see?

Dr. Brown: Steve, do you want to go first on that?

Dr. Seiner: Sure. I'll for ECT and ketamine, there's interest in you what's called ketamine assisted psychotherapy. It's hard to know exactly what that means because people are doing it all also differently. I think as a general matter, I am a big fan of doing therapy through ECT and doing it through ketamine. In fact, I think, these can be wonderful opportunities to do more intensive psychotherapy because I think there's something about the brain that's a little more malleable and a little more open during these acute treatments.

I don't think that means you need to do therapy while somebody's actively dissociating from ketamine. I think in the days in between there's still some plasticity that can really be more responsive, but I also think it just helps. We have some patients who are in residencies when they're getting ECT, and so they're getting regular psychotherapy and it really seems to make a big difference. It really does help us, and it also really helps us because we can talk to the therapist about, sometimes they're seeing improvement that we're not hearing about or we're not seeing, or side effects, just as importantly, that can really help guide it. I'm a big fan.

Dr. Brown: I agree with all those things from the TMS standpoint. I would just add as far as our protocols, we don't require that someone's in therapy, but highly encourage it during the course of TMS, that they stay on it after TMS. Medications, we really try to keep people to be on a stable dose of medications during the course of TMS. A lot of times people will feel like these aren't working, why would I even stay on them? Many cases when they do come off, they feel like, "Oh, wow, I didn't realize that they were actually helping some, didn't realize how much worse I could feel."

Typically, we'll tell people that we'd like to stay on. So if someone responds to TMS, we'll recommend that they stay on the same medication protocol, continue with

therapy, and as Steve pointed out, hopefully, be able to engage a little bit more with it. Even if they didn't have a 'response' a lot of times there's little changes. I gave you those response numbers, but I would anecdotally say like probably 90%, 95% of the people have some movement, some changes, and often those can open up the door to being able to grab, hold a little bit more of therapeutic engagement and perhaps response medications.

So we definitely encourage that people will continue to push in that after they finished EMS. Staying on medications after for at least six months is, not an evidence-based, but a general principle that many of us will tell folks.

Moderator: Wonderful. Well, thank you both so much, Dr. Seiner, Dr. Brown, and thank you to all of our listeners for your participation and your wonderful questions. Thank you to McLean Hospital for making today's webinar possible. A recording of today's presentation will be emailed to everyone in about two weeks. That email will also include a copy of the presentation slides.

As soon as the webinar has ended, a short survey will appear on your screen. We ask that you please take that survey and give us your feedback so we can continue to improve our program. With that, thank you again for your attention. Have a wonderful rest of your Friday and a great weekend. Thank you again, Dr. Brown and Dr. Seiner.

Dr. Seiner: Thank you.

Dr. Brown: Thanks for having us.

[01:00:31] [END OF AUDIO]