Quick Takes
A PODCAST BY PHYSICIANS FOR PHYSICIANS
HOSTED BY DR. DAVID GRATZER

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The past, present, and future of Neuromodulation with Dr. Daniel Blumberger

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[Musical intro]

David Gratzer:

> I remember how he looked on admission. The long, grey, unkempt beard. A deep sadness in his eyes. The team couldn't get him out of bed. We proposed ECT and, honestly, I was skeptical. It was transformative. He looked like a different person at the end of treatment.
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> The benefits of ECT of course are well established. So is the stigma. Is that stigma likely to fade with time? Is ECT itself growing less relevant in the age of ketamine and MST? What is the future of neuromodulation?

Welcome to *Quick Takes*. My name is Dr. David Gratzer. I'm a CAMH psychiatrist, and today we're joined by another CAMH psychiatrist, Dr. Daniel Blumberger. Dr. Blumberger is the scientific director of the Temerty Centre for Therapeutic Brain Intervention. He's co-chief of General Adult Psychiatry and Health Systems, senior scientist here, as well as holding the Temerty Chair in Therapeutic Brain Intervention. Welcome, Dr. Blumberger.

Daniel Blumberger: Thank you. And thank you for having me, David.

David Gratzer: I should disclose at this point in time that I'm the other co-chief of General Adult Psychiatry, and you and I might have had a couple of conversations over the years. Fair?

Daniel Blumberger: This is true.

David Gratzer: What got you interested in this field?

Daniel Blumberger: I think it was at my residency training and my geriatric psychiatry rotation where I had a patient who had a severe psychotic depression and had catatonia. And the primary treatment for psychotic depression and for catatonia is ECT and treating this patient, who was in her mid- to late-70s, was a tremendously rewarding experience. It was incredible to see the awakening and resolution of someone who was completely immobilized in bed with waxy flexibility and complete mutism returned back to her usual self. It was it was like, you know, being Oliver Sacks and discovering L-dopa. So, it was truly a kind of a very, very dramatic experience. And I think from that experience, I really became interested in ECT as a treatment for patients with severe depression and psychotic depression and other psychiatric disorders. And then in other phases during my training, I came into contact with people who were studying newer ways of stimulating the

brain and delivering electrical stimulation using a magnetic coil. And that treatment is called repetitive transcranial magnetic stimulation (rTMS). And I was fortunate enough to do a rotation with Jeff Daskalakis and then became very interested in that treatment and saw a potential avenue for using rTMS to treat older adults with late life depression. It was a new emerging treatment and people had not thought about using it very much in older adults. And that was kind of how I got my interest into rTMS and then it continued to expand and into other areas and neurostimulation treatments.

David Gratzer: And of course you're involved in a big centre that does do neuromodulation. Is CAMH the largest provider of ECT in Ontario?

Daniel Blumberger: I think we are the largest provider of ECT in Ontario. We might be the largest provider of ECT in Canada and one of the larger services in North America. There are other large centres in the US like McLean Hospital in Boston, but we're one of the largest centres in delivering treatments five days a week. You know, we have a large inpatient population here, but we also serve many, many outpatients.

David Gratzer: I remember when I was a psychiatrist at a community hospital in the GTA, I would send my patients to CAMH. You guys have quite the centre here and quite the expertise, including research. How many active trials do you have going on right now? Not just with ECT, but neuromodulation in general?

Daniel Blumberger: I think we're probably in the range of 20 to 30 active clinical trials at this point. And, you know, we're the Temerty Centre for Therapeutic Brain Intervention and we're expanded into the areas of interventional psychiatry, including IV ketamine, intranasal ketamine and s-ketamine, as well as psilocybin assisted psychotherapy are now all delivered within the Temerty Centre.

David Gratzer: And of course, metaphorically speaking, they're all your children. Is there a particular research project or research topic that's of particular interest or excitement to you right now?

Daniel Blumberger: It's hard to say that you prefer any one child over another, that they're all, they're all extremely important and relevant. You know, we just completed a large multicentre clinical trial that is exploring a new way of delivering ECT called magnetic seizure therapy. So, this essentially is the same procedure, but we're essentially inducing a seizure using a magnetic field. And because magnetic fields penetrate through the brain without being impeded the electrical field is much more focal. And as a result, the side effects of the treatment are potentially much lower than they are for ECT. And so that trial is a confirmatory efficacy trial that was conducted here in Toronto, UT Southwestern in Dallas and UCSD in San Diego. And I think the results of that trial will be really important with respect to identifying whether or not magnetic seizure therapy is clinically similar to ECT, without the cognitive side effects that could come with ECT.

David Gratzer: Let's return to MST in a moment. But before we talk about MST, let's talk about ECT, which is maybe the oldest treatment in psychiatry and perhaps the heaviest stigmatized treatment in psychiatry. I can't recall how many conversations I've had over the years where patients have objected, or family members have objected. What do you think the stigma comes from?

Daniel Blumberger: Well, I think the stigma comes from several places. One, you know, in its development ECT has gone through a number of changes. In its early incarnation, there were elements to the way the treatment was delivered that caused a lot more side effects than the way it's currently delivered. ECT has evolved. It's not the same treatment that it was in the 50s and 60s. I think in general there's some pretty negative depictions of ECT in the media, most notably "One Flew Over the Cuckoo's Nest" and where ECT is depicted as a punitive treatment. And, you know, if you look across media and the depictions, if you ever want to conceive of an evil psychiatrist, it's the evil psychiatrist delivering ECT. But in fact, you know, it's a lifesaving treatment, that has been the most effective treatment over time. Having said that, it's a very effective treatment but there are some costs. The cognitive side effects associated with ECT, even with the most advanced types of treatment that have been developed in recent years still causes cognitive side effects in a

fair proportion of people. Some people have none, but some people have cognitive side effects that are troubling to them. And so, the stigma also relates to a real adverse effect of the treatment.

David Gratzer: True though, people tend to think the absolute worst of ECT. There's that American survey data suggesting 1 in 5 patients think ECT might lead to their death.

Daniel Blumberger: Yeah, well, we know that that's absolutely not the case. You know, we've demonstrated using thousands of patients that in fact, actually you're likely to live a longer life if you have ECT and severe psychiatric illness or severe depression. And as far as medical treatments go, it's the safest medical procedure in all of medicine. The risk of something bad happening and dying, that is no greater than the risk of having a general anesthetic.

David Gratzer: What are some things that you've said to patients that you find effective in allaying some of those concerns?

Daniel Blumberger: Well, I say just that. I say that, you know, this is the safest treatment in medicine, that, we have a very caring team that takes care of every aspect of the treatment. They are monitored throughout the treatment. The outcomes and chances of things not going well are much greater if the depression or the other psychiatric illness is left untreated and continues to persist.

For example, if someone has a severe catatonia and they're mobilized in bed, there is a high potential that person is going to have a deep vein thrombosis (DVT). And potentially that could lead to a clot that causes pulmonary embolism. So, you know, which in fact was the case with the patient that I first talked to you about. The patient was so ill that they developed DVT and had a small pulmonary embolism. So, there are serious risks. The illnesses that we treat are lethal and ECT reduces the severity and actually reduces the morbidity from the illnesses that we treat.

David Gratzer: In terms of cognitive effects: while significant and in fact a deal breaker for some of our patients, the real-world data you collect shows 18% get cognitive issues and about half of them choose to opt out of ECT. Is that about right?

Daniel Blumberger: I think a much larger proportion decide not to pursue ECT because of the fear around the cognitive side effects. The reality is the vast majority of patients have a disruption in their memory because ECT disrupts the ability to lay down new memories. And ECT happens over a period of weeks. And so, as a result, there is a period around the time of the treatment that it ends up being permanently hazy to people who have a course of treatment. Now the size of that memory impairment is sometimes small, sometimes it's much larger, depending on the kind of ECT that length of time the person was ill leading up to the treatment, so it's multifactorial with respect to the severity of the cognitive adverse effects of the treatment.

David Gratzer: The CANMAT depression update came out in the spring. You are, of course, a co-author, and despite all the advances in medications and therapies, ECT is still a first line recommendation for severe depression.

Daniel Blumberger: 100%, as well it should be. I think if someone is in hospital with a severe depressive episode, they should be receiving ECT. They should at least be offered ECT because the chances that they have a good outcome and get better are much, much greater if they have ECT. We've done a study that has demonstrated that the risk of suicide death is reduced by half if you're an inpatient with depression and receive ECT. So twice the risk of dying by suicide if ECT doesn't happen when someone is an inpatient. It's pretty powerful, the effect of ECT, at reducing morbidity and mortality.

David Gratzer: With regard to people who don't have a psychotic depression, aren't in hospital, ECT is still effective, though maybe not as effective as earlier studies had found it.

Daniel Blumberger: Yeah, I think that the kind of declining remission rates over time that are being published in studies relate to a number of factors. For one, we actually have a lot of newer treatments that are available. There are treatments like ketamine. There are treatments like repetitive transcranial magnetic stimulation. There have been a number of new antidepressants released and strategies to augment and switch are pretty well entrenched. And patients are coming and considering ECT much later in the course of their illness. And we know that the longer patients struggle with depression, the more nonresponse they have to various interventions, the lower the likelihood is that they will respond to subsequent treatments, including a treatment like ECT. So I think that's partly responsible for what we're seeing and why it's harder to get some people better.

David Gratzer: You're raising alternatives, of course. rTMS is something that you've been involved in and published widely, and how enthusiastic are you about results around different approaches to rTMS, including theta wave?

Daniel Blumberger: I think rTMS is an essential evidence-based treatment for people who are not responding. And I think it's probably a treatment that should be used earlier in the course of illness because it works better for people who are in the moderate range of depression with fewer treatment failures. It's a very well tolerated and safe treatment, and most patients would prefer an option that comes with very little side effects and has a good chance of getting them better than trying other treatments that have a greater chance of causing adverse effects and may not be as effective. I think it's also a treatment that has tremendous potential to be a precision-based treatment that is personalised to the underlying pathology in each individual. We know that depression is not a singular construct, that depression is a very heterogeneous illness, and that the presentation may be similar, but the underlying biology might be very different. And so, I do think that with refinements in our understanding of how the brain works and identifying functional neurocircuitry within the brain using neuroimaging or neurophysiological techniques, we may be able, in the relatively near future, to be able to precisely deliver the right treatment to each patient based on their own individual underlying pathophysiology.

David Gratzer: Yet there's hesitation around public funding in Ontario and across Canada, in fact. How frustrating is that to you?

Daniel Blumberger: Well, it's frustrating to see that an evidence-based treatment that's widely available across the globe in every developed and some developing countries, is not readily available to people of Ontario. I think while it is available, we don't have an integrated system to be able to deliver it in an accessible way. I think there is interest and I think there is a commitment to fund a provincial program to deliver rTMS, and I've been a strong advocate for such a program and hopefully that will be coming soon. Many provinces are investing in provincial programs. In fact, probably Ontario will be one of the last to adopt it from a public system standpoint. So, it's been frustrating, but I have great hope for the future.

David Gratzer: Let's pivot. You talked about MST before. There's of course, that big paper published in *JAMA Psychiatry*, Deng et al, which talked about the potential of MST having the upside of ECT; good response, without the downside. So autobiographical test was what they used in the study, which of course is the standard cognitive test. How enthusiastic are you about MST?

Daniel Blumberger: I'm very enthusiastic. I believe that MST is potentially a first line convulsive therapy that, you know, we talked quite a bit about patients not wanting to consider ECT but some of those patients are likely to consider MST because of the likely better side effect profile. And even if it's not quite as good as ECT, but similar, I think patients would still, benefit from, trying that treatment as it may be a way to get them better. And particularly if patients have a belief that a treatment can be helpful, I think it could be very effective for patients. Similarly, you know that we see patients who say no, no, ECT is the right treatment for me, that's what I want. And so, I think it could be a potential first line, convulsive therapy.

David Gratzer: Do you think over time, and again these are early days, and we'll need more data, it has the potential to replace ECT as the go to treatment?

Daniel Blumberger: I don't think ECT will ever be replaced. I think ECT is too effective. I think even if MST becomes a treatment option, there will still be patients who need to consider ECT. There are some patients that may need to go straight to ECT because their depression is so severe and ECT likely works faster than MST, requires fewer treatments and in certain cases you would want someone better very quickly rather than waiting a little bit longer for a different treatment to work. So, I think we need more options. I also think that there may be people who may benefit tremendously from ECT and may not have cognitive side effects. And I think through our work on trying to identify predictors of both response and predictors of cognitive adverse effects, we may be able to identify people who are likely to have a good outcome without cognitive adverse effects. So, we may be able to personalise whether someone should go to MST or should go to ECT. So, I think these things are all part of the advancements that are occurring in psychiatry on the precision medicine side.

David Gratzer: Ketamine is having a moment many different applications of ketamine, including for treatment-resistant depression. There's the Anand et al paper which actually does a comparison with ECT. Now of course it's a bit of a different depression study than others involving ECT in that it's nonpsychotic depression, more of an outpatient population, but you know, credit where credit is due, ketamine does well. How enthusiastic are you about ketamine?

Daniel Blumberger: Well, I think, patients are interested in ketamine. And I think, ketamine has demonstrated some powerful effects in patients who are not responding. You know, the comparison study was really comparing the early phases of treatment and that the outcomes were similar in the early phases of treatment only within a nine-session course. And I think in that duration of span ketamine was as good as ECT and that's important to know. Again, I think you're right that that the population in that study were a population of people who probably predominantly wanted ketamine. So, there were effects probably skewing the outcomes in that regard. But nonetheless, I think it's a potentially a very promising approach. Again, we need to use the tools that we have at hand to help patients, particularly if patients are interested in them. There are things that we need to know about ketamine, particularly with respect to its durability over the long run. We have lots of data on ECT and how to prevent relapse and how to space out treatments in a relapse prevention way. But we don't have that information at the same way for ketamine.

David Gratzer: And in fact, one of the many, many, many trials, that your centre is involved in right now is looking at ketamine versus ECT comparison. Yes?

Daniel Blumberger: Yeah. So, we hope to begin enrolling participants. We're excited to be part of a next iteration of that ketamine versus ECT comparison, as it's specifically asking the question whether ketamine is similar to ECT with respect to its effects on reducing suicidal ideation. I talked a little bit about how effective ECT is in reducing the risk of suicide death, we know it's extremely effective reducing suicidal ideation as well. It's, you know, if ketamine is going to be considered alongside ECT as an option for patients with suicidal ideation, we need to know how it performs relative to ECT. So, I think it's a very important question that needs to be answered.

David Gratzer: If patients today ask about ketamine, what are some of the cautions you might advise them of?

Daniel Blumberger: You know, it's not for every patient, certainly not for patients with psychotic depression. There are risks with respect to blood pressure. But most of those risks can be managed. I think there's a little bit less known about ketamine's effect and durability. So, while it may work very quickly, the question around its effect and sustained effect over time is an important one. And if it does work for a patient, figuring out how to keep it working is important.

David Gratzer: Dr. Bloomberg as you know, it is a tradition of *Quick Takes* that we close with a rapid-fire minute with a series of questions. Are you ready?

Daniel Blumberger: Ready.

David Gratzer: Okay. Let's put a minute on the clock and just a few more questions.

What's the one biggest thing you'd like clinicians to know about neuromodulation?

thinking about it late. To think about it early in the course of their patient's illness and referring them sooner rather than later as the outcomes are likely a lot better.

David Gratzer: Biggest research question on your mind today?

Daniel Blumberger: The question around personalizing treatments and particularly personalizing rTMS. A lot of work has been done. Colleagues have conducted really groundbreaking work with respect to figuring out the underlying circuitry that is potentially targetable with rTMS. And advancing work with respect to understanding the brain state and being able to pair our stimulation to the underlying brain state. I think those are the two most important questions. So where in space and where in time do we target rTMS? And I think, answering those questions is going to lead us to being able to personalise the treatment and get a much larger proportion of patients better with that treatment.

David Gratzer: So, hopeful about the future?

Daniel Blumberger: I'm very hopeful. I think we're on the precipice of being able to advance personalised treatment like other fields of medicine. I think that that is really on the near horizon for us in psychiatry, and it's very exciting to be part of it.

David Gratzer: Now we're at the buzzer. One last question. Some time has passed since you treated that geriatric patient in residency. Are you still sometimes amazed by the results of neuromodulation, including ECT?

Daniel Blumberger: Absolutely. It's a tremendous privilege to be able to work with these treatments and to see people's lives changed where they had struggled for so long leading up to the treatment and the dramatic nature of the responses from people who are so severely ill to being back to their usual selves is a tremendous privilege to be part of.

David Gratzer: And on that note, I'll thank you for your time in explaining this neuromodulation update. Also thank you, doctor to doctor, for taking care of so many of my patients over the years and for helping so many of them get better.

Daniel Blumberger: Like I said, it's a privilege to be part of the care for those patients. Thanks, David.

David Gratzer: Thank you, sir.

[Outro:] *Quick Takes* is a production of the Center for Addiction and Mental Health. You can find links to the relevant content mentioned in the show and accessible transcripts of all the episodes we produce online at CAMH.ca/professionals/podcasts.

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