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Deep Brain Stimulation for Treatment-Resistant Depression

DEEP BRAIN STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

You are listening to ReachMD, The Channel for Medical Professionals. Researchers have been busy defining neural network models of mental illness for decades. The progress that has been made in defining the areas of the brain that play a large role in depression are leading to exciting new approaches for diagnosis and treatment. Welcome, I am Dr. Cathleen Margolin and joining me from Atlanta is Dr. Helen Mayberg, Professor of Psychiatry and Neurology at Emory University School of Medince. Dr. Mayberg studies over the past 20 years in neural network models of mood regulation in health and disease have led to the recent development of a new intervention for treatment-resistant patients using deep-brain stimulation.

DR. CATHLEEN MARGOLIN:

Welcome Dr. Mayberg.

DR. HELEN MAYBERG:

Good to be with you.

DR. CATHLEEN MARGOLIN:

As it became clear that area-25 plays a significant role in depression, you also began working with some colleagues, who were doing ground-breaking work using deep-brain stimulation for Parkinson's. Tell us about their work and why it made so much sense to generalize their findings to your work with depression?

DR. HELEN MAYBERG:

Well you know, one of the things that is very clear in research is, nothing is ever totally new. It is really about being in the right place at the right time and actually putting together available technologies and one of the lucky breaks we had at the point that our models of depression were becoming more focussed was the fact that for the previous 10 years, there had been a whole line of research in the study of movement disorder and the use of brain stimulation to modulate basal ganglia dysfunctional circuits in Parkinson's patients, who had become refractory to dopamine medications. So again, I mean this goes again back to our earlier studies on Parkinson's and depression. When I was at Hopkins, Mahlon DeLong and his colleagues were studying the intricacies of the neural circuits of the basal

ganglia that regulate motor control and they had models of Parkinson's disease that they could develop and actually test, how do drugs work, what were the nodes in this motor control circuit, what changed when an animal or a person become parkinsonian and that was the basic science ground work for why should stimulation in the subthalamic nucleus or globus pallidus alleviate Parkinsonian tremor and rigidity when Sinemet or other dopamine-agonist drugs failed to do so after they had done so for many years and so the notion of a circuit model was quite frankly an experimental model that we had there at Hopkins with our colleagues and so in the intervening years, between when we first were studying depression and Parkinson's and later when we were doing cognitive behavioral therapy and drug effects in Toronto, if fact, DBS for Parkinson's disease had become a routine procedure and what is required is the ability to stereotactically and precisely localize a very tiny wire into a very precise location in the brain and in Parkinson's disease that is done not only with MRI and visualization of the anatomy, but also with physiology and knowledge about the electrophysiology of the subthalamic nucleus. There was no data about area 25 and its electrophysiology, but we had a lot of information about the nodes and other remote areas in the brain that area 25 talked to. So literally it was trying to determine is could we apply this well developed technology used for Parkinson's to a different circuit in the brain. So same technology, different circuit.

DR. CATHLEEN MARGOLIN:

And you were able to try deep brain stimulation on a few severely depressed patients?

DR. HELEN MAYBERG:

Exactly so Dr. Andres Lozano, who is our very well known stereotactic neurosurgeon for many applications of DBS for neurological disease, he was at my institution in Toronto and literally because we had this network mapped out, we met at a neurosurgical meeting where I was giving a more general view of depression in the brain to these neurosurgeons in the context of actually lesions of the brain that are done for intractable patients in very rare circumstances, cingulotomy for instance and raising the possibility of could one apply brain stimulation in the same way that brain stimulation was applied in Parkinson's instead of doing lesions and literally you know we sat down to discuss, is it possible that you could target this brain area safely and Dr. Lozano said that in his mind this was a targetable brain location and we basically used the logic and the current state-of-the-art in Parkinson's disease including just what was the thought on how to use the frequency of stimulation to turn down the brain or turn up the brain, you know it turned out it was probably wrong based on what is now known about DBS mechanisms, but actually set up a hypothetical kind of model system and said if we can go here safely, here is where we would want to go. Here is what we want to do and then developed a protocol and proceeded to recruit patients, who quite frankly had failed everything else. So we wanted patients who had been sick long enough, so that we wouldn't run into the natural history of illness, which is that over time many patients recovery spontaneously, so that we could ensure that patients had been given a fair shot at every available treatment so that we weren't jumping the gun and offering them something that actually not only might not work might have unexpected side effects. So we really wanted them to have maximized all available conventional treatments before being considered potential candidate to try this out.

DR. CATHLEEN MARGOLIN:

Right these are genuinely treatment-resistant people and I have noticed in your most recent study that you excluded suicidal patients, why is that?

DR. HELEN MAYBERG:

Again that's more of a practical situation. You know when you start an experiment, so even now second paper report on 20 patients followed at a year. But this is still in the context of an open study, proof of principal safety. You know what is it that happens when you implant in this location and apply constant current for a continuous period of time. What happens and are there side effects that develop over time. Do you lose the effects. Does the effect happen rapidly in everyone. Is there greater defect. Because we really didn't have the

same markers that are observed in Parkinson's where as soon as you put it in, internal on the current, at a particular frequency, tremor stops. You know you are in the right place.

DR. CATHLEEN MARGOLIN:

Right.

DR. HELEN MAYBERG:

We didn't know if we would have an acute effect and even when we do, we didn't know if it was prognostic of an optimal location or prognostic of long-term effect. So when you are trying to think about the upside and the downside to an experiment, one wants to make sure that a patient can get through the experiment because you really have to set up <_____> hypothesis that this isn't going to work and that one wants to have patients that even though they are extremely and devastatingly ill, what's remarkable about patients, who haven't killed themselves up to this point is that they are in a stable almost purgatory state. They are so ill so long that that's really all they know. So in fact, they are in extremis because none of us would want to be that ill, but in fact, they are in sort of a low equilibrium state.

DR. CATHLEEN MARGOLIN:

Right.

DR. HELEN MAYBERG:

So while there is no depressed patient in that state, who doesn't have thoughts much of the time, you know, if this is how I am going to be indefinitely and I can't imagine myself any other way, I really would be better off dead. That is very different from having an active suicidal plan and intent.

DR. CATHLEEN MARGOLIN:

Right.

DR. HELEN MAYBERG:

And I think from a pragmatic point of view if we don't know what the natural history of our intervention is, seeing this as an acute treatment or a rescue treatment would be totally beyond the data.

DR. CATHLEEN MARGOLIN:

If you have just joined us, you are listening to ReachMD, The Channel for Medical Professionals. I am Dr. Cathleen Margolin and my guest is Dr. Helen Mayberg, Professor of Psychiatry and Neurology at Emory University School of Medicine.

Dr. Mayberg, you have had 4 years now to follow the first patients, who received this treatment, how are they doing?

DR. HELEN MAYBERG:

Actually the first patient was operated in May 2003 and, in fact, she had a battery replacement in June of this year and is doing well. So that patients who did well have continued to do well, but it is very clear that isn't like you correct the problem with treatment for a while. It really is behaving like some sort of a pacemaker and I say that not mechanistically, but the fact that if the battery wears out or if it turns off after about 2 weeks you lose the effect that patients become slow. We have been looking at Emory at some blind discontinuation studies where we actually plan to turn off the electrode at a point in time when patients are well and it creeps up on them. They are not aware that the stimulator is turned off. There is no acute rebound effect. It is very clear that whatever this is doing mechanistically it's creating a new rhythm that allows normal brain function to work around it, because if it is not there, patients will relapse. Now on the flip side, we aren't seeing side effects developing over time and like I said, we have got at least first 6 patients that are all of them close to 5 years. You don't lose the effect over time, you don't develop side effects over time, so there is no tardive dyskinesia or some kind of delayed side effect at least up to this point and so once it's on, it is out of your mind and patients have done remarkably well. They haven't relapsed, they can have periods particularly if they have life essence where they certainly have preserved mood regulation. This doesn't take away the dynamic range of ones mood, but in fact, they describe being more resilient. They can get through life stressors in a way they could not prior and we haven't had frank relapses and I think that is what's most interesting scientifically is you know there may be a number of ways you can get people out of an acute episode. I mean ECT can get people effectively out of episode, but it is not very good at keeping you there, particularly as you get more intractable in your illness.

DR. CATHLEEN MARGOLIN:

Well it is fascinating research and I think the questions sound like they are endless. Thank you for the great conversation Dr. Mayberg.

DR. HELEN MAYBERG:

It was good talking to you.

DR. CATHLEEN MARGOLIN:

Thank you for listening to The Clinician's Roundtable on ReachMD, The Channel for Medical Professionals. I am Dr. Cathleen Margolin and my guest has been Dr. Helen Mayberg, Professor of Psychiatry and Neurology at Emory University School of Medicine. For comments and questions, send your e-mail to xm@reachmd.com and be sure to visit our web site at reachmd.com featuring on-demand podcasts of our entire library.

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