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Titrating and Dosing Device Therapy for DRE: Best Practices for Optimizing Patient Outcomes

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[CHAPTER 1: ADULT PATIENT CASE]

Dr. Becker:
Welcome to the first chapter of this education series. We're reviewing the use of vagal nerve stimulation in both adult and pediatric patients with drug-resistant epilepsy, or DRE. Stay with us for the best practice strategies for titrating and dosing to specific patient parameters.

This is CME on ReachMD, and I'm Dr. Danielle Becker. I'm the Medical Director of Epilepsy at the MetroHealth System in Cleveland, Ohio, and I'm an associate professor at the Case Western Reserve University School of Medicine.

Dr. Stern:
And I'm Dr. John Stern. I'm Professor of Neurology at the Geffen School of Medicine at UCLA and the Director of the Epilepsy Clinical Program.

Dr. Becker:
So each year, [40,000] adults and [26,000] children are diagnosed with drug-resistant epilepsy. This is when a patient continues to have seizures despite trying 2 or more medications at adequate doses. The thought is if they've tried 2 or more medications at adequate doses, that if that doesn't help their seizures, the likelihood of a third, fourth, or fifth medication helping control their seizures is less than 5%. And for many of these patients, they will turn to neuromodulation, specifically an implantable vagal nerve stimulator, also known as vagal nerve stimulation, or the VNS.

So now we're going to talk about our approach to initiating VNS therapy. John, can you tell us how you start a patient?

Dr. Stern:
Certainly. I think the approach after the patient has received the implantation is a reminder to the patient that this is a treatment that requires titration or adjustment just like any medication requires adjustment or titration to find the best dose for the patient. Of course, we have understanding of what might be the best target parameters, but we also have to think about the timing of reaching those parameters, and we have new information about this. In a publication last year, 2022, by Tzadok and colleagues, there was an analysis looking at the timing of reaching that optimized set of parameters with the finding that it can be reached in 3 months without compromise to the tolerability for the vast majority of patients. A slower titration has been used in the past, and when I started using VNS, I had a slower titration where often I would take 6 months to get to target parameters with the idea this would allow for better tolerability. So it was interesting to see that their analysis showed that a faster titration is possible, and, of course, the benefit of this is bringing patients to

settings that can have maximal impact on the seizure control in a faster fashion.

Dr. Becker:
So one of the parameters, I think, that's most important is the AutoStim parameter. What this does is it highlights that we know that 80% of seizures can start with an increased heart rate, and so what the VNS does with this AutoStim feature is it actually senses for a rapid increase in heart rate above baseline, and when you're setting the device, you have an option of how sensitive you want that increase to be above baseline. And so I actually set everyone at 20%, and initially, I didn't fully realize the difference between 20% and 40% sensitivity above the baseline heart rate, but what 20% means is that when that baseline heart rate goes up 20%, that is when a stimulation is sent. What that means is that you are sending a stimulation to interrupt that abnormal electrical activity as soon as possible. So for me, I set everyone at 20% because I want to make sure that if we're going to try to stop the seizure or shorten it, we can do it as soon as possible, ideally before the patient even feels any clinical sign of the seizure.

Dr. Stern:
So I think the next step in the adjustment of parameters is thinking about the amplitude, which is the current that's being delivered through the stimulation. And typically this is set to 0 when the patient leaves the operating room, and it's during that first visit that we begin the adjustment of current. In the early days of VNS, we didn't have much guidance as to what should be the target current, and sometimes people had the idea that more was better, but we quickly learned that that wasn't the case. And there was a realization years ago that currents greater than 2 or 2.25 milliamps didn't provide much greater seizure control than lower currents, but a paper from Fahoum and colleagues, in 2022 that is, showed that perhaps an even lower current of 1.75 milliamps could be considered. Their analysis was a statistical modeling of the clinical data we have from VNS trials and showed that a target of 1.6, which is close to 1.75, demonstrated benefit, where going beyond that, there was a drop off in benefit.

Dr. Becker:
So I actually do something similar. What I do is I target 1.75. So as I mentioned, I have the patients come back every 2 weeks to titrate up to maximal parameters or optimal parameters at 14 weeks, and what I do is at that last visit – visit 7 – I put the output current to 1.75, and now I know I could even put it to a little bit lower. But I put it to 1.75, and then the other thing that I do, that was actually also supported by Dr. Fahoum's paper, is I put the duty cycle to 16%. What duty cycle is the amount of time that the device is on in the day, and when you're first titrating the device, typically the device is on about 10% of the day. I put the output current at 1.75, and I put the duty cycle at 16 just to make sure it's on a little bit more, and it's nice to see that that was actually supported in scientific literature.

Dr. Stern:
The other parameters to think about are the pulse width and the frequency. The pulse width is the duration of each stimulation because the VNS does not provide a direct current continuous stimulation, and it can provide stimulation in pulses of electrical stimulation, and this was 500 microseconds initially, but we now know that 250 microseconds may be better optimized for eliciting a response from the nerve while also preserving the battery.

The frequency was initially thought to be best at 30 hertz, and that was what was tested in the trials, but long-term observational experience shows that lower frequencies are better tolerated and also preserve the battery. And now convention is that 20 hertz may be ideal, and this was mentioned in Fahoum's paper as well in that 20 hertz may provide a better evoked potential, and that is, lower frequencies may produce a better vagus potential than higher frequencies of 200 hertz.

So these are all parameters that can be adjusted in the office, and there's another opportunity here with the current devices, which is scheduled programming. Do you want to talk a little bit about that, Danielle, in your experience?

Dr. Becker:
I do want to bring up scheduled programming, and I have to say that after COVID, I probably started utilizing this a lot more and realized the benefit for our patients, so because of COVID and the fact that I work with an underserved population where it may be very hard to get to their office visits. So with the scheduled programming, what it lets you do is the patients will come in for their initial visit, and then you can actually schedule the device to self-auto-titrate every 2 weeks or a half step every week, depending on how you like to program it, up to the optimal parameters that we've talked about today. So I'll check in just to make sure how they're doing, but otherwise, I can see them after it's auto-titrated and then allow that neuromodulation to take effect and also allow the titration to happen in less than 3 months' time, which we've already talked about shows a huge benefit in optimizing settings and also in outcomes.

Dr. Stern:
And it's all about outcome, isn't it? So what do you think are some key takeaways from the new data on VNS? I think one key point is that we don't need to go to the highest settings in order to get the best response for seizure control, whereas lower settings – an amplitude of 1.75, a frequency of 20 hertz, a duty cycle of 16% – can provide efficacy while also minimizing side effects and allowing for a faster acquisition of the settings over the titration.

Any thoughts you have, Danielle?

Dr. Becker:
You know, we talked about, earlier, about optimizing treatment, and you want to make sure that the patient gets the right dose and with the 2 papers that we discussed today, we actually can see that this is supported in scientific literature. The other take-home point that I want to stress is the AutoStim feature. I think this is one of the most important features to highlight because it allows the VNS to be responsive to a patient's seizure. Especially if their seizures start with increased heart rate, it allows a responsive stimulation to be sent as soon as possible and ideally stop that seizure before it becomes even clinical to the patient.

Dr. Stern:
Absolutely. This has been a great conversation.

Dr. Becker:
Thank you so much, John, and thank you all for joining us. Please stay tuned in Chapter 2 where there will be a discussion on dosing and titrating the VNS in a pediatric patient with drug-resistant epilepsy.

This is CME on ReachMD, and I'm Dr. Danielle Becker.

[CHAPTER 2: PEDIATRIC PATIENT CASE]

Dr. Abdelmoity:
Well, welcome everyone. In Chapter 1, we walked through the dosing and titrating VNS in an adult patient. In this chapter, we'll go through the dosing and titration in a pediatric patient and address some of the differences between an adult and a pediatric patient.

My name is Ahmed Abdelmoity. I am Director of Neurology at Children's Mercy Hospital, University of Missouri at Kansas City.

Dr. Holder:
Hi, I'm Dr. Deborah Holder, and I'm a pediatric epileptologist at Children's Hospital Los Angeles, University of Southern California, and Program Director for the Pediatric Epilepsy Fellowship.

Dr. Abdelmoity:
Let's go ahead and get started. So, Debbie, can you please go ahead and give us an overview of one of your pediatric patients? I know you have a vast experience with VNS. If you can give us some highlights of your approach of how do you titrate VNS, and what's the best practice for dosing and titrating of VNS in a pediatric patient?

Dr. Holder:
I'd be happy to. I have a patient I just saw this week who has VNS that was implanted a few years back but has had a really nice response. I'd like to share a little of her story. She initially got her VNS implanted, and we like to use a fast-titrating program at our institution. So we immediately started her on scheduled programming where she was titrated up by .25 milliamps every 2 weeks. So this is a nice feature of the new VNS's that allow you to do scheduled programming, which we found really beneficial. So every 2 weeks, her VNS up-titrated .25 milliamps without her needing to come into the office to see us. We saw her back after 5 of these up-titrations in about 10 weeks, and we were able to see that she had tolerated her program without any difficulty, and she was already up to what would be considered a therapeutic dose. And to our surprise, her seizures had already really decreased significantly. What we found most beneficial for this young girl – she was about 10 years old when we implanted her – she had a problem with really long seizures. Every time she seized, her seizures were prolonged, requiring her to go to an emergency room, and with the new VNS, her seizures had stopped really quickly after they started, and she had not had any trips to the emergency room since she had gotten her VNS implanted. The combination of that autostimulation feature, which senses seizures, turns on, and fires, and the magnet to supplement when the dosing levels were still at a low point enabled her to stop the seizures very quickly and not have to be taken to an emergency room.

So this was a really good goal of the initial titration to get the output currents up to a dose that works really quickly and enable her to have a nice response of her seizures being shorter in that really short time frame.

Dr. Abdelmoity:
Well, thank you, Debbie. This is actually an interesting perspective, and it's something that we actually see quite often in our patients. And as you mentioned, the seizure burden – not just the seizure frequency – it's the frequency, the duration, severity, and the postictal period improve. You mentioned something that's very, very important, which is the scheduled programming, something, especially during the COVID, that we have to ration some of the patients that will or can come to the hospital, in addition to a level of convenience that adds to families not having to drive or miss appointments. So it adds another level of adherence or compliance. And to your point, as mentioned in Tzadok's paper, that fast titration, it's worth trying to get to that therapeutic window which the paper by Dr. Fahoum kind of really talked about how at different levels – that 1.5 or 1.75 all the way up to 2.25 milliamp – you're going to have different tiers of

patients that are going to be responding to those levels. So it's not just the fast titration, but it's also the ability to reach that therapeutic window while continuing to make sure of the tolerability.

Dr. Holder:
Yeah, I agree completely. Our goal is to get our patients to the dose that we think is effective, which I think we all agree is in that 1.5 to 2.5 milliamp range, and we want to get there as quickly as possible. I found that most of my patients tolerate that up-titration every 2 weeks by .25 milliamps. And how better to do it than at home and not require our patients to come into the clinic every 2 weeks? So if we can get to that goal dose as quick as possible, we can really achieve the best seizure control for our patients.

Dr. Abdelmoity:
That's absolutely the goal, and one of things that you mentioned about your patient, which is more noticeable now with the autostimulation model, is that early response, even though we always will tell our families and that's the expectation, is that within 12 months – so 12 months is when we start to see the full efficacy, but with the autostimulation, we're starting to see this much, much sooner, and that's been very clear through many publication by Hamilton and others.

Dr. Holder:
The other thing we should probably mention is side effects, which do sometimes occur with the VNS. Although they're usually mild and only occur when the VNS is in the "on" mode, there are some things we can do to decrease the side effects that were seen. The things that I like to work with when I see side effects is, first, I adjust my frequency, which is what I find gives me the best control of side effects with the least impact on efficacy. Generally, we can decrease that frequency from 30 hertz to 20 hertz, and usually you'll get a nice response in your side effects if you're seeing any change in the voice or any coughing, if the patients are experiencing that. The other option you can do is decrease your pulse width. You can change your pulse width from 500 microseconds to 250 microseconds and get even a bigger response if you're having side effects.

Dr. Abdelmoity:
What's interesting now and what's unique about pediatrics is they tend to actually tolerate the rapid titration or the faster titration a lot more than adults as quoted in the Tzadok's paper. One of the things that I also do is, even before addressing any of those side effects, is trying to ask some quality of life questions. Is it really affecting quality of life? In which case, sometimes it might need just some reassurance and some medication.

Dr. Holder:
The kids are really quite robust in their toleration of whatever we do and really seem to be quite tolerant of the VNS, which has really made it very useful in this population of patients. We should also mention the scheduled programming can be used even after that initial titration. But you can even use it later in your programming. Once the patient gets up to 1.5, if you think they need a little bit higher, you can use scheduling programming then. So it's really customizable to each individual patient.

Dr. Abdelmoity:
Well, Debbie, so what are your thoughts on duty cycle? And when you start adjusting duty cycle, how far into the programming that you start utilizing duty cycle for better efficacy?

Dr. Holder:
So, you know, our first goal is to get that output current up to the dose where we really think it allows VNS to work, which would be that 1.5 to 2.25 range. After I give the patient a little time there to see how seizures are going to respond, then I start working with my duty cycle, which is an estimate of how long the VNS is on during the day. We start off the VNS with a 30 seconds on, then 5 minutes off at about a 10% duty cycle, but you can really maximize that up closer to 50% or even a little bit higher. So I usually start working with duty cycle maybe 6 months into using VNS, and we slowly increase duty cycle, usually by decreasing off time, and you can do that every 3 months and see how the patients respond.

Dr. Abdelmoity:
Well, this has been really great. Debbie, it's always a pleasure to talk with you again and also how we're aligning with what's in the literature. What are takeaway things that you would like people to take out of this chapter?

Dr. Holder:
I think the most important thing is to make sure you get your patient's output currents escalated quickly, that you're not wasting any time, and if – that really the key thing you can use to do that is scheduled programming. So really use that scheduled programming, get the output currents up, and really have that goal dose be between that 1.5 and 2.25. And our whole goal is to really control seizures in these kiddos, and we need to get that dose where it needs to be really as fast as tolerated.

Dr. Abdelmoity:

This is great, yeah. Well, unfortunately, that's all the time we have for today. So I really want to thank our audience for listening in, and especially thanks to Dr. Holder for joining me and sharing the very valuable experience with all of us and those insights. I also want to thank Dr. Becker and Dr. Stern for providing their perspective on the best practice for VNS in an adult patient. It was a great pleasure speaking with all of you today, and I appreciate you tuning in.

Dr. Holder:
Thank you.

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