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### Mechanism to Match: Choosing the Right VMAT2 Strategy for the Patient

#### Announcer:

Welcome to ReachMD. This activity, titled **"Mechanism to Match: Choosing the Right VMAT2 Strategy for the Patient"** is provided by **Global Learning Collaborative**.

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#### Dr. Anderson:

When you're treating TD, how do you decide what's the right approach for each patient? This is CE on ReachMD, and I'm Dr. Karen Anderson from Georgetown University.

#### Dr. Fernandez:

And I'm Dr. Hubert Fernandez from Cleveland Clinic.

#### Dr. Anderson:

Hubert, how do you personalize treatment for your patients with tardive dyskinesia?

#### Dr. Fernandez:

Well, each patient presents differently, right? So the severity of tardive dyskinesia is probably the biggest factor in deciding what treatment options there are for your patient. The severity, and even more importantly perhaps, is how it affects them and the disability that it causes.

Assuming that it is severe enough, and it is disabling enough or bothersome enough, and you have decided to treat them, the first rule is to decide or to determine whether the offending dopamine receptor-blocking agent is actually needed or can be lowered. Assuming that it is already as low as it can be, or it cannot be adjusted because of the risk of exacerbating the behavioral condition, then you're actually left with 2 FDA-approved VMAT2 inhibitors.

We have 2 now. One is called deutetrabenazine, and the other one is called valbenazine. I think these are the 2 best medications we have for tardive dyskinesia. The older predecessor of this, tetrabenazine, is far less available and is actually less tolerated than these 2 newer VMAT2 inhibitors.

Now, selecting between the 2 is almost like a coin toss. Sometimes the payers or the patient's insurance would have a preference, and that would make your decision a lot more straightforward.

Now, assuming that the patient's insurance would be open to 1 or the other, 1 clear difference between deutetrabenazine and

valbenazine is the dosing and the titration, or the spectrum, of the dosing. What do I mean by this? In deutetrabenazine, you start with 12 mg per day, and every week or so, depending on the control of tardive dyskinesia symptoms, you can increase by 6 mg up to a total of 48 mg per day. So that's a big spread. Valbenazine, on the other hand, really has for the longest time just 2 doses, 40 mg per day and 80 mg per day, and more recently they now have a middle dose of 60 mg per day.

Regardless, it's just 3 steps, whereas you have a lot more steps for deutetrabenazine. Now, that is good or bad on either drug, depending on what you're trying to achieve or your goal. So the advantage of a wider spectrum of dosing choice is that you can really customize the dosing based on the efficacy of the drug and the side effect it provides, so you could be really tight in your titration, and you have a higher ability of finding that fine line of providing optimal TD symptom alleviation without causing the side effect.

On the other hand, there is something about the simplicity of 2 or 3 steps, and so if you have a patient that has other issues that you have to deal with, and you really want to control it rather quickly and don't have much time on a more complex titration scheme, having something so simple would be a good benefit, but you lose that kind of fine titration ability with that. So I think those are just 2 practical differences between the 2.

Now, there are different drug interactions that you need to consider when prescribing 1 or the other. In paper, there is more drug interaction with valbenazine, but in practice I'm not sure how often and how practical this theoretical advantage is. There is a warning about use of valbenazine, at least in some literature, being careful with taking valbenazine with grapefruits and/or grapefruit juice. I'm not a big fan of grapefruit, so I think it doesn't apply to me, or maybe not for most patients, but it's something to consider.

**Dr. Anderson:**

Yes, those are great considerations. Again, you really want to pick the right medication for the right patient. Valbenazine does come in sprinkles, so if you have somebody maybe who's older, who has trouble swallowing pills, that can be a helpful differentiator. And in terms of the titration schedule, deutetrabenazine does have starter packs for titration that are available that can make the dose jump a little bit easier when patients and families are dealing with multiple dosing levels as you're slowly ramping up the medication.

**Dr. Fernandez:**

So, Karen, given that many of these patients are on multiple medications, practically polypharmacy, how do you navigate selecting a VMAT2 inhibitor?

**Dr. Anderson:**

Well, you really do need to consider the other medications that someone is taking, Hubert. In particular, for psychiatric patients, the medicines that are CYP2D6 inhibitors would be paroxetine, fluoxetine, and bupropion. And this is important, because you can have an increase in the dose of your VMAT2 when someone is on 1 of these medications, which could lead to a lot more side effects from your VMAT2 and could also lead to QTc prolongation. So you could run into cardiac complications if someone is on 1 of these other medications. So really think about the dosing. Maybe go more slowly with the dosing. Maybe don't go to the top dosing limit with a VMAT2 if somebody is on 1 of those medications.

Also think about the titration. As you're titrating, you may run into side effects from VMAT2s. The most common ones that I've seen are somnolence. I think that's a little more common in valbenazine than deutetrabenazine. It can be helpful, actually, the somnolence, if a patient has insomnia or a lot of anxiety, a little bit of a sedating effect can be helpful. But the side effects that can pop up are somnolence. You can also see mood effects, so if a patient begins to experience depression, low mood, that's a sign that maybe you've gone too far in the dose, and you need to reduce the dose. And if you start to see parkinsonism in a patient with tardive dyskinesia, that's a sign that you have caused drug-induced parkinsonism in your patient with tardive dyskinesia. So if the patient's walking is slowed down, if their movements become slowed, then you know that you've gotten too high on the dose, and you want to reduce the dose a bit and see if the patient tolerates a lower dose and still has suppression of the TD movements.

Certainly, I think it's reasonable to switch from one VMAT2 inhibitor to the other if a patient doesn't tolerate one or gets to a dose level that has too many side effects to really get effective suppression of the tardive dyskinesia. I certainly do switch patients from one to the other.

**For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Karen Anderson, and here with me today is Dr. Hubert Fernandez. We're discussing individualizing treatment for tardive dyskinesia.**

I think the other important factor to think about is long-term safety and efficacy. So these drugs have both been studied for several years. People have been followed on them for several years. It seems that the efficacy is very well sustained once a patient has good suppression of tardive dyskinesia, and the safety profile seems to be pretty stable over long term. Obviously, if you have a patient on a VMAT2 who starts to experience worsening depression, you would consider lowering the dose of VMAT2, but otherwise it does seem like the safety profile is very good over long term, 2 or 3 years or even longer.

**Dr. Fernandez:**

Absolutely. I just read a meta-analysis, a review article looking at all published reports on VMAT2 inhibitors. It's really gratifying to know that the tolerability of the medication over the long haul has been quite satisfactory. Having said that, they're not exempt from causing or worsening parkinsonism, so it's something to be vigilant about.

**Dr. Anderson:**

Hubert, when you see a patient for follow-up after starting treatment for TD, what are you assessing?

**Dr. Fernandez:**

Well, I'm assessing, basically, efficacy and tolerability, so we're looking at how effective the current dose of the VMAT2 inhibitors are in alleviating tardive dyskinesia symptoms. So I'm looking at abnormal involuntary movements, the choreic movements in their mouth, dystonic movements in their neck, flickering or twitching in their eyelids, and things like that to determine whether it's working or not, and whether I need to increase or decrease the dose.

The other one that I'm looking at are potential side effects. So at least in movement disorders, drug-induced parkinsonism is probably the number 1 side effect that I'm most vigilant with. And so I'm looking for tremors, I'm looking for rigidity or stiffness, and I'm looking for slowness. And sometimes it's just a generalized body bradykinesia, and sometimes it's a bit more subtle, and you would see them when you ask them to walk or do finger tapping or hand movements and things like that.

**Dr. Anderson:**

And when a patient has a partial response, I tend to switch from one VMAT2 to another. Sometimes you might talk with the patient's psychiatrist to see if you can reduce the dopamine-blocking agents after the TD has been partially treated.

I know our listeners will find this as engrossing as I did, but before we wrap up, Hubert, would you care to bring us home with your 1 take-home message for the audience?

**Dr. Fernandez:**

Well, my 1 take-home message is that tardive dyskinesia and their response to VMAT2 inhibitors and their tolerability to it is not a static condition. It is a dynamic disorder, and, therefore, with every visit you need to assess whether it's still the right dose that is controlling their symptoms or need more if it's not. Or if it's causing some side effects and, therefore, you'll need less, or you may need to switch it to something else.

**Dr. Anderson:**

My take-home message is to think about medications the patient is taking in addition to the VMAT2 inhibitor. Make sure you know all the other medications your patient is taking, and, in particular, look out for CYP2D6 inhibitors, which can increase the dose of your VMAT2 inhibitor and lead to side effects.

**Dr. Fernandez:**

Thank you, Karen, and goodbye.

**Closing:**

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