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Are All VMAT2s The Same? Data Driven Treatment Decisions for Tardive Dyskinesia

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Welcome to CE on ReachMD. This activity, titled “Are All VMAT2s The Same? Data Driven Treatment Decisions for Tardive Dyskinesia” is provided by TotalCME.

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Dr. Correll:
We currently have 2 FDA-approved VMAT2 inhibitors for treating tardive dyskinesia, or TD. Are you familiar with the recent data released at the Psych Congress 2025 to help differentiate between these 2 treatment options?

This is CE on ReachMD, and I'm Dr. Christoph Correll, and I'm joined by Dr. Jonathan Meyer.

Dr. Meyer:
Christoph, great to be here. I think what I want to say to the audience as much as anything is that we've come to appreciate that while we as clinicians may rate patients’ movements as they respond to a VMAT2 inhibitor, it's maybe important to incorporate the patient outcomes in our analyses. And they're the end users, and it's their experience which is most important. But we haven't had really a lot of data on patient-related outcomes in response to VMAT2 inhibitor treatment.

Dr. Correll:
I think this is very, very important, because we're not just treating movements and amplitude; we're treating people. And so since we're currently at Psych Congress 2025 in San Diego, let's talk about some of the exciting data on VMAT2 inhibitors that were presented here.

I'll start by discussing some data on valbenazine. So there was first a KINECT-PRO paper, and let's talk about this. There are different scales now. There's the TD Impact Scale and the Impact TD Scale. So Impact TD is actually a scale that is rated by a clinician that goes over movements but also how the person feels and can function. The TDIS, or the TD Impact Scale, is a patient self-report measure which may be even easier to implement. And so the idea would be that every time we see a patient and we want to do an AIMS, the Abnormal Involuntary Movement Scale, we should also really hand them, before we see them, the TDIS so that they can score how they feel.

Now there were 3 posters that I want to briefly talk about. The first one looked even at a different measure, and that is the Sheehan Disability Scale. And I think most of you are very familiar with it. It has basically 3 different domains. It has the home environment, it has the work, and it has also the social environment and is often used for depression studies.

And here, what was shown is that patients were quite impaired, especially in the home and social realm, not so much in the work and school realm. And many of our patients don't actually work, and that's maybe one of the reasons. But by improving the movement symptoms with the valbenazine treatment, there was also robust improvement in the Sheehan Disability Scale scores, particularly in the home environment and social environment.

The second study was looking at the TDIS scale itself. Now this has 11 items. There are 3 that have to do with movements of the mouth and other areas, throat. There are 2 on dexterity. There are 2 on balance. There's 2 on emotional, 1 on pain, and 1 on social.

And what was shown is that with valbenazine, not only the AIMS scores that were quite remarkable before valbenazine started, also the items on the TDIS went down. And what was the highest actually—and you may already, since you see patients with TD, most likely surmise—the ones that were the highest were the ones that had the embarrassment or self-consciousness and feeling that you had unwarranted attention by other people. After that came the movements of the mouth, the face, and the throat, and these were really robustly improved with the treatment with valbenazine.

And then the third poster looked at subgroups. Because when we treat people with a VMAT2 inhibitor—in this case valbenazine—we ask ourselves, well, are there subgroups that respond better or worse? And in this case, the differentiation was people with schizophrenia or bipolar disorder. And basically both groups improved.

And that just adds another datapoint to other subgroups that had been published already with valbenazine. An improvement that was age—people younger than 55 or older were equally well improving with valbenazine. And this is treatment for tardive dyskinesia. And also people who are still on an antipsychotic and postsynaptic dopamine blocker or who are off it already. And that's interesting, because we could fear that if there's still the antipsychotic on board, that the VMAT2 inhibitor wouldn't work.

Now, Jonathan, what can you tell us about other data?

Dr. Meyer:
So subgroups were mentioned, as you talked about, whether they're on a current dopamine blocker, what their underlying diagnosis is, but sometimes we're concerned simply on the patient's underlying biology with reference to their race or ethnicity. We know around the world there are differences in sometimes in pharmacodynamic response to medications. Sometimes there are differences in kinetics of medications. We live in a diverse population in the United States, and the question is, do I need to tailor my treatment or need to be concerned about dosing or implementing valbenazine depending on the patient's heritage?

What we have is a post hoc analysis of data from KINECT-4, and it looked at individuals based upon their self-identified ethnicity, Hispanic or not, or their racial heritage, white or non-white, which was predominantly African American. And the conclusions from this are very reassuring. Whether we look at changes in movements, whether we look at treatment-emergent adverse effects, whether total or serious, they were numerically very similar across all the subgroups.

And I think the important conclusion clinically is that regardless of the patient's underlying diagnosis, regardless of whether the patient's on a D2 blocker or not, regardless of their heritage or ethnicity, we have confidence that valbenazine will be a tolerable and effective regimen despite all the differences we might see in underlying patient demographics.

Dr. Correll:
So that's really important. So meaning we shouldn't say up front, well, this is not a person for valbenazine or VMAT2 inhibitor, even if they're more severe or less severe in movements. Basically, everyone deserves at least a trial, because there are only 2 approved treatments for tardive dyskinesia, valbenazine and also deutetrabenazine.

For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Christoph Correll, and here with me today is Dr. Jonathan Meyer. We're discussing new clinical data on VMAT2 inhibitors for the treatment of tardive dyskinesia.

Were there other data?

Dr. Meyer:
Well, it gets to the point that an astute clinician knows how to use all the FDA-approved tools. When there's only 2, you should be comfortable using both of them.

A poster was presented of people who are currently on deutetrabenazine but analyzed subjective outcomes in terms of satisfaction as well as changes in movement on the basis of whether there was prior exposure to valbenazine. The sample sizes were 54 prior valbenazine users and 100 people on deutetrabenazine who were de novo, meaning no prior VMAT2 exposure. And guess what? The outcomes were comparable. Whether we're looking at changes in movements or patient satisfaction, they were very similar.

And I think this gives you confidence. You will inherit people who have maybe tried another VMAT2 inhibitor and didn't have the optimal response. I think it makes sense to offer them the other. But now you have data to back that up as a clinician saying, I think you might get a good outcome from this. I think the possibility of changes in movements, the idea that you'll tolerate it and be satisfied with treatment will be just the same whether or not you were treated previously, in this case with valbenazine, before you tried deutetrabenazine.

Dr. Correll:
These are very important data. Don't you also get asked a lot when you present on schizophrenia or tardive dyskinesia, “Well, if one has failed, is that the end game? Basically, that's it because this mechanism won't work?” And I always ask back, well, if someone didn't respond to an SSRI, do you change to another one? Or what about the second-generation antipsychotic? But we didn't have the data, and now we actually have. So that's really reassuring.

So, Jonathan, how do we then differentiate between valbenazine and deutetrabenazine? Which one should come first? And how do we prescribe these 2 different drugs?

Dr. Meyer:
Well, I hate to say it; sometimes the choice is made for you by access. The patient has a certain type of coverage, and you're going to be driven one way or the other. Assuming you have access to both, then you get into some subtleties of the differences between medications.

For example, does a patient prefer maybe a faster titration versus a slower one? We know when initially approved, valbenazine was studied with a 1-week titration from 40 up to 80. I think we now realize that's not always necessary, but some people may really want to get to the maximum dose sooner, perhaps because they've been suffering from their dyskinesia symptoms.

On the other hand, for those who might prefer a slower titration, you do have 2 options. There's now a titration pack for deutetrabenazine, which gets you to a dose of 30 mg after a month, with then the clinician advancing the dose at least to 36 initially, and then maybe higher. As we know from the long-term studies, people on deutetrabenazine seem to do best with a mean dose of around 39. Some patients might prefer that. They like the idea, “I'm starting slowly,” and progress slowly across different doses. Some clinicians might like that because perhaps they perceive, “I have more dose flexibility within the range.”

Now, for valbenazine, there is some dose flexibility. We have 40-mg capsules, we have 60, and we have 80. And we now have some long-term data which shows that 40 is actually a very effective dose. You may get some more efficacy from 80, but if people want the luxury of time, staying at 40 is not an unreasonable thing to do.

Also some subtleties in terms of who can take the medication, really based on the issue of whether there's underlying cirrhosis. It's not a common problem in a lot of our population, but it's not absent. And valbenazine has been studied in people who have mild or moderate levels of cirrhosis, and it can be taken.

Deutetrabenazine cannot be taken in that population. Again, you're not going to see these people very often, but the take-home comment is, when the FDA discusses hepatic impairment in a package insert, they're talking about cirrhosis, not inflammation. Most of the time we see the abnormalities in liver function tests, it's inflammation, AST, ALT, GGT—that's not what we're talking about. We're talking about cirrhosis, Child-Pugh criteria. For those few patients with that problem, deutetrabenazine can't be taken.

Also, deutetrabenazine, though, on the plus side, seems to have less propensity for drug-drug interactions through 3A4. That's not true for valbenazine.

So these are some differences which may come into play as you pick a variety between these 2 medications. You only have 2 choices. I think it's good to know the subtleties, but I think, again, that switch data is really informative.

Know how to use both. Somebody may do better on one or the other. We have no a priori way of picking that. And when there's only 2 options for a disorder of which we really have no other effective FDA-approved treatments, might as well give both a try.

Dr. Correll:
Thank you, Jonathan. These were really important points, and especially some misinterpretation of the FDA-regulated data on liver dysfunction. So many patients with schizophrenia have liver dysfunction because they may have hepatitis C, they may have NASH because they are obese or have also diabetes. So it's really cirrhosis, more severe liver dysfunction, where you may want to go more into the direction of valbenazine, which is a prodrug and makes it therefore a little easier on the liver. But otherwise, that's not really a determining factor.

And it's very important also that we know both agents, because if we want to be good clinicians, we need to be able to choose one over the other in certain patients.

And then finally, the dosing, I think, is also relevant. We have options, but don't stay low when patients are not getting the full benefit, because really, these medications, both valbenazine and deutetrabenazine, are very well tolerated, and the underlying psychiatric disorder doesn't worsen. There's no real additional add-on side effect profile. Some patients might get a little stiff or have akathisia, but this is very, very few people. So be bold and really try to treat and go the whole way so that patients can benefit with their tardive

dyskinesia symptoms but also, what we talked about today, with the impact of these symptoms on their well-being and functioning.

So, well, this was really a fantastic conversation. But before we wrap up, Dr. Meyer, what's your one take-home message for our audience?

Dr. Meyer:
Know how to use both drugs. And most importantly, it's not just movements; it's the patient's life which are impacted by TD. Don't forget to assess what else is going on besides the change in the AIMS score.

Dr. Correll:
I can't agree more. I think you actually put it very, very nicely. And this means that we're broadening our approach to psychiatry, in general, from symptoms to people, and that also applies to people with tardive dyskinesia.

Now, that's all that we have today. So I want to thank the audience for listening to us. And thank you, Jonathan, for joining me and sharing all of your valuable insights. It was really great speaking with you today.

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