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Not All VMAT2s Are the Same: Understanding the PK/PD Differences

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Dr. Hicks:
This is a CE on ReachMD, and I'm Dr. Tracy Hicks, and with me today is Dr. Melissa Moody. Today we're comparing PK/PD differences among VMAT2 inhibitors used for tardive dyskinesia.

Melissa, can you walk us through the key PK/PD differences between valbenazine and deutetrabenazine?

Dr. Moody:
Sure, I'd be happy to. Valbenazine and deutetrabenazine are both reversible VMAT2 inhibitors that improve tardive dyskinesia by reducing presynaptic dopamine release, but their pharmacodynamic profiles differ in ways that are mechanistically informative yet clinically limited when considering on PK/PD data alone.

Valbenazine is a prodrug that yields a single active metabolite, the [+]-α-HTBZ, which is a potent, highly selective VMAT2 inhibitor with a relatively long half-life, resulting in stable, predictable VMAT2 inhibition and minimal off-target receptor activity.

In contrast, deutetrabenazine is metabolized into multiple active stereoisomers with differing potencies, abundancies, and receptor affinities. Notably, its most abundant metabolite is a relatively weak VMAT2 inhibitor with measurable dopamine and serotonin receptor binding, producing a more complex and heterogeneous pharmacodynamic signal.

From PK/PD alone, it is reasonable to infer differences in metabolite selectivity, temporal stability of VMAT2 inhibition, dosing schedules, and mechanistic rationale for differing warnings, but PK/PD data cannot establish comparative efficacy, overall safety or tolerability, or clinical superiority between the 2 agents. Consequently, PK/PD explains how these drugs differ biologically but does not determine which is clinically better for an individual patient.

Dr. Hicks:
That was a lot of great information, Melissa, but what about when we're thinking about choosing a treatment option, when we're talking about PK and PD?

Dr. Moody:
I think there's many factors there. For one, let's kind of first mention that once-daily versus twice-daily dosing. We kind of mentioned why

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it's happening, why 1 medication is able to be dosed once a day, while the other needs to be dosed twice a day. That's a really big deal for adherence for patients. They're often already taking many other medications. Adding 1 pill once a day versus multiple pills multiple times a day might be preferable for those patients. So that's the first thing to think about, right, are the patients going to be adhering to the regimen that we suggest for them?

The next thing we want to think about is is this medication going to potentially interfere with other medications the person might be on? And there are several layers to that, right? We need to think about are they on other inhibitors or inducers, because that can change the way medication is available. But most notably, we mentioned off-target activity. One medication that we mentioned, deutetrabenazine, has off-target activity much more so than valbenazine, which has minimal off-target activity. That's relevant because it may cause interference with other medications patients might have.

Dr. Hicks:
So what I'm hearing is this is where PK/PD really translates into practice, the way you broke that information down for us. So valbenazine basically offers once-daily dosing with a more stable exposure profile, while deutetrabenazine requires titration and divided dosing. So clinically that matters, and you've really explained that for us very well. So in patients with adherence, simplicity, or cognitive load concerns, that once-daily option can be very impactful.

So we also need to consider metabolism and interactions, particularly hepatic considerations and CYP pathways. So while both are effective, the differences shape how we individualize treatment.

So at the end of the day, both are valuable tools, but the right choice depends on the patient in front of you.

Thanks, Melissa, and thank you to our listeners.

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