TD Podcast Series
Episode 2: Treatment Approaches to Tardive Dyskinesia
Length: 16:24 min
Script

TITLE Treatment Approaches to Tardive Dyskinesia

HOSTS Dawn Vanderhoef, PhD, DNP, PMHNP-BC, FAANP
Kaylee Mehlman, PharmD, RPh, BCGP, FASCP

LEARNING OBJECTIVES:

- Define TD and understand its signs, symptoms, and pathophysiology
- Discuss the burden of TD and the importance of appropriate treatment
- Review non-approved and approved TD management strategies

SCRIPT

Intro

Voice Over – This podcast has been sponsored and co-developed by Neurocrine Biosciences, Inc. The speakers are presenting on behalf of and are paid consultants for Neurocrine Biosciences. The information provided herein is based on the healthcare provider's clinical judgement and personal experience.

Opening

DV- Good afternoon, and thanks for joining us! I'm Dr. Dawn Vanderhoef, Associate Medical Director at Neurocrine Biosciences. Today, we're diving into treatment approaches for tardive dyskinesia. Before we start, let me share a bit about my background. In my previous life, I was an academic clinician and nurse scientist. I directed the Psychiatric Nurse Practitioner Program prior to transitioning to Neurocrine and I practiced in a psychosis clinic. About four years ago, I made the exciting transition to Neurocrine. I work in Medical Affairs where my work is focused on psychiatry. I'm thrilled to be with you here today.

I am delighted to have a pharmacist with me. I believe a pharmacist should be part of every treatment team. Dr. Kaylee Mehlman, welcome! Would you please introduce yourself?

KM- Thanks, Dawn, and absolutely! Hi, everyone, my name is Dr. Kaylee Mehlman, and I'm a clinical, geriatric pharmacist currently practicing in the state of Rhode Island. I spent the first part of my career actually working closely with institutionalized patients with severe mental health disorders and currently I am working in the ambulatory care space. My passion resides with our geriatric patients, as I'm board-certified in geriatrics, and I am thankful for those experiences I've had both inpatient and now in the outpatient settings.

DV- Fantastic! Today, we aim to bring you valuable insights about the recognition, diagnosis, and management of tardive dyskinesia. It is our hope that this content will resonate with prescribers and healthcare professionals alike and that you will build upon your existing understanding and add new knowledge. So Dr. Mehlman, let's get started!

Intro to TD – Definition

DV- Alright, so you may be wondering what exactly is tardive dyskinesia? "Tardive" meaning delayed, "dys" implies abnormal, and "kinesia" refers to movement. So, in simple terms, tardive dyskinesia, or often referred to as TD, is a hyperkinetic movement disorder characterized by abnormal, involuntary, repetitive movements of the face, trunk, or extremities that are associated with prolonged exposure to medications that blocks dopamine, or what we would call a dopamine receptor blocking agents—let's say DRBAs for short.

When we talk about DRBAs, we typically think of antipsychotic medications. There are older or first-generation antipsychotics like haloperidol or chlorpromazine, and then the newer second- and third-generation antipsychotics that have a slightly different mechanism of action, such as risperidone or ziprasidone.

But it's also important to remember that tardive dyskinesia risk is not limited to antipsychotics but can extend to antiemetics as well. We can't forget about these antiemetics, such as metoclopramide and promethazine, as DRBAs. Kaylee, I'm sure you've seen this in your clinical practice.

KM- Yeah, Dawn. I actually have a current patient here in Rhode Island. She's actually in her early 70s, she's developmentally delayed and has been dealing with chronic nausea for most of her life. She has received numerous work ups which have not defined any specific cause, but she continues to suffer with these symptoms. So, over the years, she's been routinely prescribed prochlorperazine as it is most effective for her and has now unfortunately developed TD, or tardive dyskinesia, from her treatment. So, it's definitely a reminder to us that any medication which blocks dopamine, regardless of its indication for use, could contribute to the development of TD.

Pathophysiology of TD

DV- So Kaylee, using your pharmacy background and knowledge, could you give us a quick lesson on how DRBAs are theorized to cause tardive dyskinesia?

KM- Sure. I really like the word that you used, "theorized". So, the exact cause of TD isn't fully clear, however, there is a leading theory. But before we get into that, I first want to explain how a normal, healthy neuron that's not receiving dopamine receptor blocking therapy works. In this neuron, dopamine molecules are released from the presynaptic neuron into the synaptic cleft, where they bind to their specific dopamine receptors on the postsynaptic neuron. This then triggers a signaling cascade that transmits messages, or signals, along the neuron. These dopamine signals can do things like help our muscles move smoothly with intentionality.

Now when a patient is taking a DRBA such as an antipsychotic or antiemetic medication, that medication works by blocking the postsynaptic dopamine receptors, which inhibit dopamine binding and signaling. This is thought to lead to an improvement in symptoms such as hallucinations or delusions or may contribute to the relief of nausea and vomiting. It's hypothesized that when a patient is on a DRBA for a prolonged time, their body realizes it's not getting all the dopamine signaling that it wants. So, what does it do? It creates more dopamine receptors on that post-synaptic neuron to increase the probability of getting back to that desired signaling. Unfortunately, those newly created, upregulated receptors are also hypersensitive. This leads to larger, exaggerated signals when dopamine binds to the post-synaptic receptors. So, instead of those smooth, intentional muscle movements described earlier, we can see abnormal, repetitive, and involuntary movements characterized as tardive dyskinesia.

DV- Thank you. I appreciate that explanation. I'm just curious, are you encountering cases of TD in patients taking second-generation antipsychotics?

KM- Unfortunately, Dawn, yes. It's important to recognize that second-generation antipsychotics, or SGAs, still carry the risk for TD due to their mechanistic nature. While the incidence of TD with first-generation antipsychotics may be higher, TD remains as an important consideration in patients taking SGAs due to their growing use as well as the broadening of on-label uses for these medications.

Traditionally, these movement disorders were commonly associated with conditions such as schizophrenia or bipolar disorder. But with the approval of newer indications for these SGAs, patients with treatment-refractory depression are now being prescribed these medications, which puts them at risk for developing TD.

TD Signs and Symptoms

DV- Thanks so much for sharing. I think now would be a good time to learn about how TD presents. Can you describe what TD looks like in the patients you've seen and where in the body do you usually see the movements?

KM- Certainly. It's important to note that describing TD phenomenology for one patient is only describing TD for that one specific patient. TD can occur in any skeletal muscle of the body, so that would be any muscle that is considered a voluntary muscle or within our control. However, there are also muscles in our body that are half within our control and half not within our control, like the diaphragm. So unfortunately, TD can develop in any of those types of muscles as well.

But traditionally, when we think of TD, we may think of the classical oral, buccal, lingual movements right? It could look like tongue twisting and protrusion, lip smacking, along with chewing movements in the jaw.

Those are historically thought of as hallmark signs and symptoms and a classical presentation of TD.

DV- Right, we often think about the "check up from the neck up." But I really like your description of how TD can occur anywhere. In addition to those facial movements, TD can manifest in other parts of the body such as "piano-playing" fingers, flexion and extension of the limbs, foot tapping, and as you mentioned, in the diaphragm or even esophagus.

KM- And we also can't forget about TD in the trunk, which could look as if the patient is swaying from side to side or shrugging their shoulders.

DV- Absolutely, it's important to really understand these visual cues of TD since TD is a delayed onset DRBA movement disorder. However, we cannot forget about the acute DRBA movements such as dystonia, akathisia, and drug-induced parkinsonism, all with a distinct pathophysiology and different treatment options.

KM- That's a great point, Dawn, because treatment options for one DRBA-induced movement disorder could possibly worsen others. Take anticholinergics for example; they could help improve drug-induced parkinsonism, for instance, but have been shown to worsen TD symptoms. So, it's crucial to be able to appropriately differentiate these movement disorders and provide treatments distinct to their unique presentation and pathophysiology.

TD Burden and Impact

DV- Thank you for that. Well now that we've learned about the pathophysiology and clinical presentation of TD, I'd like to touch on the broader impact of TD that can extend beyond these abnormal movements. Can you speak to how TD has impacted the overall quality of life in the patients that you've seen?

KM- Absolutely. I used to consult at a nursing home with 178 beds and worked with many geriatric patients dealing with life-long schizophrenia. As they were receiving often multiple antipsychotic therapies, many of them unfortunately developed TD and were debilitated by their movements. They were unable to perform ADLs (activities of daily living) and IADLs (instrumental activities of daily living) necessary to live independently and participate in social activities, and on top of that, had to face the stigma associated with these visible signs of TD. Now we also have studies that show the tangible impact of TD on their quality of life beyond just healthcare-related aspects. These patients tend to isolate more, they tend to feel more self-conscious or embarrassed about their movements, which are all things I've seen out in the real-world with my patients. It really emphasizes the importance of recognizing and appropriately treating TD in order to help alleviate these burdens that patients experience.

DV- Right, Kaylee, thanks for sharing. I definitely agree that it's crucial to provide a holistic approach and address the impact of TD on patients' overall well-being, not just the disease state itself.

Historic, Non-approved TD Management Strategies

DV- Let's transition and talk about the historical management of TD. When I started as a clinician, we didn't have any FDA-approved treatments. Good news—as of April 2017, we had the approval of the first vesicular monoamine transporter 2, or VMAT2 inhibitor for the treatment of TD in adults, followed by a second approval a few months later.

But when I was actively practicing before we had those approved VMAT2 inhibitors, what did we do when we saw TD? We couldn't just take them off the offending agents. Maybe we could decrease or try and switch the medication? I was also taught back then that if it moved, we should just give it an anticholinergic like benztropine. Can you speak to these historical prescribing practices?

KM- Interestingly, Dawn, everything you mentioned was on the table back then. When I started my career, I had a few psychiatrists who co-prescribed antipsychotics with benztropine, almost like it came in a combination pill if you will. And if we saw TD, we'd maybe try switching to a different antipsychotic or decreasing the dose. However, lowering the patient's antipsychotic dose isn't supported by the literature and can sometimes reveal a withdrawal dyskinesia, and simultaneously put them at risk of losing their psychiatric stability, which can be so hard to obtain in the first place.

It's important to recognize that back then, we didn't have any better treatment options, and the understanding of TD pathophysiology was limited, meaning we didn't know we could possibly be making TD worse by giving an anticholinergic or reducing or switching the offending agents.

However, we now have access to more information and the 2020 American Psychiatric Association's schizophrenia guidelines even state that there is insufficient evidence to support the use of withdrawal, dose reduction, or switching of DRBAs to treat TD symptoms. These guidelines also caution against the use of anticholinergics, stating that they do not improve and may even worsen TD.

TD Treatment Recommendations Based on 2020 APA guidelines

DV- I'm so glad you mentioned these guidelines! 2020 was an important year in that we had the American Psychiatric Association release schizophrenia guidelines that included treatment recommendations for TD. Can you speak to the guidelines a bit more on how they can be useful for our audience?

KM- Absolutely. Firstly, they state that for any individuals who have moderate to severe or disabling TD, a reversible VMAT2 inhibitor is recommended. They also mention that if a patient has mild TD, but they find it to be impeding their ability to live their life normally, then a VMAT2 inhibitor can certainly be considered. I really appreciated that because as we know, TD movements affect patients differently. TD symptoms that might be considered mild or scored lower on the Abnormal Involuntary Movement Scale, or AIMS exam, could be significantly and

adversely impacting the patient's overall quality of life. So, I think it's great that we have a lot of license with these guidelines to use VMAT2 inhibitors in any patients we might feel is appropriate as a part of shared clinical decision making.

And lastly, I just have to acknowledge again how these guidelines specifically cautioned against the use of anticholinergics, such as benztropine and trihexyphenidyl, in the treatment of TD alone.

DV- Yeah, I think that avoiding anticholinergics in TD is a paradigm shift in practice for many clinicians, patients, and caregivers.

MOA of VMAT 2 Inhibitors

DV- Well, just going back to our earlier conversation, talking about the pathophysiology of TD. You nicely outlined the theory of how TD may be caused by the dopamine binding to those upregulated and hypersensitive postsynaptic receptors. Now could you teach us how VMAT2 inhibitors work in treating TD?

KM- Yes of course. To begin though, it's important to note that the precise mechanism of action of VMAT2 inhibitors in treating TD remains unclear. But let me start by explaining what a VMAT2 is. It's a presynaptic protein that regulates the packaging and subsequent release of dopamine and other molecules from these vesicles into the synaptic cleft. So, with that being said, a VMAT2 inhibitor works to block that packaging and release of dopamine, reducing the amount of dopamine available for binding in the synaptic cleft. The hypothesis underlying this mechanism suggests that with less dopamine available to bind to the hypersensitive postsynaptic receptors, it could potentially lead to reduced TD movements.

Impact of Appropriate TD Management

DV- Thanks for that great explanation. Can you please share some of the impacts you have observed when a patient with TD receives appropriate and timely treatment?

KM- Certainly. In my experience, it's been very impactful witnessing a patient's journey from their initial TD diagnosis to having their symptoms well-managed with appropriate treatment. While not all patients respond to all medications, for those that do experience improvement in their movements, I think it can be quite transformative for them. I've observed patients rekindle activities they once enjoyed, engage more with society, and experience a notable boost in their overall self-esteem. It really is wonderful to watch.

DV- That is so heartening to hear. It really does re-emphasize the importance of appropriate TD management and how its impact extends beyond just mere symptom control for these patients.

Conclusion and Call to Action

DV- As we reach the end of this podcast, do you have any concluding thoughts?

KM- Yes, there are two things I'd like to mention. Firstly, I think as healthcare providers, it's essential for us to inform patients about the availability of treatment options for TD. If I were a patient facing TD, knowing there are FDA-approved treatments would make me feel more willing to discuss my TD and impact with my clinician.

DV- That's a great point. It's been quite a while since we've had the approval of VMAT2 inhibitors, but I think there's still a long runway to educate folks.

KM- Absolutely. And secondly, I would just say, once we recognize TD, I think it's important to treat early so patients don't suffer any longer than they have to.

DV- Well, I have to say I've thoroughly enjoyed my time with you and I'm certain that the listeners have lots of nuggets of information that they can take into their practice the next time they're in the clinic. I appreciate you sharing your expertise and time with me today.

KM- Absolutely, Dawn. Thank you, the pleasure was all mine!