

Strategies for Successfully Diagnosing and Treating Tardive Dyskinesia: Enlisting the Help of Caregivers, Improving the Lives of Patients

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Educational Objectives

- Demonstrate knowledge of the prevalence of TD among patients taking dopamine antagonists
- Explain the effect that TD has on patients' quality of life and ability to function, as well as on caregivers' wellbeing
- Identify strategies to promptly detect and diagnose TD that can be integrated into a busy practice
- Describe approaches that promote the long-term success of TD treatment plans

Introduction

At any given time, roughly 1 of every 4 patients taking antipsychotics experiences tardive dyskinesia (TD).¹ Antipsychotics inhibit dopaminergic neurotransmission, but dopamine is an important neurotransmitter in motor pathways.² TD is caused by these dopamine receptor-blocking agents and is characterized by involuntary movements of the tongue, lips, face, trunk, and extremities.^{1,3} If involuntary movements are sufficiently severe, they can attract negative attention in public or prevent patients from carrying out everyday tasks, often leading to depression and social withdrawal.^{1,4} TD also affects the people who care for patients. Not only do caregivers share in the feelings of stigma associated with their loved ones' involuntary movements, but they must also provide the support needed when a patient is unable to function at work or at home. In short, TD is a devastating disorder, and today more and more patients are at risk for the condition as a result of expanded drug indications and increasing off-label prescription of antipsychotics.⁵

Psychiatry professionals play a key role in minimizing the impact of TD on patients' lives. Fortunately, after many years in which few evidence-based TD treatment options existed, effective pharmacologic treatments are now available.^{6,8} The prognosis for patients diagnosed with TD is better than ever before. Moreover, early diagnosis of TD can lead to early action, increasing the chances that a patient's involuntary movements prove reversible and providing help before that individual withdraws from social and occupational activities.¹

With many responsibilities and little time, however, it can be challenging for clinicians to assess patients for TD, keep up to date on new agents, and create personalized treatment plans that facilitate long-term treatment success. Assessment can be particularly challenging as virtual office visits have become increasingly common.^{7,8} The COVID-19 pandemic has hastened the adoption of telepsychiatry, but the use of virtual visits is likely to become a permanent feature of modern psychiatry practice.⁹ Therefore, this article contains tips and tricks for recognizing and responding to TD in today's practice environment, including strategies to help form a strong therapeutic alliance, even virtually, that includes patients, caregivers, and health care staff.

The impact of TD on patients and their caregivers

Research shows that the involuntary movements of TD significantly reduce patients' quality of life (Figure 1).^{4,10} Most clinicians are aware that moderate-to-severe movements may be painful or physically disabling.¹ What is less appreciated is that even mild movements can have an outsized impact on the lives of patients, especially those who have developed TD after being treated for conditions such as depression, bipolar disorder, or hyperactivity. These individuals are often very aware of their movements and the way that people perceive them. Indeed, in one recent survey, 70% to 80% of outpatients with possible TD reported being aware of their movements, and 50% to 60% felt self-conscious or embarrassed by them.¹

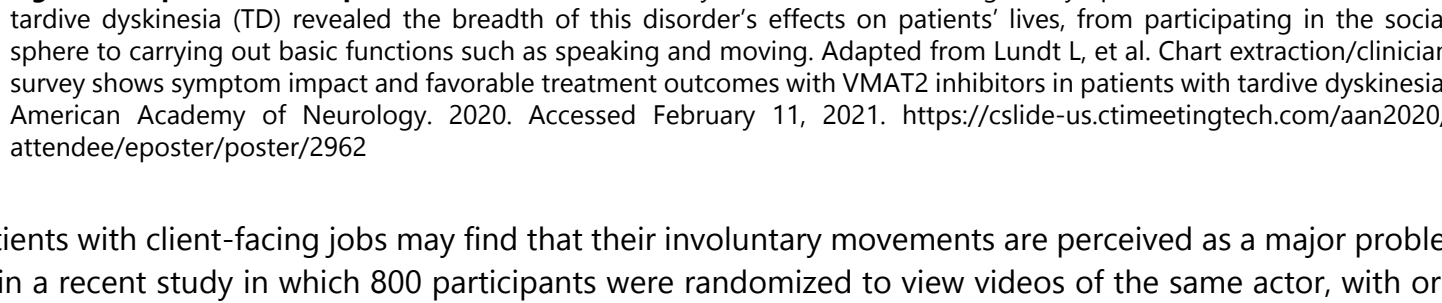
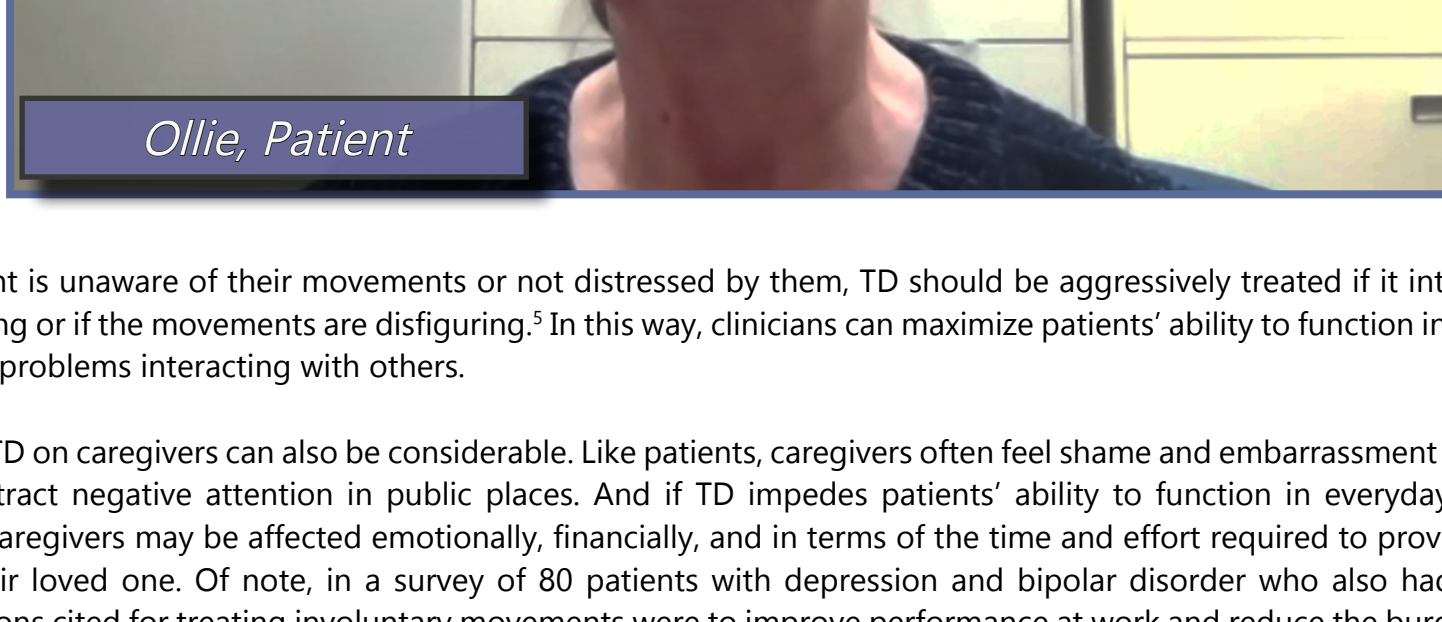


Figure 1. Impact of TD on patients' lives. A recent survey of clinicians concerning the symptoms of 601 individuals with tardive dyskinesia (TD) revealed the breadth of this disorder's effects on patients' lives, from participating in the social sphere to carrying out basic functions such as speaking and moving. Adapted from Lundt L, et al. Chart extraction/clinician survey shows symptom impact and favorable treatment outcomes with VMAT2 inhibitors in patients with tardive dyskinesia. American Academy of Neurology. 2020. Accessed February 11, 2021. <https://slide-us.ctimeingtech.com/aan2020/attendeeposter/poster/2962>

In addition, patients with client-facing jobs may find that their involuntary movements are perceived as a major problem. This issue was demonstrated in a recent study in which 800 participants were randomized to view videos of the same actor, with or without mild-to-moderate TD movements.¹¹ Those who viewed the videos with simulated TD movements were significantly less likely to agree that the actor would be suitable for a client-facing job, as a dating partner, or as a friend.

Faculty and Patient Video

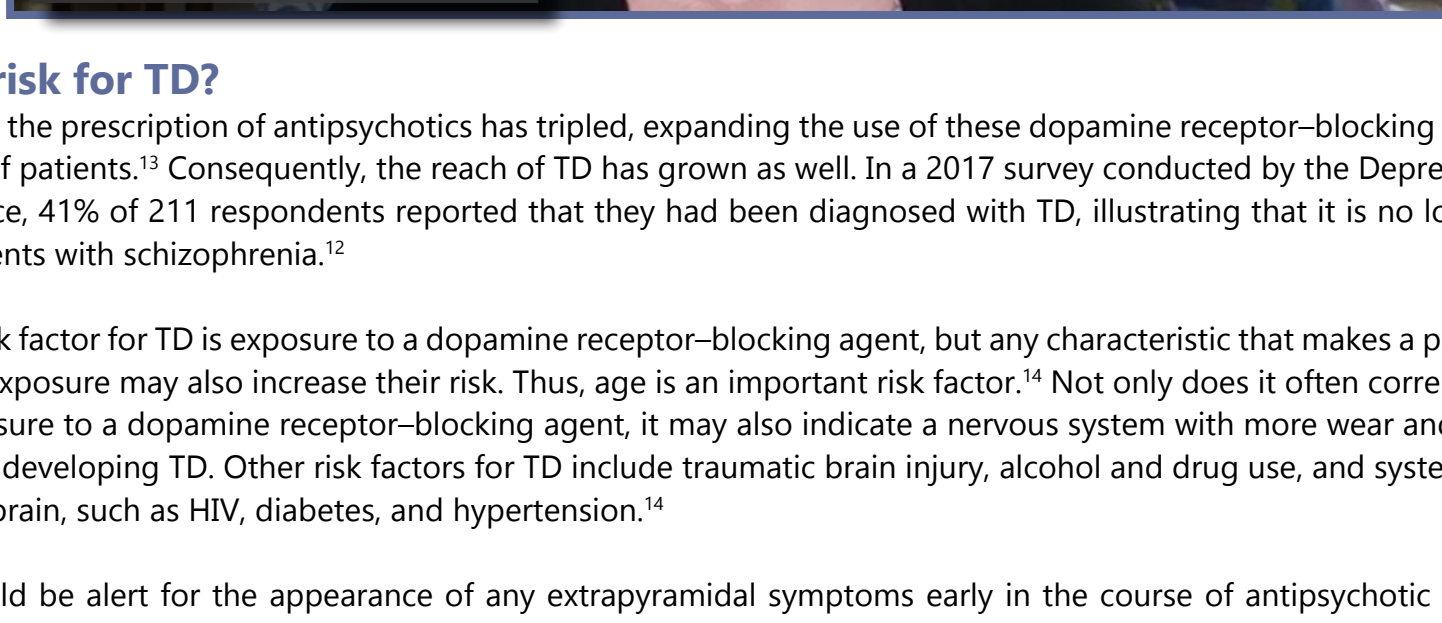


Ollie, Patient

Even if a patient is unaware of their movements or not distressed by them, TD should be aggressively treated if it interferes with their basic functioning or if the movements are disfiguring.⁵ In this way, clinicians can maximize patients' ability to function independently and minimize their problems interacting with others.

The impact of TD on caregivers can also be considerable. Like patients, caregivers often feel shame and embarrassment when involuntary movements attract negative attention in public places. And if TD impedes patients' ability to function in everyday life or maintain employment, caregivers may be affected emotionally, financially, and in terms of the time and effort required to provide the necessary support to their loved one. Of note, in a survey of 80 patients with depression and bipolar disorder who also had TD, the 2 most important reasons cited for treating involuntary movements were to improve performance at work and reduce the burden on family and caregivers.¹²

Faculty and Family Member Video



Paula, Family Member

Who is at risk for TD?

In recent years, the prescription of antipsychotics has tripled, expanding the use of these dopamine receptor-blocking agents to a much broader pool of patients.¹³ Consequently, the reach of TD has grown as well. In a 2017 survey conducted by the Depression and Bipolar Support Alliance, 41% of 211 respondents reported that they had been diagnosed with TD, illustrating that it is no longer a condition limited to patients with schizophrenia.¹²

The primary risk factor for TD is exposure to a dopamine receptor-blocking agent, but any characteristic that makes a patient particularly vulnerable to exposure may also increase their risk. Thus, age is an important risk factor.¹⁴ Not only does it often correlate with a longer length of exposure to a dopamine receptor-blocking agent, it may also indicate a nervous system with more wear and tear, one that is more prone to developing TD. Other risk factors for TD include traumatic brain injury, alcohol and drug use, and systemic diseases that can affect the brain, such as HIV, diabetes, and hypertension.¹⁴

Clinicians should be alert for the appearance of any extrapyramidal symptoms early in the course of antipsychotic treatment,¹⁴ such as restlessness or parkinsonism, as they can be harbingers of a nervous system that is sensitive to the effects of dopamine receptor-blocking agents. Rather than masking such extrapyramidal symptoms with anticholinergics, it is important to address the root problem as soon as possible by reducing the level of dopamine D2 receptor blockade before the involuntary movements of TD begin and irreversible damage occurs.

Best practices for assessing and diagnosing TD

The American Psychiatric Association provides guidelines for how often patients taking antipsychotics should be assessed for TD.¹⁵ Normal-risk patients should be assessed when treatment begins and then every 6 months, if they are taking first-generation antipsychotics (FGAs), or every 12 months, if they are taking second-generation antipsychotics (SGAs). Patients at increased risk should also be assessed when treatment begins and then every 3 months if they are taking FGAs or every 6 months if they are taking SGAs. Health care providers should be aware that though the involuntary movements of TD often manifest during a patient's exposure to a dopamine receptor-blocking agent, they can also emerge shortly after the withdrawal of such an agent.¹⁶

Informal assessment strategies

I find the following strategies useful for fitting TD assessments into busy office visits (Text Box 1). First, clinicians can create a 2-item questionnaire for patients that asks about involuntary movements. They can keep a stack of these forms on their desks, for easy access during visits, to rapidly assess whether a more thorough assessment is needed. Second, health care providers can ask a patient to perform 2 or 3 "activation maneuvers," modeling the desired actions themselves.¹⁷ These activation maneuvers, which take just a few minutes, allow the clinician to see whether involuntary movements emerge when the patient is not in a resting state or is exposed to a low level of stress. Third, both clinical and office staff can be trained, such as by watching short online videos about TD, to look for the involuntary movements associated with TD when they spend time with patients. This increases the chances that the movements will be detected during office visits, whether in the waiting room or the exam room.

Informal strategies for rapid tardive dyskinesia assessment

Mini questionnaire

Question 1. Have you noticed any movements of your fingers? What about movements of your jaw, your mouth, or your tongue? What about of your feet and toes?

Question 2. Have you noticed any movements that seem to occur out of your control?

Activation maneuvers¹⁷

Ask patient to:

1. Extend both arms outward, level with the chest, palms down, and provide 5 words beginning with the letter "T"
2. Hold hand up, near the face, and tap each finger, one at a time, to the thumb
3. Walk around

Enlisting the help of caregivers to detect and monitor involuntary movements

It is extremely helpful to engage a patient's caregiver when assessing for TD, as they are often the first to notice involuntary movements and also have valuable insights into their impact. For example, in a recent study of 204 patients with possible TD, clinicians, patients, and their caregivers were all asked to rate the severity of the patients' movements.^{18,19} Although ratings from all 3 sources were similar overall, caregivers tended to perceive the movements as more severe than did clinicians or patients. This may indicate that caregivers are more sensitive to their loved ones' involuntary movements.

A health care provider can reach out to a caregiver or loved one early in the course of a patient's care, so that TD or other problems can be detected quickly. If a caregiver cannot be present during a visit, quick check-ins between clinician and caregiver via phone are worthwhile. By asking a few simple questions, such as "Is the patient moving normally? Do they look stiff, slowed down, or restless? Have you noticed any twitching?" the clinician can gain invaluable information about how the patient is doing outside of the office.

A few common misperceptions can prevent health care providers from including caretakers in the therapeutic alliance. First, some clinicians mistakenly believe that HIPAA prevents them from discussing a patient's care with caregivers. In reality, a patient can grant permission to include their caregiver in such discussions. These conversations need not be private; instead, the caregiver can become a valuable part of the care team. When discussing the benefits of talking with the caregiver to the patient, the health care provider can explain that the caregiver often has unique insights into involuntary movements and other problems, as well as how the treatment plan is working. Second, clinicians may fear that speaking with caregivers about TD will take up an unacceptable amount of office visit time. However, even brief conversations with caregivers can pay dividends for patients if they result in better management of involuntary movements and other serious problems.

Assessment via telepsychiatry

Increasingly, clinicians will find themselves performing TD assessments during virtual visits. During in-person visits, patients can be observed in the waiting room, walking to the exam room, and inside the exam room. During virtual visits, the health care provider typically has much more constrained opportunities to see how a patient moves. For example, the clinician typically sees the patient's head and upper chest on camera, but TD can affect many other parts of the body (Figure 2). Involuntary movements of the body parts that are often not visible, such as hands and feet, can easily go undetected. Therefore, it is key that the clinician work with the patient and their caregiver to make sure that the patient's body is adequately visualized. The limited opportunity to observe a patient's body, from top to bottom, also makes it especially important to ask the caregiver about involuntary movements. Finally, if the patient is at a health care facility during a virtual visit, while the clinician is offsite, clinic staff may be able to aid the health care provider in assessing involuntary movements.

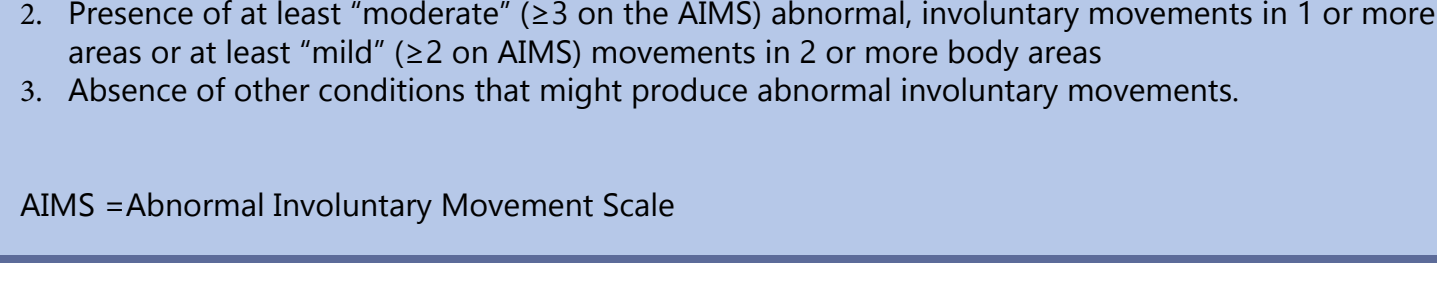


Figure 2. Though TD typically involves involuntary movements of the head and face, it can also affect many other parts of the body. A recent survey of clinicians concerning the symptoms of 601 patients with tardive dyskinesia (TD) demonstrates that many patients experience symptoms that affect multiple parts of their body. Adapted from Lundt L, et al. Chart extraction/clinician survey shows symptom impact and favorable treatment outcomes with VMAT2 inhibitors in patients with tardive dyskinesia. American Academy of Neurology. 2020. Accessed February 11, 2021. <https://slide-us.ctimeingtech.com/aan2020/attendeeposter/poster/2962>

TD diagnosis

The differential diagnosis for TD includes akathisia, parkinsonism, and tremor related to the use of mood stabilizing agents.¹⁹ Of note, whereas a tremor always consists of the same movement, TD is characterized by relating to movements that can vary in presentation. This may help the clinician differentiate between the 2 types of movement. During the diagnostic process, it is also important for health care providers to ask the caregiver whether anyone else in their family has experienced involuntary movements, to rule out hereditary disorders such as Huntington's chorea.

When TD is suspected based on an informal assessment and other potential causes of involuntary movements have been ruled out, healthcare providers can administer the Abnormal Involuntary Movement Scale (AIMS).²⁰ This scale, which consists of 12 provider-administered items, can be used to determine whether involuntary movements are present and, if so, what part of the body is affected and how severe the movements are. The results can then be used to determine whether a patient meets the Schooler-Kane Criteria for TD (Text Box 2).²¹

Schooler-Kane Criteria for tardive dyskinesia^{20,21}

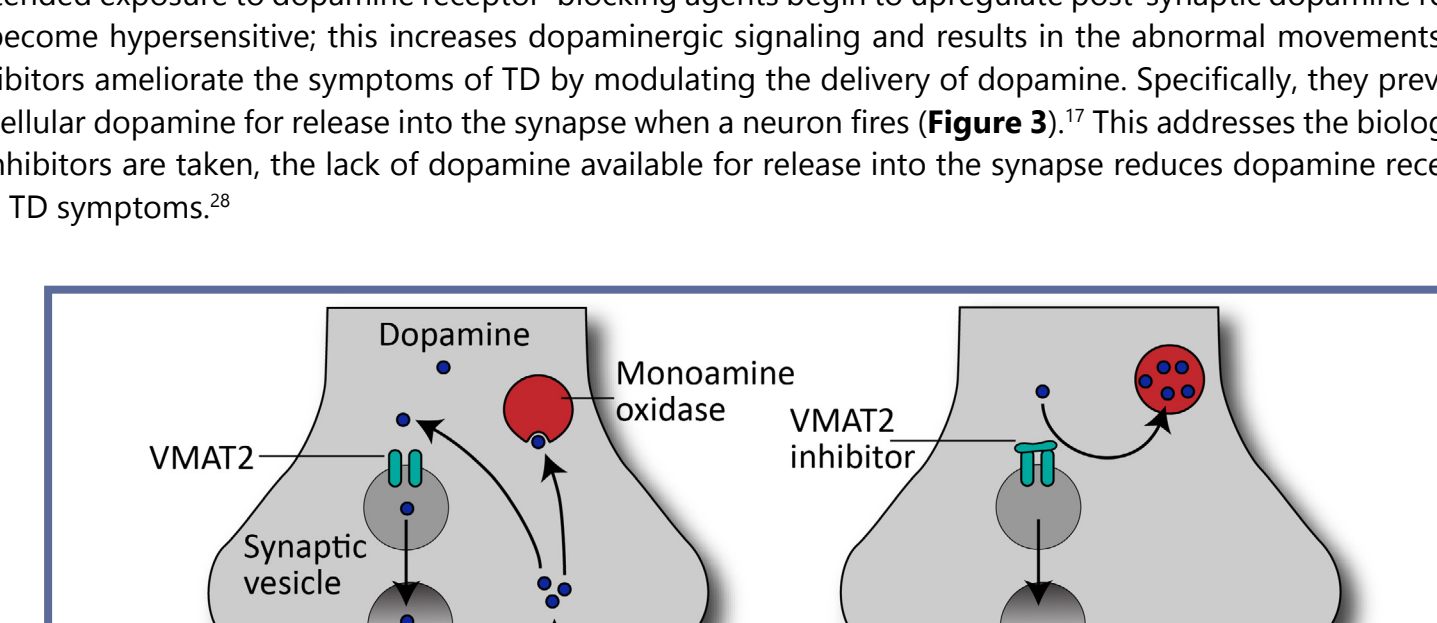
1. A history of at least 3 months' total cumulative exposure to a dopamine receptor-blocking agent
2. Presence of at least "moderate" (≥ 3 on the AIMS) abnormal, involuntary movements in 1 or more body areas or at least "mild" (≥ 2 on AIMS) movements in 2 or more body areas
3. Absence of other conditions that might produce abnormal involuntary movements.

AIMS = Abnormal Involuntary Movement Scale

Good clinical judgment should be used in determining whether a diagnosis of TD is warranted, and there are a few caveats. A low AIMS score does not necessarily indicate a mild problem. Even involuntary movements that yield low scores may require action if they are causing a patient distress or may portend a worse problem in the future. For example, a patient may feel humiliated by even mild lip-smacking, and tic-like lingual movements may be a sign that early intervention is required.¹

Supplementing the AIMS with information on functional impairment can also be very helpful. Clinicians can ask patients and their caregivers questions about how involuntary movements affect their lives. These concrete examples of impaired function can be used alongside AIMS to gauge how well a patient's TD treatment plan is working. It may even be helpful to record a patient's own words at baseline, to see if their descriptions of their movements and the impact of those movements change over time.²²

Faculty Video



Joseph P. McEvoy, MD

Preventing and managing TD

A conservative approach to the use of antipsychotics is critical in preventing TD from developing or worsening.⁵ This approach should include prescribing dopamine receptor-blocking agents only when they are indicated and minimizing the duration of their use.²³ It is also important to establish the lowest effective dose of a patient's dopamine receptor-blocking agent: TD is more likely to occur at higher doses.²³ Lowering the dose of a patient's antipsychotic should be done with care, however. Among patients with schizophrenia or mood disorders,²³ research shows that tapering the dose of their antipsychotics more than 10% is associated with an increase in all-cause and mental health-related hospitalizations.^{24,25} Clinicians should also be aware that reducing the dose of a dopamine receptor-blocking agent can actually temporarily worsen TD symptoms.²⁶

Discontinuing a dopamine receptor-blocking agent entirely should be approached with even more caution than reducing the dose, due to the potential for relapse.²⁶ Discontinuation might be an appropriate option for a patient with a mood disorder who has achieved recovery using an antipsychotic to control their psychosis, however.²⁶ It should also be noted that discontinuing dopamine receptor-blocking agents may not stop many patients' involuntary movements. In one study of 108 patients who discontinued the medication causing their TD, only 13% saw their involuntary movements completely resolve within the next 3 years.¹³

In reality, many patients choose to remain on TD-causing agents to control their psychiatric symptoms. Fortunately, these patients have several treatment options. Currently, vesicular monoamine transporter (VMAT2) inhibitors are the first-line therapy for patients experiencing TD despite being on the lowest effective dose of their dopamine receptor-blocking agents.⁶ Other potential TD treatments include vitamin B6 and amantadine, though the evidence base for these options is weaker.²⁷ Finally, some patients may be able to switch to a dopamine receptor-blocking agent that is less likely to cause or worsen TD; eg, they may be able to switch from an FGA to an SGA.²⁶

VMAT2 inhibitors

Patients with extended exposure to dopamine receptor-blocking agents begin to upregulate post-synaptic dopamine receptors, and the receptors also become hypersensitive; this increases dopaminergic signaling and results in the abnormal movements associated with TD.²⁸ VMAT2 inhibitors ameliorate the symptoms of TD by modulating the delivery of dopamine. Specifically, they prevent VMATs from delivering intracellular dopamine for release into the synapse when a neuron fires (Figure 3).¹⁷ This addresses the biological cause of TD. When VMAT2 inhibitors are taken, the lack of dopamine available for release into the synapse reduces dopamine receptor stimulation and ameliorates TD symptoms.²⁸



Figure 3. Mechanism of action for VMAT2 inhibitors. VMAT = vesicular monoamine transporter. Adapted from Cummings MA, Proctor GJ, Stahl SM. Deuterium tetrabenazine for tardive dyskinesia. *Clin Schizophr Relat Psychoses*. 2018;11(4):214-220.

Both short-term²⁹⁻³² and long-term³³⁻³⁵ clinical trial data show that the VMAT2 inhibitors valbenazine and deutetrabenazine significantly improve TD symptoms relative to placebo. These agents have been shown to be effective regardless of age, the underlying psychiatric disorder, or whether or not the patient is still taking a dopamine receptor-blocking agent.^{31,36,37} Both short-term²⁹⁻³² and long-term³³⁻³⁵ clinical trial data also show that the drugs are well-tolerated. In fact, at this point, multiple studies lasting a year or longer have demonstrated continued safety, improvement in involuntary motions, and patient satisfaction.³³⁻³⁵

Several approaches can be used to individualize TD treatment with VMAT2 inhibitors. With regard to selecting an agent, a major difference between valbenazine and deutetrabenazine is the two agents are metabolized, and thus how many times a day they need to be taken (once a day for valbenazine, twice a day for deutetrabenazine) and whether it is necessary to take them with food (required for deutetrabenazine).¹⁷ Some patients and caregivers may feel it is important to have a once-daily treatment, whereas others may not. Dosing also differs between the 2 agents.²⁶ Valbenazine is initiated at 40 mg/d for a week and can either be maintained at that level or increased to 80 mg/d; deutetrabenazine can be titrated in up to 4 steps, starting at 6 mg twice daily per week and then increasing weekly in 6 mg intervals per dose, if needed, up to 24 mg twice daily.²⁶ After a patient has initiated VMAT2 inhibitor treatment, AIMS scores, in concert with discussions with patients and their caregivers about function and quality of life, can be used to track symptom improvement over time.²²

Clinicians can also use several practical strategies to ensure the long-term success of a TD treatment plan, including involving both patients and caregivers in therapy selection and implementation. VMAT2 inhibitors do not cure TD. Many patients will need to continue following their TD treatment plan indefinitely, which will often require the ongoing support of their caregivers. Thus, input from all parties involved about issues such as effectiveness, tolerability, and adherence is helpful. In particular, the unique insights that a caregiver has into the severity of a patient's involuntary movements can be invaluable for tracking how effective the treatment plan is—and when a modification is in order. Clinicians should also ask patients and their caregivers about sleepiness during the day, sadness, and parkinsonism, which are among the adverse events associated with VMAT2 inhibitors.²²

Conclusion

For many frustrating years, clinicians had no effective treatments to offer patients with TD, and the condition was largely ignored. With the approval of VMAT2 inhibitors, which are both effective and tolerable, this situation has changed. Now that TD can be managed, it is critical to detect it early. Even mild cases can cause misery for patients whose involuntary movements result in stigma or functional impairment, and patients' loved ones are affected as well. In short, the time for action is now: Any healthcare provider who treats patients taking dopamine receptor-blocking agents has the potential to improve lives by promptly diagnosing and treating TD.

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