Revisiting Tardive Dyskinesia: Focusing on the Basics of Identification and Treatment

Leslie L. Citrome, MD, MPH, and Stephen R. Saklad, PharmD, BCPP

Tardive dyskinesia (TD) is a potentially permanent, hyperkinetic movement disorder associated with the use of dopamine-receptor blocking agents (DRBAs).1 It is often believed that TD is associated only with antipsychotics; however, other DRBAs are also associated with this neurologic disorder, such as the promotility agent metoclopramide.

The prevalence of TD is higher than commonly thought. A meta-analysis2 of 41 studies included over 11,000 patients with an average age of 43 years. Two-thirds of these patients were men, and more than three-quarters had a schizophrenia spectrum disorder. The overall prevalence of TD in this sample was 25%. The TD rate for those with current use of a second-generation antipsychotic (SGA) was lower than in those with current use of a first-generation antipsychotic (FGA); 21% vs 30%, respectively. The small number of patients with current SGA use and no prior FGA exposure had a TD prevalence rate of 7.2%,2 perhaps because they represent a different group of patients who have not been exposed to antipsychotics for as long as the other cohorts who have been exposed to FGAs.

Clinicians must detect TD early to minimize the risk of the patient’s DRBA-induced movement disorder worsening or becoming permanent. The management of TD is a challenge for clinicians whose patients rely on DRBAs for treatment of their chronic conditions. In this Academic Highlights, Drs Citrome and Saklad discuss best practices for improving the early recognition and diagnosis of TD and tailoring treatment strategies, including the use of valbenazine and deutetribenazine, which have been approved by the US Food and Drug Administration (FDA) for the treatment of TD in adults.

IDENTIFYING TARDIVE DYSKINESIA

Dr Saklad explained that many people with TD are unaware of their abnormal movements until someone else points them out. A family member described noticing the symptoms and seeking help:

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Academic Highlights

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Impact of TD on Functioning and Quality of Life

The abnormal, involuntary movements of TD contribute to functional impairment, negatively affecting patients’ quality of life. To investigate the burden of TD in a real-world population of patients taking antipsychotics, a study evaluated health-related quality of life in participants without visible signs of involuntary movements (Cohort 1) and participants with visible signs and clinical assessment of possible TD (Cohort 2). A higher percentage in Cohort 2 reported having problems in mobility, self-care, usual activities, and pain/discomfort than those in Cohort 1. Those with probable TD also had greater impairment in work/school, social life, and family life/home responsibilities compared to those without TD.

Risk Factors for TD

The risk-benefit ratio of DRBAs must be evaluated and individualized with each patient. In an effort to prevent TD, clinicians must consider the type and dose of medication, as well as whether other interventions (e.g., psychosocial) could be used to treat the patient’s illness instead of a DRBA. Dr Saklad emphasized the need for clinicians to communicate clearly with patients and document their discussions about treatment options. All patients taking DRBAs, he said, should be educated on the risk for and symptoms of TD.

The pathophysiology of TD is unknown but is believed to involve postsynaptic dopamine receptor hypersensitivity. Other possible explanatory models for TD include abnormalities in GABA and/or cholinergic neuronal activity, neurotoxicity and oxidative stress, changes in synaptic plasticity, and defective neuroadaptive signaling, with potential overlap with all of these mechanisms.

According to Dr Saklad, factors increasing the risk of TD may involve the patient directly or may be related to treatment, illness, or other factors. Both patient and other factors can be non-modifiable or modifiable. The most important risk factors for developing TD are advancing age and cumulative exposure to DRBAs. A more complete list and additional details follow.

Non-modifiable factors. Non-modifiable patient factors include the following:
specific than the Schooler-Kane criteria in the time of exposure to DRBA medications as clinically indicated and to minimize the dose and duration of exposure to DRBA medications as clinically appropriate.

Concomitant anticholinergic medications can increase the risk of TD.9 Anticholinergic medications that cross the blood-brain barrier can include agents used to treat acute drug-induced parkinsonism, acute dystonia, Parkinson’s disease, gastrointestinal problems, and enuresis. According to Dr Saklad, clinicians should avoid these medications if possible because they can worsen symptoms of TD and also cause cognitive impairment and many other problems.10

Diagnostic Tools for TD

Dr Saklad recommended that clinicians be familiar with diagnostic criteria, differential diagnosis, and use of an assessment tool such as the Abnormal Involuntary Movement Scale (AIMS). The criteria. The Schooler–Kane criteria12 for TD are widely used in clinical practice to determine probable TD. Schooler–Kane criteria require (1) at least 3 months of cumulative exposure to a DRBA; (2) at least moderate dyskinetic movements in 1 body area (≥3 score on an AIMS dyskinesia item) or mild dyskinetic movements in 2 body areas (≥2 score on ≥2 AIMS dyskinesia items); and (3) absence of other conditions that might cause involuntary movements.

The criteria for TD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,13 are less specific than the Schooler–Kane criteria in the time requirement for DRBA exposure, stating that involuntary movements develop with the use of neuroleptic medication for “at least a few months” and that the time may be shorter for older adults.14

The involuntary movements are frequently observed in the tongue, jaw, and perioral area, as well as in the trunk and the extremities. Common oro-facial movements include chewing; lip smacking, puckering, or pursing; tongue protrusion; grimacing; or cheek bulging.15 Other signs include contracting, twisting, or writhing movements of the fingers, hands, arms, or legs. These involuntary movements are usually choreiform or athetoid and are usually clearly distinguishable from the regular rhythmic 3–6 Hz movements seen with drug-induced parkinsonism.13

Differential diagnosis. Many conditions and syndromes can cause abnormal movements that resemble TD and must be ruled out; thus, TD is a diagnosis of exclusion (Table 1).14

Dr Saklad stated that spontaneous dyskinesias are often difficult to differentiate from TD. Spontaneous dyskinesias are fairly common in elderly patients and patients with schizophrenia who have never been exposed to DRBAs and are often noted in the same body areas typically associated with TD. While TD is the most common abnormal movement syndrome,16 clinicians should be familiar with the other tardive syndromes.17,18 Drug-induced dyskinesias from stimulants can present a diagnostic challenge because amphetamines and methamphetamines interact with some of the same neurotransmitter transporter systems that are involved in the treatment of TD.19

Distinguishing characteristics can help clinicians determine if patients have TD versus drug-induced parkinsonism (previously called pseudoparkinsonism; Table 2).20

Abnormal Involuntary Movement Scale. A rating scale cannot be exclusively used to diagnose TD, but it can establish and quantify the presence of abnormal
movements and be used in follow-up. Dr Saklad pointed out that other rating scales besides the AIMS may also be used (such as the Dyskinesia Identification System: Condensed User Scale [DISCUS]) as long as training is provided. Whatever scale is used, a baseline assessment is essential to document the presence of any movements before DRBA treatment begins.

In addition to conducting an initial assessment before treatment, the APA guideline recommends that patients be evaluated for TD every 6 months while receiving an FGA and every 12 months while receiving an SGA. Patients with risk factors for TD should be examined every 3 months while receiving an FGA and every 6 months while taking an SGA. Dr Saklad noted that clinicians may assess more frequently as indicated.

The AIMS takes about 10 minutes to administer. Items 1–7 are the specific dyskinesia items for 7 different muscle groups, and the other questions relate to overall severity, incapacitation, awareness of movements, and dental issues. Below are general steps for clinicians to follow:

- Observe patients unobtrusively at rest either before or after administering the exam, such as while they are sitting in the waiting room.
- Have patients sit in a firm unpadded chair or stool without arms and remove their shoes and socks.
- Ask patients if they have experienced involuntary movements and, if so, whether they are bothered by them.
- Ask patients about any problems with their teeth or gums, if they have dentures, and if they are chewing anything.
- Look for evidence of involuntary movements in the patient's entire body while asking them to perform tasks that include sticking out their tongues, tapping their thumbs to each finger, and extending their limbs. These tasks occupy the patient's attention and decrease their ability to suppress abnormal movements. Moreover, voluntary movements in one muscle group may facilitate the production of involuntary movements in other muscle groups, and these “activating maneuvers” can simulate what happens to persons with TD when they go about with their routine activities, such as getting dressed, walking, talking, and eating.

For scoring movements on the AIMS 5-point scale (from 0 = none/normal to 4 = severe), Dr Saklad recommended clinicians keep in mind that minimal is the extreme edge of normal. So, a questionable movement would be rated as 1 = minimal, and 2 = mild is the first point where movements are definitively abnormal. For item 8 of the AIMS (global judgment of the severity of abnormal movements), the overall severity is the highest rating assigned in items 1–7. Item 9, global judgment of incapacitation due to abnormal movements, is rated from 0 = none/normal to 4 = severe. Item 10 rates the patient's awareness of abnormal movements and level of distress due to the abnormal movements on an adjusted scale of 0 = no awareness to 4 = awareness with severe distress. Items 11 and 12 document dental status. Additional items have been included in other versions of the AIMS.

### Case Practice Question

**Discussion of the best response is at the end of the activity.**

**Case 1.** Frank is a 32-year-old man with bipolar disorder and TD. You want to assess how the TD symptoms may be impacting his functioning. What rating scale will best help you evaluate this aspect of Frank's care over the long term?

- a. Functional Impairments Scale for Tardive Dyskinesia
- b. The AIMS
- c. Simpson-Angus Scale
- d. Sheehan Disability Scale

### TREATMENT FOR TARDIVE DYSKINESIA

The American Academy of Neurology (AAN) published evidence-based recommendations in 2013 regarding management of tardive syndromes, including TD. These guidelines also described treatment options that are not recommended and those that lack sufficient data to support (or refute) their use. Since the publication of the guidelines, valbenazine and deutetrabenazine were approved by the US FDA for the treatment of TD in adults. Recently, new evidence was combined with existing guidelines to provide updated recommendations. Notably, the reviewers found insufficient evidence to support or refute the treatment strategies of withdrawing causative agents or switching from an FGA to an SGA. An individual living with TD described her experience with switching her DRBA:

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Based on Ward and Citrome.

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The Evolution of TD Treatment Options

Options prior to FDA-approved medications. Some evidence-based options that were outlined in the 2013 AAN recommendations included clonazepam, Ginkgo biloba, amantadine, and tetrabenazine. Not recommended were diltiazem, galantamine, and eicosapentaenoic acid. The following options had insufficient data to support or refute their use for the management of TD: bromocriptine, thiamine, baclofen, and vitamin E. The medication benzotropine is sometimes incorrectly used for TD, but it is not approved nor effective for the treatment of TD; Dr Citrome explained that it may increase the risk of TD and can even make TD symptoms worse.

FDA-approved TD medications. Approved by the FDA in 2017, valbenazine and deutetrabenazine are reversible vesicular monoamine transporter type 2 (VMAT2) inhibitors and are related to tetrabenazine, an FDA-approved drug for the treatment of chorea in Huntington’s disease but not for TD (at least in the US). The normal function of VMAT2 is to transport monoamines, such as dopamine, into synaptic vesicles for release into the synaptic cleft when the neuron fires. VMAT2 inhibitors block the transport of dopamine into synaptic vesicles, thereby reducing the amount of dopamine released into the synapse, particularly in the dorsal striatum, a key area of the brain that controls motor movements. This mechanism of action is believed to ultimately decrease the occurrence of dyskinetic movement.

Two individuals described how treatment for TD has improved their lives:

"I thought while I had those tremors and everything that I wasn’t ever going to get past this, that I was going to have to live that way the rest of my life. And it’s like I just didn’t think I could handle that forever, until I got put on this last medicine and it was able to calm everything down. But I did not think I would live through that if I didn’t have help."

"When I first started the medicine, I wouldn’t go anywhere in public. I pretty much stayed in my house and tried to hide the movements, but . . . about a week after I got on this medicine, I started being able to go out in public. I went to the mall with my mom and walked around and, nope, didn’t feel awkward about it. I’ve been able to do a lot of things like play baseball or softball or football or volleyball with my nieces and nephews, and that’s something I couldn’t do before."

Valbenazine and Deutetrabenazine Evidence

The treatment of TD with valbenazine and deutetrabenazine is supported by clinical trial evidence with much larger sample sizes than in studies of tetrabenazine, noted Dr Citrome. These newer medications were examined in randomized, double-blind, placebo-controlled trials, using both flexible-dose and fixed-dose designs. The results showed significantly greater reductions in TD symptoms in patients receiving valbenazine (fixed-dose, with target of 80 mg/d) and deutetrabenazine (flexibly dosed within the range of 6 mg BID to 24 mg BID, with food) than in patients who received placebo.

Adverse effects. In 3 placebo-controlled studies of valbenazine, somnolence was the most common adverse effect (10.9%, more than twice the rate with placebo). Few patients discontinued the trials because of adverse events (3% for valbenazine vs 2% for placebo).

In trials of deutetrabenazine, 2 adverse events occurred in 4% of patients treated with the drug and at an incidence greater than that observed with placebo: nasopharyngitis and insomnia. Few patients required a dose reduction because of adverse events (4% for deutetrabenazine vs 2% for placebo). Few patients discontinued the trials because of adverse events (3.6% for deutetrabenazine vs 3.1% for placebo).

Efficacy. The efficacy of deutetrabenazine and valbenazine can be indirectly compared by examining the number of patients who experienced at least a 50% reduction in the AIMS dyskinesia score from baseline to endpoint and calculating the number needed to treat (NNT) versus placebo and the respective 95% confidence intervals (CIs). The results of the phase 3 fixed-dose studies (ie, a 6-week valbenazine study and a 12-week deutetrabenazine study) resulted in an NNT of 5 for both VMAT2 inhibitors at doses considered efficacious. Specifically, these NNTs are based on pooled data from the 12 mg BID and 18 mg BID deutetrabenazine doses and the 40 mg/d and 80 mg/d valbenazine doses. An NNT of 5 for a medication vs placebo can be considered to be a moderate “effect size” and denotes a potentially useful intervention.

Clinical Strategies

According to Dr Citrome, deutetrabenazine and valbenazine are both effective medications, but...
Academic Highlights

**Figure 1. Valbenazine vs Deutetrabenazine for Tardive Dyskinesia: Key Differences**

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Valbenazine: Once daily</th>
<th>Deutetrabenazine: Twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titration</td>
<td>Valbenazine: Titrate to target dose of 80 mg/d</td>
<td>Deutetrabenazine: Dose to efficacy/tolerability</td>
</tr>
<tr>
<td>Need for food</td>
<td>Valbenazine: No</td>
<td>Deutetrabenazine: Yes</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Valbenazine: CYP2D6 and CYP3A4 modulators</td>
<td>Deutetrabenazine: CYP2D6 modulators</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Valbenazine: Known hypersensitivity to valbenazine or any components of the product</td>
<td>Deutetrabenazine: Hepatic impairment; taking reserpine, monoamine oxidase inhibitors, tetrabenazine, or valbenazine</td>
</tr>
</tbody>
</table>

clinicians should be aware of key differences (Figure 1).\(^{28,38,39}\) Differences include dose titration and daily frequency, need for dosing with meals, potential drug interactions, and contraindications.

Dr Citrome highlighted the following important facts about deutetrabenazine and valbenazine\(^{28,41,42}\):

- Both medications are effective and well-tolerated in reducing abnormal TD movements, which often cause substantial physical, social, and psychological impairment (irrespective of the patient's underlying psychiatric diagnosis)
- Patients taking VMAT2 inhibitors can remain on antipsychotic therapy, which will reduce the risk of psychiatric decompensation; there is no need to discontinue, reduce, or change the treatment regimen. This is especially important in persons with stable schizophrenia for whom changes in antipsychotic regimens can be difficult to manage
- The treatment goal with VMAT2 inhibitors is to reduce the severity and impact of TD
  - Treatment may not eliminate all signs of TD
  - Attempting to completely suppress all TD symptoms will likely result in overtreatment and a greater potential for adverse effects
- Customize medication selection by considering
  - Ease of adherence
  - The ability to fine-tune the daily dose
  - Side-effect profile

If the patient is already taking mood stabilizers and/or antidepressants, he or she can continue therapy with them
- Neither of the FDA-approved TD medications, relative to placebo, destabilizes depression, mania, or psychosis or induces suicidality\(^{36,43}\)
- Long-term data are reassuring; no new safety signals or concerns emerged with either medication\(^{44,45}\)
- Tolerability and efficacy could vary among individual patients.

A family member of an individual living with TD described how treatment has lifted the burden that TD had placed on his uncle’s life:

Assessing functional impairment. After a patient's treatment for TD is initiated, Dr Citrome emphasized the need for follow-up assessments to be conducted on a regular basis. It is not adequate to measure the AIMS dyskinesia items alone, he said. The follow-up questions regarding functional impairments attributable to TD must be asked (interference with daily activities such as eating, drinking, speaking, breathing, dressing, writing, working, and socializing). Dr Citrome reiterated that clinicians must be proactive in discussing these issues with patients.

Case Practice Question

Discussion of the best response is at the end of the activity.

**Case 2.** Susan is a 50-year-old woman with schizophrenia who is now experiencing dyskinetic movements of her mouth and jaw. She is also having difficulties tying her shoelaces because of intermittent dyskinetic movements of her fingers. You make the diagnosis of TD, and you want to select treatment. Which of the following would be among the best options?

- a. Valbenazine, deutetrabenazine, and possibly benzotropine
- b. Valbenazine, deutetrabenazine, and possibly vitamin E
- c. Valbenazine, deutetrabenazine, and possibly amantadine
- d. Valbenazine, deutetrabenazine, and possibly galantamine
Clinical Points

- Assume that TD exists in your practice and will continue to occur because of greater use of antipsychotic medications.
- Consider and communicate the risks and benefits of DRBA use with patients.
- Be aware of risk factors for TD that can and cannot be modified.
- Regularly assess for TD using a rating scale like the AIMS in patients taking DRBAs.
- Prevent TD if possible by minimizing acute drug-induced parkinsonian symptoms by selecting agents with lower risk for this problem and minimizing the use of anticholinergic medication.
- Treat TD as quickly as possible after it appears with effective, well-tolerated, approved medications.

Discussion of Case Practice Questions

Case 1: Preferred response is b.
The AIMS already includes items that address not only subjective distress and awareness of TD but also any incapacitation due to abnormal movements. No extra scale is necessary.

Case 2: Preferred response is c.
Both valbenazine and deutetrabenazine are FDA-approved specifically for the management of TD. Amantadine has some evidence of efficacy in ameliorating TD. Benzotropine can worsen TD; vitamin E has insufficient evidence for use in treating TD; and galantamine is not recommended for use in treating TD.

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Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, the only interventions that are approved by the US Food and Drug Administration for the treatment of tardive dyskinesia are valbenazine and deutetrabenazine.

REFERENCES

Academic Highlights

1. You are evaluating a 65-year-old African American man, Lenny, with abnormal motor movements, and you suspect that he has developed tardive dyskinesia (TD). Your reasoning includes the following factors:
   a. Advancing age can cause TD.
   b. Lenny has been taking a second-generation antipsychotic agent for severe recurrent depression.
   c. Lenny has been taking a serotonin-norepinephrine reuptake inhibitor for severe recurrent depression.
   d. Lenny has taken methylphenidate-containing agents in the past.

2. You are ready to perform a complete evaluation of Lenny for TD, with follow-up as needed. Measurement tools for evaluating TD and the recommended schedule are ___.
   a. AIMS, DISCUS, PHQ-9, and MADRS every 6 months
   b. AIMS and DSM-5 criteria annually
   c. AIMS or DISCUS every 6 months
   d. AIMS, PANSS, and DISCUS every 12 months

3. You are treating a 40-year-old woman, Sherry, who has cognitive impairment associated with schizophrenia and has developed abnormal motor movements. If you add an anticholinergic medication, Sherry may experience which of the following effects?
   a. Amelioration of drug-induced parkinsonism and reduction of dyskinetic movements but worsening of cognitive functioning
   b. Amelioration of drug-induced parkinsonism but worsening of dyskinetic movements and cognitive functioning
   c. Worsening of drug-induced parkinsonism and dyskinetic movements but improvement in cognitive functioning
   d. Amelioration of drug-induced parkinsonism, worsening of dyskinetic movements, and improvement in cognitive functioning