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TARGET AUDIENCE

This activity is intended for physicians, physician assistants, nurse practitioners, registered nurses, and pharmacists engaged in the care of patients with psychiatric illness.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:
- Discuss an overview of tardive dyskinesia (TD).
- Identify the traditional treatment approaches for TD and understand their limitations.
- Recognize details from recent research relating to efficacy and safety of novel treatment options for TD.

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Diagnostic Dilemmas in Patients With Tardive Dyskinesia

Greg W. Mattingly, MD

BOTTOM LINE

While many clinicians are familiar with the need to screen for tardive dyskinesia (TD) in schizophrenia, current data show that >75% of atypical antipsychotic use is for other indications, emphasizing the need to screen for medication-induced movement disorders in patients with depression, bipolar disorder, anxiety, and other psychiatric disorders for which antipsychotic treatment is used.

While most clinicians remember a schizophrenia patient with complex tardive dyskinesia (TD), very few were taught to screen the variety of patients who now receive dopamine-modulating medications. Patients with complex mood and anxiety disorders were historically treated with antidepressants and mood stabilizers, but clinical trends in treatment have shifted dramatically over the past 20 years.[1,2]

With the development of atypical antipsychotics, we have seen substantial changes in how bipolar, mood, and complex anxiety disorders are treated. Over the past several decades, the use of lithium and other traditional mood stabilizers has decreased, and these agents have been replaced by atypical antipsychotics. More than 50% of individuals with bipolar disorder now receive atypical antipsychotics. Statistics show the use of atypicals increased from 4.6% to 19% in adults with major depression from 2000 to 2015.[3,4]

Prescription statistics indicate that only 23% of atypicals are currently prescribed for schizophrenia, with 26% for bipolar disorder, 21% for major depression, and 30% for other conditions.[5] A review of 164,000 adults receiving atypicals found that, among individuals with TD, the most common overlapping diagnoses were neurotic/anxiety disorders (53%), mood disorders (50%), and schizophrenia (46%).[6]

In 2020, the American Psychiatric Association published a list of risk factors associated with increased vulnerability to TD, including:
- Age >55 years
- Female sex
- White or black race
- Past or current extrapyramidal side effects (EPS)
- Presence of mood disorder, intellectual disability, or central nervous system (CNS) injury[7]

A recent study found that antipsychotic exposure was an obvious risk; however, individuals on benztropine had the highest overall TD rate with a 225% relative risk.[8]

Diagnosing TD

It is crucial to differentiate TD from other movement disorders seen in patients receiving psychotropic medications. Numerous medications can cause tremors, including lithium, valproate, stimulants, and selective serotonin reuptake inhibitors (SSRIs).[9] Medication-induced tremors are typically dose-related, regular, and rhythmic, which are features not typically seen with TD. Recommended treatment for acute/subacute medication-related tremors not due to antipsy-

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chotics includes decreasing the dose of the precipitating medication and/or the use of propranolol.

Antipsychotic-induced parkinsonism is hypokinetic, involving a "pill rolling" tremor, "cogwheel" rigidity, bradykinesia, retropulsion, and slow gait.[10] Parkinsonism often occurs after starting an antipsychotic or increasing the dose. Reducing antipsychotic exposure usually improves symptoms over time, and anticholinergics or amantadine usually improve parkinsonian tremors. On the other hand, TD-related movements are irregular and nonrhythmic. Onset usually begins after prolonged exposure to dopamine-modulating medications. Reduction of the antipsychotic dose temporarily worsens TD while increasing the dose temporarily masks TD. Anticholinergics are *not* recommended and may worsen TD symptoms and possibly accelerate the progression of TD.

Both TD and akathisia can be induced by antipsychotics. Complex TD can be confused with akathisia especially when the trunk or lower extremities are involved. An inner sense of restlessness often seen with akathisia is usually absent with TD. Akathisia worsens with increasing the dose of antipsychotic, improves with decreasing the dose, and often improves with benzodiazepines or beta blockers, which have little benefit for patients with TD.

TD most often involves areas of the body represented neurologically in the "homunculus" or primary motor strip: the tongue, lips, and fingers. Correspondingly, TD is most often seen in the tongue, lips, face, and fingers, but can also involve the trunk and feet. Over 53% of patients have 2 or more body regions affected.[11]

The Abnormal Involuntary Movement Scale (AIMS) is the gold standard for evaluating TD, but recent studies have examined the value of patient self-screening. One study found that, in patients who were given a diagrammatic image of the body and asked to report abnormal tremors in the tongues/lips, fingers/hands, lower extremities, and trunk/torso, patient identification was highly correlated with clinician evaluation ($P<0.001$) and very sensitive for detecting TD.[12]

TABLE 1. Parkinsonism vs tardive dyskinesia

	Parkinsonism	TD
Current exposure to dopamine receptor 2 (D2) antagonist (especially more potent agents)	Yes	Not necessarily (requires past exposure)
Tremor	Yes	No
Predominant movement type	Hypokinetic, regular	Hyperkinetic, irregular
Rigidity	Often	No
Onset	After dosage increase	After prolonged exposure
Effect of antipsychotic reduction/discontinuation	**Improves symptoms**	**May transiently worsen symptoms**
Effect of anticholinergics or amantadine	Improves tremor, rigidity	Worsens dyskinesia
Note: TD and parkinsonism can co-exist		

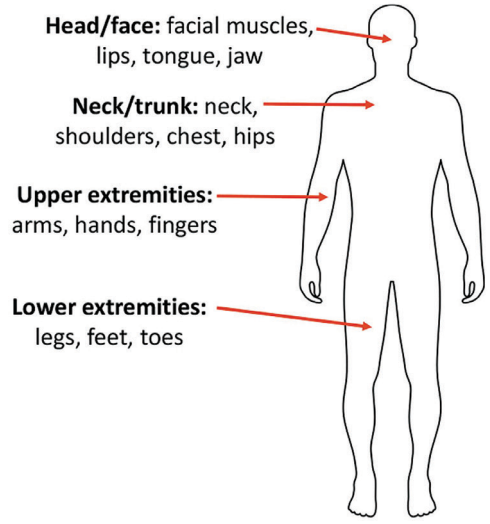
Hot tip: Increasing the dose of antipsychotic temporarily masks TD but worsens it over time!

With the advent of telehealth, physical examination has become less frequent, making patient-reported screening more important. Overall mental health visits increased from pre-pandemic levels, with the vast majority involving telehealth.[13] Nearly 60% of visits were audio only with no visual component.

It is essential for clinicians to screen consistently and ask the right questions. The "TD-3" questions should be asked of any patient taking dopamine-modulating medications:

1. Have you noticed unusual movements in your tongue or lips?
2. Have you noticed any unusual movements in your hands or fingers?
3. Is there any other part of your body where you have noticed abnormal tremors or movements?

FIGURE 1. Patient Screening for TD



Body Location	None	Some	A lot
Face, lips, jaw, tongue			
Arms, wrists, hands, fingers			
Legs, ankles, feet, toes			
Neck, shoulders, hips			

Summary: With increased use of atypical antipsychotics for numerous indications, TD will present not only in schizophrenia but also in patients with mood or complex anxiety disorders or developmental disabilities. Recent self-report screeners have shown patients can be very sensitive in detecting TD *when asked the right questions*. Patients at high risk for developing TD include those who previously developed EPS, patients receiving anticholinergics, women, and those over the age of 55. Three mistakes that can place both your patients and your practice at risk include:

1. Forgetting to screen for TD in mood, anxiety, and other mental health conditions
2. Missing the diagnosis of TD in individuals prescribed anticholinergics
3. Increasing doses of antipsychotic, temporarily "masking" TD

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Choosing the Right Treatment for Tardive Dyskinesia

Manish K. Jha, MBBS

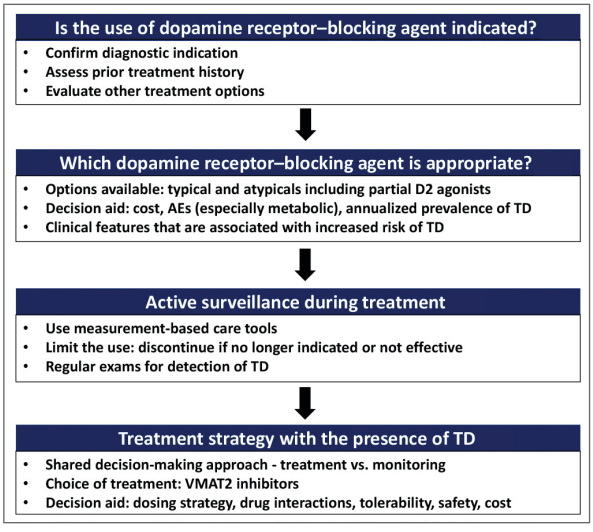
BOTTOM LINE

Valbenazine and deutetrabenazine are US Food and Drug Administration–approved medications for improving tardive dyskinesia, a movement disorder associated with use of dopamine receptor-blocking agents including antipsychotics. In the absence of head-to-head comparisons between these 2 medications, patients and clinicians may choose based on dosing considerations, titration schedule, administration with food, medication interactions, tolerability, and cost.

Tardive dyskinesia (TD) is a movement disorder associated with chronic use of dopamine receptor-blocking agents (DRBAs) including first- (FGA) and second-generation (SGA) antipsychotics. Despite the risks of developing TD, these medications are often used given their efficacy in psychiatric conditions such as schizophrenia, autism spectrum, bipolar disorder, and major depressive disorders.[1-4] Patients often take these medications for prolonged periods given the chronic nature of these conditions.[5]

Management of TD **(FIGURE 1)** starts with deciding to use a DRBA after confirming the diagnostic indication and evaluating response to prior treatments. Cross-sectional studies show that patients who have only received SGAs have on average a 4-fold lower prevalence of TD compared to those on FGAs.[6] Measurement-based care should be used when prescribing DRBAs to maximize likelihood of improvement while minimizing side-effect burden and promoting adherence.[7-9] Antipsychotics should be discontinued if they are no longer

FIGURE 1. Systematic approach to TD management



D2, dopamine receptor D2; VMAT, vesicular monoamine transporter.

TABLE 1. Considerations for selecting VMAT2 inhibitors

	Valbenazine	Deutetrabenazine
Metabolites	[+] alpha HTBZ, highly selective for VMAT2 receptors	[+]/[-] alpha and beta HTBZ, varying affinity for VMAT2, also binds to dopamine and serotonin receptors
Interactions	Strong CYP3A4 inhibitors and inducers, CYP2D6 inhibitors, CYP2D6 poor metabolizers, monoamine oxidase inhibitors	Strong CYP2D6 inhibitors, CYP2D6 poor metabolizers, monoamine oxidase inhibitors
Dosing	Start at 40 mg/day, after 1 week increase to 80 mg/day. A 60-mg dose is now available	Start at 12 mg/day (2 divided doses), titrate weekly by 6 mg/day. Maximum dose is 48 mg/day
Food	Can be taken with or without food	Administered with food
Cost	Varies based on payer	

HTBZ, dihydrotetrabenazine; CYP, cytochrome P450 enzymes.

indicated or effective. Patients prescribed these medications on a chronic basis should be examined regularly for TD.

After the onset of TD, rapid withdrawal of DRBAs may temporarily worsen dyskinesia, and the benefits of this strategy remain uncertain.[10] A recent systematic review found insufficient evidence regarding utility of discontinuing DRBAs or suggest that switching from FGAs to SGAs after TD onset.[10] Findings suggest that reducing doses of antipsychotics during the maintenance phase of schizophrenia below the standard dose range used for acute stabilization increased relapse risk.[11] Therefore, treatment for TD often includes continuation of DRBAs.

There are 2 US Food and Drug Administration (FDA)-approved selective vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, both of which have established efficacy in improving dyskinesia, including patients who remain on antipsychotics.[10,12-14] Both agents inhibit transport of dopamine within presynaptic neuronal vesicles, thereby reducing dopamine release in the synaptic cleft.[12] Evidence that this mechanism can improve TD symptoms is supported by multiple, small, open-label studies with tetrabenazine.[15-17] However, therapeutic utility of tetrabenazine is limited by side effects, short half-life, and lack of placebo-controlled studies. Tetrabenazine is rapidly metabolized to alpha- and beta-dihydrotetrabenazine (HTBZ), the basis for the 2 FDA-approved medications.[12] Valbenazine is a prodrug of [+]-alpha-HTBZ, a metabolite with very high affinity for VMAT2 and limited to no affinity for dopamine or serotonin receptors.[12] Deutetrabenazine, or deuterated tetrabenazine, has slower breakdown of metabolites allowing for less frequent dosing than tetrabenazine.[10]

Efficacy of valbenazine 40 mg and 80 mg vs placebo was established in phase 3 trials, and a 60-mg dose is now also available.[13] In phase 3 trials, deutetrabenazine flexible dosing (12-48 mg/day) or fixed dosing (24 and 36 mg/day) was associated with greater improvement in dyskinesia severity vs placebo.[14] However, improvement with deutetrabenazine 12 mg/day was not statistically different from placebo.[14] Longer-term studies of valbenazine and deutetrabenazine demonstrated sustained improvement in dyskinesia. Upon discontinuation of valbenazine, TD symptoms reverted to baseline within 4 weeks.[18]

Efficacy of valbenazine and deutetrabenazine in improving dyskinesia has not been compared directly, so a shared decision-making approach[19] that empowers the patient is recommended. Management of TD starts with decisions regarding use of DRBAs and continues with active surveillance during treatment, with shared decision-making strategies in selecting treatment upon emergence of TD. Key differences between the 2 medications are listed in **TABLE 1**.

Valbenazine and its metabolites are selective for VMAT2, whereas metabolites of deutetrabenazine also bind to select dopamine and serotonin receptors.[12] Metabolites of the 2 drugs also differ in their half-lives, requiring twice-daily dosing for deutetrabenazine vs once-daily dosing for valbenzaine.[13,14] Deutetrabenazine had 50% higher concentrations under food conditions and should be taken with food.[14] Valbenazine can be taken with or without food.[13] The 2 drugs are titrated differently to attain maximal therapeutic benefit. While the starting dose of valbenazine (40 mg) proved superior to placebo with only 1 week of titration needed to get to the maximum approved dose (80 mg/day),[13] the starting dose of deutetrabenazine (12 mg) did not differ from placebo, and requires titration by 6 mg/week over the ensuing weeks to attain doses in the therapeutic range of 24-48 mg/day.[14] Cytochrome P450 (CYP) enzyme-related interactions also differ for these agents. Valbenazine has potential interactions with strong CYP3A4 inducers and inhibitors, strong CYP2D6 inhibitors, and in CYP2D6 poor metabolizers, whereas deutetrabenazine has potential interactions with strong CYP2D6 inhibitors and in CYP2D6 poor metabolizers. Finally, coverage by payer and cost are important considerations.

Summary: Valbenazine and deutetrabenazine are 2 efficacious, much-needed medications for patients with TD. A shared decision-making approach is recommended when selecting between them as their comparative efficacy has not been tested. Valbenazine has some favorable kinetic features compared to deutetrabenazine including less frequent dosing, shorter titration to maximum approved dose, and no requirement for food. Factors including cost and drug-drug interactions also influence the decisions of patients and clinicians.

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