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This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the planning teleconference series "Emerging Treatment Strategies for Patients With Tardive Dyskinesia," which was held in April 2017. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Teva Pharmaceuticals.

**CME Objectives**

After studying this article, you should be able to:

- Use evidence-based strategies to prevent tardive dyskinesia symptoms
- Assess patients for tardive dyskinesia symptoms using standardized screening tools
- Use evidence-based strategies to treat tardive dyskinesia symptoms

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# Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment

Christoph U. Correll, MD; John M. Kane, MD; and Leslie L. Citrome, MD, MPH

**T**ardive dyskinesia (TD) is a condition characterized by involuntary movements of the face, torso, extremities, and sometimes the respiratory system. It is usually observed in patients after long-term treatment with antipsychotic agents.<sup>1</sup> This extrapyramidal symptom was first described by Schonecker<sup>2</sup> in 1957, a few years after the first antipsychotic agents were used.<sup>1</sup> While evidence suggests that patients being treated with second-generation antipsychotics (SGAs) have less risk for developing TD than those treated with first-generation antipsychotics (FGAs), the decreased risk is not as great as was originally expected.<sup>3</sup> Because FGAs are still in use and SGAs are being used for multiple illnesses, the potential development of TD among patients taking antipsychotics (or other agents that block dopamine receptors)<sup>4</sup> needs to be monitored and, if it does occur, managed.

This ACADEMIC HIGHLIGHTS, based on a series of teleconferences given by **Christoph U. Correll, MD** (Chair); **John M. Kane, MD**; and **Leslie L. Citrome, MD, MPH**, will address the prevalence, risk factors, and prevention of TD; assessment strategies and tools; and evidence for TD treatments.

## EPIDEMIOLOGY AND PREVENTION OF TARDIVE DYSKINESIA

Dr Correll discussed the clinical syndrome of TD, which consists of involuntary, repetitive movements that are mostly in the oral, lingual, and buccal regions. Common movements are tongue protrusion, puckering, chewing, and grimacing. Less commonly, abnormal involuntary movements occur in the hands, legs, feet, or torso. The condition can be severe and persistent and may have both medical and psychosocial consequences.<sup>3</sup> Treatment with dopamine receptor blocking agents, such as antipsychotics, increases the risk for TD.<sup>3,5</sup>

In many cases, once TD is established, it cannot be reversed, and it has been associated with poorer quality of life<sup>6</sup> and increased mortality.<sup>7</sup> The indications and off-label uses for dopamine antagonist antipsychotic medications have expanded over the last 2 decades (including not only psychotic disorders but also mood disorders, such as bipolar disorder and unipolar depression, as well as anxiety disorders and insomnia).<sup>8</sup> Therefore, a larger number of patients are receiving antipsychotic medications than in the past.

Dr Correll noted that the symptoms of TD are typically observed in patients who have received long-term treatment

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The teleconference was chaired by **Christoph U. Correll, MD**, Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead; Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset; and Recognition and Prevention (RAP) Program, Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, New York. The faculty were **John M. Kane, MD**, Department of Psychiatry, Hofstra Northwell School of Medicine, Hempstead; Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset; and Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, New York; and **Leslie L. Citrome, MD, MPH**, Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla.

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with antipsychotic medications, especially at higher doses associated with extrapyramidal symptoms (EPS), but TD may occur in untreated patients.<sup>9</sup> Similar movement disorders had been described in patients with schizophrenia prior to the existence of dopamine antagonist medications, which could indicate that schizophrenia itself may be associated with aberrations in the dopamine system that may give rise to abnormal, involuntary movements in some patients.

**Prevalence of Tardive Dyskinesia**

Next, Dr Correll presented data on the prevalence of TD, while first considering some limitations in the literature.

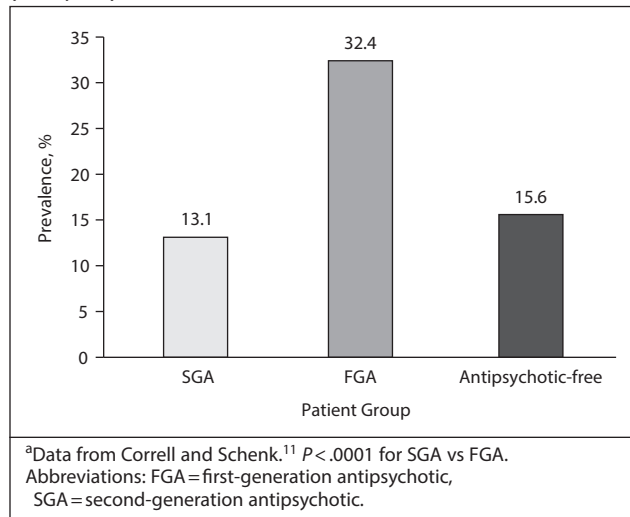
**Study limitations.** When evaluating studies of the prevalence of TD, it is important to consider differences in study methodology. Retrospective chart reviews rely on clinical coding, which is often incomplete. Database studies include large samples of generalizable patients who are not required to provide informed consent, and patients can be followed for a long period of time. However, patient characteristics, treatment characteristics, and diagnostic evaluations of TD depend on clinical coding, which again is not always accurate. Cross-sectional prevalence studies provide a snapshot of a patient on a given treatment, but causality cannot be assigned. Prior treatments may result in TD even after they have been discontinued. Randomized controlled prospective studies compare different treatments and assess TD in a more or less detailed way. However, randomized trials rarely have TD as a primary focus, and only patients who agree to participate in a rigorous and often double-blind study are included. Prospective cohort studies are designed to assess TD and collect data about treatment effects and outcomes at predefined intervals, but this careful focus on TD might overemphasize its presence. Meta-analyses can pool available data but depend very much on the quality of the included studies.<sup>10</sup>

Ideally, generalizable samples would be used, which can be achieved by consecutive enrollment of patients. At different times and in different studies or regions, doses may be higher or lower, and dropout of patients in different treatment arms may vary greatly. These 2 factors—dosing differences and dropout rates—can affect observed rates of TD and need to be considered in the analysis and interpretation of the data. Similarly, whether TD is a primary or secondary outcome may affect sensitivity of the assessments, and the measurement and definition of TD will also affect outcomes. Furthermore, training, reliability of raters, and blinding differ across studies. Rating scale-based TD rates are more sensitive than spontaneous reports.

**Prevalence data.** A study by Correll and Schenk<sup>11</sup> reviewed the prevalence of TD with FGAs and SGAs from 4 studies among adults between 2004 and 2008. Of the 2,088 patients, the mean age was 41.2 years, 71.2%

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**Figure 1. Prevalence of Tardive Dyskinesia in 4 Adult Studies (N = 2,088)<sup>a</sup>**



were men, and 62.0% were white. The authors found that the prevalence of TD among patients taking SGAs was lower than for those taking FGAs and similar to that of patients who were not taking any antipsychotic at the time of assessment (Figure 1).<sup>11</sup> Nevertheless, the TD prevalence rate with SGAs was higher than had previously been reported.

In a recent comprehensive meta-analysis, Carbon et al<sup>4</sup> reviewed 41 studies from 2000 to 2015, a time period when both SGAs and FGAs were prescribed under similar conditions. These studies included 11,493 patients with a mean age of 42.8 years; 66.4% were male, and 77.1% had schizophrenia-spectrum disorders. The mean pooled TD rates were 20.7% with SGAs and 30.0% with FGAs ( $P = .002$ ).

In the 20 studies that had at least 2 arms, one of which was an FGA arm and one of which was an SGA arm, the risk for TD was significantly lower with SGAs than with FGAs ( $P = .011$ ).<sup>4</sup>

In the 9 studies in which an SGA and an FGA were combined, the risk of TD was lower with the combination than with an FGA alone ( $P < .001$ ).<sup>4</sup> This finding might suggest that combining an SGA with an FGA could potentially reduce TD rates seen with FGA use alone. Conversely, noted Dr Correll, it is also possible that the FGA was only added later and at a low dose to augment an SGA treatment that was ineffective. This strategy may have reduced the TD rate compared with higher-dose FGA monotherapy.

Four studies included patients who had never received an FGA; the TD prevalence rate with SGA-only exposure was 7.2%. The TD rate among SGA-treated patients who had probable previous FGA exposure (in 28 studies) was 23.4% ( $P < .001$ ).<sup>4</sup> This finding may suggest that prior FGA treatment could be responsible for at least a subgroup of patients who were found to have TD while being

treated with SGAs. Nevertheless, due to the limitations mentioned above, cross-sectional studies need to be supplemented with carefully designed prospective studies to compare the risk directly between FGAs and SGAs.

A review<sup>12</sup> from 2004 of studies of annual incidence rates of TD found a lower rate in adults taking various SGAs (0.8%) than in those taking an FGA (haloperidol; 5.4%). The same was true in pooled studies of non-elderly adults published between 2004 and 2008, with lower annual incidence rates of TD for SGAs than FGAs (2.98% vs 7.7%,  $P < .0001$ ).<sup>11</sup>

### Risk Factors for TD

Dr Correll also described risk factors for TD, which should help clinicians closely monitor specific patients for signs of TD. Risk factors include the following<sup>1</sup>:

- Older age
- Female sex
- African American ethnicity
- Preexisting mood disorder
- Cognitive disturbance
- Alcohol or substance abuse
- Higher dose/longer use of antipsychotic medications
- Treatment with typical neuroleptic (FGA) agents
- Use of lithium or antiparkinsonian agents
- Early occurrence of EPS
- Diabetes
- HIV positivity

Older age is consistently found to be a risk factor for TD.<sup>13</sup> In the review of incidence studies that found a 0.8% annual incidence of TD in adults taking SGAs,<sup>12</sup> a much higher incidence of TD was found in older patients. The 3 studies with older patients (mean age = 78.3 years) who were taking SGAs showed a pooled TD incidence rate of 5.3%.

In a separate study<sup>13</sup> that investigated the incidence of TD in elderly patients being treated with FGAs, incidence rates were much higher (25% after 1 year of treatment, 34% after 2 years, and 53% after 3 years). These patients were 55 years or older when they started taking antipsychotics. Although most patients were being treated with low doses of FGAs, incidence rates of TD were 3 to 5 times higher than those found in studies of younger patients.<sup>13</sup> A greater incidence of TD in this sample was associated with a history of electroconvulsive therapy, the presence of EPS early in treatment, and higher doses and greater cumulative antipsychotic exposure.<sup>13</sup>

Incidence of TD was also examined in a prospective study<sup>14</sup> of older patients taking SGAs who had not previously taken FGAs. Patients were aged 55 years or older (mean age = 79.8 years). The cumulative TD rates after 1 year were 5.3% for risperidone and 6.7% for olanzapine, and the 2-year rates were 7.2% and 11.1%, respectively. The risk was greater in women, African Americans, and those with concurrent FGA treatment.

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African American patients are at risk for developing TD. One study<sup>15</sup> evaluated American outpatients with schizophrenia for TD over 1 to 10 years of follow-up. The European American group (n = 329) had significantly less TD than the African American group (n = 199; *P* < .05), despite controlling for differences in age and dosing.

While age and medication dose are well established risk factors, less established ones include cognitive impairment, mood disorders, preexisting movement disorders, alcohol and drug abuse, and diabetes.<sup>16</sup>

**Case Practice Question**

*Discussion of best response can be found at the end of the activity.*

**Case 1.** Casey is a 31-year-old patient of European descent beginning antipsychotic treatment for bipolar disorder. He experiences parkinsonian symptoms during the up-titration to a dose that is close to the package insert maximum to control acute manic symptoms and agitation. Which of Casey's characteristics is *not* an established risk factor for TD?

- a. Presence of acute EPS
- b. Younger age
- c. Mood disorder
- d. Higher antipsychotic dose

**Prevention of TD**

Because TD can be irreversible in some patients, Dr Correll provided some measures to limit the risk of TD (Table 1).<sup>17</sup> Clinicians should follow the prescribing information for antipsychotic agents carefully. Long-term use of antipsychotic treatments should be considered only in cases in which discontinuing medication leads to worsening illness, such as chronic psychotic conditions. Dopamine antagonists should be prescribed at the lowest effective dose and for the shortest duration necessary.<sup>1,18</sup> To avoid acute EPS, treatment should include dosing the medication carefully until efficacy is achieved and not increasing the dose more than is needed. The use of SGAs may lower the liability for EPS<sup>19</sup> and TD compared with FGAs.<sup>4,12</sup>

**Table 1. Preventative Measures to Limit the Risk of Tardive Dyskinesia<sup>a</sup>**

Follow critical, objective indications for prescribing antipsychotic agents
Limit long-term use of antipsychotic agents to research-supported indications (mainly chronic psychotic illness)
Avoid off-label use of antipsychotic agents
Choose alternative treatments when antipsychotic treatment is optional or early dyskinesia is identified
Use low but effective doses of single drugs, especially in the elderly
Perform regular and specific assessments for early tardive dyskinesia
<sup>a</sup> Based on Tarsy et al. <sup>17</sup>

Anticholinergic medications may worsen TD in some patients<sup>1</sup> (although they may also be a marker of acute EPS that increases the TD risk). Clinicians should advise patients and their families about the risk for TD before starting an antipsychotic agent.<sup>1</sup> Clinicians should also carefully monitor patients for abnormal movements using baseline and ongoing rating scale scores, such as the Abnormal Involuntary Movement Scale (AIMS),<sup>20</sup> so that treatment can be changed if involuntary movements emerge.<sup>1</sup>

**Conclusion**

Dr Correll concluded that the prevalence of TD is still considerable despite predominant SGA use. Prevalence of TD is lower in patients currently taking SGAs versus FGAs and lower in patients taking SGAs without prior FGA treatment. Despite these findings, limitations in the literature hinder clinicians from getting an accurate picture of prevalence rates. The persistence, severity, and effect on quality of life of TD require further study. Clinicians should look for specific risk factors for TD in their patients, especially in the elderly, those taking high doses of antipsychotics, those using antipsychotics for longer durations, or those showing symptoms of acute EPS. Using preventive measures and careful monitoring, clinicians can help manage the risk of TD among patients who require treatment with antipsychotics and other dopamine receptor blocking agents.

**ASSESSING PATIENTS FOR TARDIVE DYSKINESIA**

Dr Kane outlined assessment strategies for TD. Because of the serious and potentially irreversible nature of TD, accurate diagnosis is crucial, but it can present a clinical challenge. The onset of TD is insidious, with fluctuating symptoms that can be masked by or confused with symptoms of other disorders or medication-induced side effects.<sup>21,22</sup> Most commonly, TD will present as involuntary, repetitive, purposeless orofacial movements including chewing; lip smacking, puckering, or pursing;

tongue protrusion; grimacing; or bulging of the cheeks.<sup>22-24</sup> Patients may also experience contracting, twisting, or writhing movements of the fingers, hands, arms, or legs.<sup>22</sup>

**Diagnostic Criteria**

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*,<sup>21</sup> criteria for TD simply state that to receive this diagnosis an individual should exhibit involuntary movements lasting at least several

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weeks in association with neuroleptic medication use of at least a few months' duration. The involuntary movements should be athetoid or choreiform and typically of the tongue, jaw, and extremities. Dr Kane and his colleague, Nina R. Schooler, PhD, developed a more in-depth set of diagnostic criteria for TD, known as the Schooler-Kane criteria,<sup>25</sup> which were originally intended for research settings but have been widely used in clinical practice.<sup>22</sup>

The first of the 3 Schooler-Kane criteria is that the patient must have at least 3 months of antipsychotic exposure, which may be continuous or discontinuous. Second, the patient must exhibit abnormal, involuntary movements of moderate or greater severity in 1 or more body regions or mild severity in 2 or more body regions, according to a rating scale such as the AIMS. Third, the patient must be free of other conditions that may cause abnormal, involuntary movements. A patient who meets all 3 criteria has probable TD. Further evaluations are necessary to determine if movements improve, worsen, or stay the same; if dosing changed; and the length of time during which movements and medication have or have not been present.<sup>25</sup> The rationales behind the Schooler-Kane criteria are presented below.

### Antipsychotic Drug Exposure

Dr Kane explained that involuntary movements and EPS can be observed in untreated patients with schizophrenia. Drug-naive individuals with schizophrenia are significantly more likely to experience movement disorders such as dyskinesias compared with healthy controls (odds ratio = 3.59; 95% CI, 1.53–8.41).<sup>26</sup> Dopamine dysregulation in specific brain regions may be involved in both the etiology of schizophrenia and the increased risk of movement disorders.<sup>26</sup> Although the pathophysiology of TD is not fully understood, one hypothesis is that the antipsychotics' dopamine receptor blocking action in combination with the altered striatal dopamine activity found in individuals with schizophrenia creates an imbalance between direct and indirect pathways of the basal ganglia, which are necessary for normal movement.<sup>24</sup> Thus, clinicians should evaluate patients for the presence of involuntary movements before initiating antipsychotic treatment to ensure that any preexisting movements are not later incorrectly attributed to the medication.<sup>23</sup> By requiring patients to have at least 3 months of cumulative antipsychotic exposure, the Schooler-Kane diagnostic criteria<sup>25</sup> help clinicians confirm the association between medication and involuntary movement symptoms.

### Rating Scales

To receive a diagnosis of TD according to the Schooler-Kane diagnostic criteria,<sup>25</sup> a patient must exhibit either moderate involuntary movements in 1 or more body areas or at least mild involuntary movements in 2 or more body areas. Dr Kane specified that the presence of these movements should be determined by using a standardized

- Consider risk factors that could make patients more likely to develop TD.
- Seek to prevent TD by treating patients with the lowest dose of antipsychotics for the shortest duration necessary.
- Use TD diagnostic criteria combined with a rating scale (such as AIMS) assessment and differential diagnosis to determine if involuntary abnormal movements are caused by antipsychotic treatment.
- Consider treatments for TD based on evidence given in the American Academy of Neurology guidelines as well as the novel FDA-approved agents.

rating scale,<sup>25</sup> such as the Simpson Dyskinesia Scale,<sup>27</sup> the Extrapyramidal Symptom Rating Scale (ESRS),<sup>28</sup> or the AIMS.<sup>20</sup>

Clinicians must remember that these are screening and not diagnostic tools. Dr Kane noted that these instruments are useful for identifying signs and symptoms of involuntary movement and assessing the severity of these movements, but they should be used in conjunction with diagnostic criteria. Rating scales are also useful to facilitate communication between patients and clinicians regarding the adverse effects of treatment patients are experiencing. Patients may be reluctant or unable to share side effects voluntarily, and clinicians may underestimate the rate of side effects from antipsychotics in their patients.<sup>29</sup> Consistent use of rating scales can help solve these problems by giving clinicians information on the severity, frequency, and impact of involuntary movement symptoms and by enabling patients to recognize and describe their symptoms.

The Simpson Dyskinesia Scale, specific for TD, was developed in both a long (34-item) and an abbreviated (13-item) version to help clinicians describe the breadth of TD syndrome and quantify the disorder.<sup>27</sup>

The ESRS<sup>28</sup> is a 41-item scale plus 4 global impression questions to assess the types of drug-induced movement disorders: parkinsonism, akathisia, dystonia, and TD. In a cross-scale comparison, the ESRS and AIMS were found to have a 96% (359/374) agreement between TD cases defined by *DSM* criteria.<sup>28</sup>

The AIMS was developed by the National Institute of Mental Health as a research tool, but because of its utility for identifying the abnormal, involuntary movements characteristic of TD, it has become widely recommended for use in clinical practice to screen for the involuntary movements required to diagnose TD using the Schooler-Kane criteria.<sup>23</sup> The 12-item AIMS assesses 10 items on a 5-point scale (0–4: none, minimal, mild, moderate, severe) in different parts of the body, including the face, extremities, and trunk, as well as global assessment items addressing overall severity, impact, and awareness of abnormal movements. The final 2 yes or no questions address problems with teeth or dentures. Items 1 through 7 quantify the different abnormal movements that can be

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evident in the face, extremities, and trunk. These 7 items are usually summed to form a total dyskinesia score.

Although the AIMS is a useful tool, Dr Kane pointed out that clinicians must administer the scale properly in order to obtain accurate and consistent results.<sup>30</sup> The clinician cannot simply observe the patient for a few seconds or a minute. Ideally, the clinician should attempt to discreetly observe the patient at rest, perhaps while he or she is in the waiting room, and also should look for involuntary movements when first greeting the patient.

Once in the office, a more systematic examination can take place, and a firm chair will be needed. Dr Kane recommended that the chair have either no arms or arms that are short enough for the patient's hands to hang over the ends. The clinician must ask the patient if anything is in his or her mouth (like chewing gum) and if so to remove it, about any problems with his or her teeth, and whether dentures are being worn.<sup>23</sup> The clinician should also inquire about the patient's awareness of any involuntary movement.

As the AIMS examination proceeds, the clinician will continually look for any abnormal movements as the patient performs a variety of different movements. The patient should sit in the chair with hands on knees, legs slightly apart, and feet flat on the floor. Then the patient should sit with his or her arms and hands unsupported.

The clinician should ask the patient to open his or her mouth so that the clinician can observe the tongue at rest, and then the patient should be asked to protrude the tongue and keep it extended. Repeating these tongue observations later in the evaluation may be beneficial, noted Dr Kane.

The patient should be asked to rapidly tap his or her thumb to each finger on that hand for 10 to 15 seconds, and then switch to the other hand, while the clinician observes the entire body for any abnormal involuntary movements that may be elicited. The clinician should ask the patient to rise from the chair, walk, and then extend his or her arms in front with palms down, while continually observing the patient's entire body.

When scoring the AIMS, the clinician should record the incidence of a movement regardless of whether the movement was activated by the requested actions. That is, some clinicians have assigned a lower score to movements that did not appear until they asked the patient to perform an action, and they assigned a higher score to movements that existed when the patient was at rest. Instead, Dr Kane recommended that all movements should be rated in the same way. An AIMS score of at least 2 in 2 or more body regions or a score of 3 or 4 in  $\geq 1$  body region is used for a probable diagnosis of TD with the Schooler-Kane criteria.<sup>25</sup>

According to the American Psychiatric Association (APA),<sup>31</sup> all patients taking an antipsychotic medication should be regularly monitored for movement disorders. The APA recommends that patients taking FGAs be assessed every 6 months, whereas patients taking

SGAs should be assessed every 12 months. If patients have risk factors for TD (eg, older age, presence of an affective disorder<sup>1</sup>), they should be monitored more frequently. Patients at increased risk who are receiving an FGA should be assessed every 3 months, and patients at increased risk who are receiving an SGA should be assessed every 6 months.<sup>31</sup> If a patient has recently initiated antipsychotic treatment and early involuntary movement has been detected, this patient should be considered at risk for TD and monitored more frequently to determine if the symptoms persist long enough (ie, 3 months) to meet the criteria for TD.<sup>1,31</sup>

### Case Practice Question

*Discussion of best response can be found at the end of the activity.*

**Case 2.** Beverly is a 68-year-old new patient with treatment-resistant major depressive disorder (MDD). Two months ago, she had an SGA added to her third antidepressant treatment. Beverly was referred because her MDD has improved but not quite remitted. Her referring physician had administered the AIMS before adding the SGA, and she had no involuntary movements. You administer the AIMS and find mild involuntary lip movements. Which of the following next steps would be *most* appropriate?

- Diagnose Beverly with probable TD
- Consider Beverly to be at risk for TD and assess her again in 6 months
- Consider Beverly to be at risk for TD and assess her again in 3 months
- Consider Beverly to be at risk for TD and assess her again in 1 month

Dr Kane emphasized that before diagnosing TD, the clinician must rule out other possible conditions that might be producing the involuntary movements.<sup>25</sup> Patients who develop dyskinesias after starting antipsychotic treatment should be evaluated for clues to a cause for the dyskinesia, such as family history, sudden onset versus progressive course, or associated neurologic or medical abnormalities.<sup>22</sup> Once neurologic causes have been eliminated, numerous differential diagnoses must be considered. Conditions that may resemble TD include spontaneous dyskinesias (ie, not associated with antipsychotic exposure), various syndromes, Huntington disease, and Wilson disease (Table 2).<sup>22,23</sup>

Additional conditions that may resemble TD are other movement disorders known collectively by the term *tardive syndromes*, which include tardive dystonia (constant or recurrent muscle contractions), tardive akathisia (restless or jittery feeling), tardive stereotypy (repetitive coordinated movements that may look purposeful), tardive myoclonus (quick, uncontrollable muscle jerks), tardive tourettism or tics (repeated brief movements or sounds), or tardive tremor (shaking movements).<sup>16,24</sup> While some of these syndromes may occur simultaneously with TD, they have distinct clinical characteristics from TD. For example, tardive stereotypy

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**Table 2. Conditions to Consider in the Differential Diagnosis of Tardive Dyskinesia<sup>a</sup>**

Spontaneous dyskinesias
Huntington disease
Senile chorea
Chronic motor tic disorder
Autism
Wilson disease
Drug-induced dyskinesia caused by another agent
Meige syndrome
Sydenham chorea
Tourette syndrome
Rett syndrome
Restless leg syndrome

<sup>a</sup>Based on Caroff et al<sup>22</sup> and Citrome et al.<sup>23</sup>

may present as abnormal movement in the oro-buccal-facial region similar to TD, but the movements are more predictable, continuous, and are typically distractible. Tardive dystonia is more common in young male patients, while TD is more common in the elderly and women. Tardive akathisia is characterized by an inner restlessness, causing an inability to sit or stand still.

Patients with tardive akathisia may shift from foot to foot, walk in place, rock their bodies, or cross/uncross their legs.<sup>24</sup>

Dr Kane noted that clinicians must also rule out whether the movements are caused by drugs or substances known to be associated with dyskinesias, such as caffeine, antihistamines, stimulants, phenytoin, estrogens, or antidepressants, or even simply caused by oral problems or ill-fitting dentures.<sup>22,23</sup> Once all of these possible explanations for involuntary movements have been eliminated, the patient meets criteria for a diagnosis of probable TD.<sup>25</sup>

### Conclusion

Although the sometimes subtle and fluctuating symptoms of TD can be difficult to identify, Dr Kane stated that clinicians can improve their recognition of this disorder through careful monitoring and consistent use of diagnostic criteria and rating scales. The Schooler-Kane criteria combined with a properly administered rating scale, such as the AIMS, will enable clinicians to increase early recognition of TD.

## COMPARING TREATMENTS FOR TARDIVE DYSKINESIA

Once TD has been recognized in a patient, what are the treatment options? Dr Citrome examined the evidence for various treatments for TD. Different treatments have been assessed for the management of TD, with studies typically using the AIMS to measure symptoms.<sup>20</sup>

### Treatment Circa 2007

For a long time, the treatment of TD was an unmet clinical need, with few options having strong evidence of efficacy without substantial side effect risks. Dr Citrome explained that, a decade ago, one treatment strategy for TD would be to gradually switch a patient from an FGA to an SGA (other than clozapine) and discontinue any anticholinergic medications.<sup>23,32</sup> If TD improved, the SGA was continued. The next step, if TD persisted, was to switch to a second SGA other than clozapine. If TD remained, the next step was to switch to clozapine. If TD continued after the above steps were taken, suppression therapy was often considered and usually consisted of the combination of an FGA and an SGA.

Other treatment options included tetrabenazine, which is discussed later, or branched-chain amino acids (BCAAs). The BCAAs were studied as a possible intervention for TD because of the observed association between dyskinesic movements and impaired clearance of phenylalanine. It is thought that ingesting BCAAs decreases the availability of phenylalanine to the brain; thus, BCAAs might improve TD by decreasing amine neurotransmitter synthesis.<sup>33,34</sup>

A 3-week randomized double-blinded study<sup>34</sup> compared high-dose BCAAs with placebo in men with

TD (n = 36). The dyskinesic movements decreased by a mean of 36.5% in the BCAA group but increased by a mean of 3.4% in the placebo group. One-third of the BCAA group had a reduction of 60% or more in dyskinesic movements, compared with none of the subjects receiving placebo.<sup>34</sup>

A combination of 3 BCAAs was approved by the US Food and Drug Administration (FDA) as a medical food for the dietary management of TD in male patients.<sup>35</sup> The product was a flavored powder to mix with water and then drink 3 times daily.<sup>33</sup> However, the drink mix was not calorie free and was unpalatable for some. Although the branded product is no longer available, compounding pharmacies can make it using the same ratio of ingredients (L-leucine, L-valine, and L-isoleucine) tested in the clinical trial.<sup>34</sup>

Proposed treatments for TD also included donepezil, melatonin, vitamin B<sub>6</sub>, and vitamin E, which had mixed results in clinical trials.<sup>23,32</sup>

### 2013 Recommendations From the American Academy of Neurology

Moving ahead several years, Dr Citrome discussed the 2013 American Academy of Neurology (AAN) evidence-based guidelines for the treatment of TD.<sup>36</sup> The AAN determined that data were insufficient as to whether stopping the medication associated with TD would suppress symptoms.<sup>36,37</sup> The strategy of switching from an FGA to an SGA was also determined to have insufficient evidence. Raising the antipsychotic dose may slightly reduce symptom severity, but the symptoms may

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be masked, and a temporary improvement could lead to ever-increasing doses.<sup>38,39</sup> Insufficient data to support (or refute) their use was found for acetazolamide, bromocriptine, thiamine, baclofen, vitamin E, vitamin B<sub>6</sub>, selegiline, melatonin, nifedipine, levetiracetam, buspirone, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, α-methyl-dopa, reserpine, and pallidal deep brain stimulation. The guidelines did not recommend diltiazem, galantamine, and eicosapentaenoic acid.

According to the guidelines,<sup>36</sup> the following interventions have some evidence to support their use: clonazepam, *Ginkgo biloba*, amantadine, and tetrabenazine.

**Clonazepam.** The antianxiety agent, clonazepam, is a benzodiazepine with indirect GABA agonist activity and has been explored as a treatment for TD since the 1970s.<sup>3</sup> A 1981 study<sup>40</sup> compared clonazepam with phenobarbital in 21 psychiatric patients with TD. While both agents reduced dyskinesic movements, clonazepam showed greater efficacy for orofacial dyskinesia while phenobarbital was more effective for abnormal limb and axial movements.

A decade later, clonazepam was assessed in a 12-week, double-blind, placebo-controlled, randomized crossover study<sup>41</sup> with an open-label, 9-month extension. Of the 19 chronically ill patients with TD, 11 received 4.0 to 4.5 mg/d of clonazepam, 6 received 3.0 mg/d, and 2 received 2.0 mg/d. Treatment alternated between active medication and placebo. The primary efficacy endpoint was change in dyskinesia score using the Maryland Psychiatric Research Center Movement Disorder Scale as assessed by blinded video raters. Clonazepam treatment reduced dyskinesia scores by approximately 37%, an effect that was reversed during placebo administration. However, tolerance developed in the 5 patients who received clonazepam in the long-term extension after 5–8 months of use.<sup>41</sup>

**Ginkgo biloba.** Extract of *Ginkgo biloba* (EGb), a potent antioxidant with free-radical scavenging activity, was assessed in a meta-analysis<sup>42</sup> of 3 12-week, randomized-controlled trials in schizophrenia patients with TD (n = 299) in China. The primary outcome measure was severity of TD symptoms measured by the AIMS. Results showed that adjunctive EGb (240 mg/d) reduced TD symptoms compared with patients taking antipsychotic monotherapy ( $P < .00001$ ). Discontinuation rates were similar between the EGb group and control group.

**Amantadine.** Amantadine blocks *N*-methyl-D-aspartate receptors.<sup>3</sup> Amantadine was assessed in 2 double-blind, placebo-controlled, crossover studies.<sup>43,44</sup> In a study by Pappa and colleagues,<sup>43</sup> 22 patients were treated with amantadine (up to 400 mg/d) or placebo, along with antipsychotic medications. With amantadine, the average total AIMS score reduction was 22%, compared with no reduction with placebo.<sup>43</sup> In the

other study,<sup>44</sup> 16 patients were treated with amantadine (300 mg/d) or placebo, as well as their antipsychotic medication. With amantadine, 4 patients' AIMS scores increased, but overall, a mean 15% reduction was found, which was significant compared with placebo ( $P < .05$ ).<sup>44</sup>

**Tetrabenazine.** Tetrabenazine was originally developed in the 1950s and approved in the United States in 2008 as an orphan drug for the treatment of choreiform movements associated with Huntington disease.<sup>39,45</sup> Tetrabenazine is a reversible and specific inhibitor of vesicular monoamine transporter 2 (VMAT2), a protein in the brain that transports monoamine neurotransmitters (ie, dopamine, norepinephrine, serotonin, histamine) into vesicles for release into the synapse.<sup>46</sup> The reduction of synaptic dopamine levels limits overstimulation and reduces the symptoms of involuntary movements associated with Huntington disease, Tourette syndrome, and TD.

The first TD study with tetrabenazine<sup>47</sup> was published in 1972. After a 4-week placebo period, 24 inpatients were placed on tetrabenazine for 6 weeks. The antidyskinetic effect was marked in two-thirds of the patients. Another study<sup>48</sup> compared haloperidol use with tetrabenazine use in 13 subjects and found that tetrabenazine produced significant reduction in the frequency of oral dyskinesia, with almost complete suppression in 2 patients. In a single-blind study<sup>49</sup> that compared tetrabenazine efficacy using a randomized videotape protocol pre- and posttreatment, a 54% mean improvement on the AIMS motor subset scores was found.<sup>49</sup> The above short-term results for tetrabenazine are further supported by long-term observational studies.<sup>36</sup>

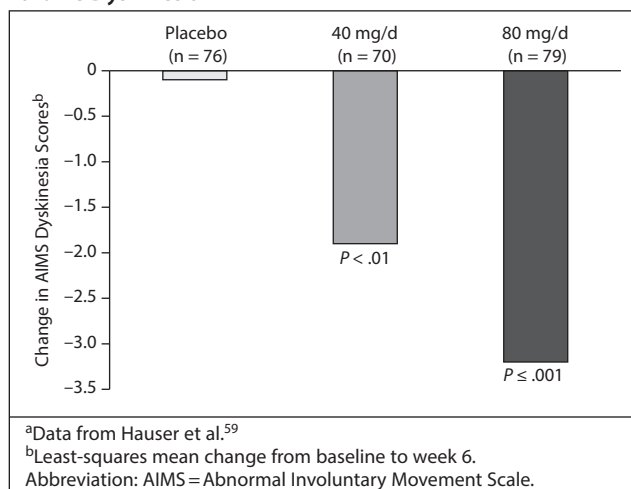
Despite these positive results, tetrabenazine has limiting adverse effects—somnolence, parkinsonism, insomnia, and akathisia—as well as a short half-life (requiring 2–3 doses/d) and potential drug-drug interactions.<sup>39,50,51</sup> These effects are related to the pharmacokinetics and pharmacodynamics of tetrabenazine, which is a one-to-one mixture of enantiomers.<sup>52</sup> The α and β enantiomers each give rise to 2 isomers of a dihydrotetrabenazine metabolite for a total of 4 isomers. Those derived from the α-tetrabenazine isomer are active VMAT2 inhibitors and contribute to the therapeutic effects of the drug. These are metabolized via cytochrome P450 2D6 and 3A4 isoenzymes. The 2 derivatives of β-tetrabenazine are antagonists at the dopamine D<sub>2</sub> receptor and can induce sedation and parkinsonism.<sup>52</sup> These β-tetrabenazine derivatives are metabolized solely by CYP2D6; thus, side effects are more pronounced in the presence of CYP2D6 inhibitors. Consequently, for tetrabenazine doses above 50 mg/d, genotyping for the cytochrome P450 2D6 enzyme is required.<sup>51</sup>

The product label for tetrabenazine<sup>51</sup> also carries a warning for depression (possibly related to serotonin depletion<sup>46</sup>) and suicide risk.



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**Figure 2. Phase 3 Fixed-Dose Trial Results for Valbenzine Versus Placebo in Patients With Tardive Dyskinesia<sup>a</sup>**



### New VMAT2 Inhibitors

Due to the limitations of prior TD treatments, other agents have been explored as alternatives. Since the AAN guidelines were published, the US Food and Drug Administration (FDA) acknowledged the need for new treatment options with breakthrough therapies.<sup>52,53</sup> Novel agents include valbenzine and deutetrabenazine, which are both reversible VMAT2 inhibitors.<sup>54</sup> Valbenzine was approved as treatment for TD by the FDA in April 2017.<sup>55</sup> Deutetrabenazine was FDA-approved for the treatment of TD in August 2017.<sup>56</sup>

**Valbenzine.** Valbenzine is metabolized slowly to a potent, selective VMAT2 antagonist, which enables once-daily dosing, does not require genotyping, and provides efficacy for TD as shown in placebo-controlled studies.<sup>57</sup>

A 6-week, double-blind, placebo-controlled phase 2 trial<sup>58</sup> examined valbenzine (25–75 mg/d) in 102 patients with moderate-to-severe TD. These patients' TD was associated with the use of neuroleptics or metoclopramide, taken for schizophrenia, schizoaffective disorder or mood disorders, or gastrointestinal disorders, respectively. The primary outcome was change on the AIMS (total score on items 1–7) from baseline to week 6 as assessed by blinded video raters who were movement disorder specialists otherwise not involved in the study. The once-daily starting dose of valbenzine was 25 mg, which could be escalated by 25 mg every 2 weeks up to 75 mg/d. After titration, 76% of those taking valbenzine reached the 75-mg/d dose (9 reached 50 mg/d, and 5 maintained 25 mg/d). The least-squares mean change in AIMS dyskinesia scores from baseline to endpoint was significantly greater with valbenzine (–2.6) than placebo (–0.2;  $P = .0005$ ). No patients discontinued because of an adverse event.<sup>58</sup>

A 6-week, double-blind, randomized phase 3 trial<sup>59</sup> compared fixed-dose valbenzine (40 and 80 mg/d) with

placebo in patients with schizophrenia, schizoaffective disorder, or a mood disorder and TD ( $N = 234$ ). The primary efficacy endpoint was change in AIMS dyskinesia scores (assessed by blinded video raters) from baseline to week 6 in the 80 mg/d group versus the placebo group. Valbenzine reduced AIMS dyskinesia scores, with the least-squares mean change from baseline to endpoint significantly greater for 80 mg/d versus placebo ( $P \leq .001$ ; Figure 2).<sup>59</sup> The AIMS dyskinesia score was also reduced in the 40 mg/d group compared with placebo (–1.9 vs –0.1;  $P < .01$ ). In terms of robust response (ie,  $\geq 50\%$  reduction in AIMS dyskinesia score from baseline), the percentage of participants responding was significantly higher in the 80 mg/d group than placebo at all study visits. At week 6, 40% of the 80-mg group had responded, compared with 8.7% in the placebo group.<sup>59</sup> Discontinuation because of an adverse event occurred in 3.8% of those taking valbenzine (both doses pooled) versus 2.6% of those taking placebo.<sup>60</sup>

Product labeling for valbenzine recommends starting at 40 mg once daily with or without food and, after 1 week, increasing the dose to 80 mg once daily. The most common adverse reaction (at  $\geq 5\%$  and twice the rate of placebo) is somnolence (11% vs 4%).<sup>55</sup> Additionally, there was no difference in low incidences of depression or suicidality between valbenzine and placebo.

### Case Practice Question

*Discussion of best response can be found at the end of the activity.*

**Case 3.** Andy, your 52-year-old patient, has received antipsychotics on and off for the past 30 years for the treatment of schizophrenia. When examined, he appears to be grimacing, and when he opens his mouth, his tongue sometimes sticks out. You administer the AIMS, and his total score on items 1–7 is 12. In terms of best evidence, which of the following treatments could be offered?

- Vitamin B<sub>6</sub> and/or vitamin E
- Galantamine
- Ginkgo biloba*
- An FDA-approved VMAT2 inhibitor

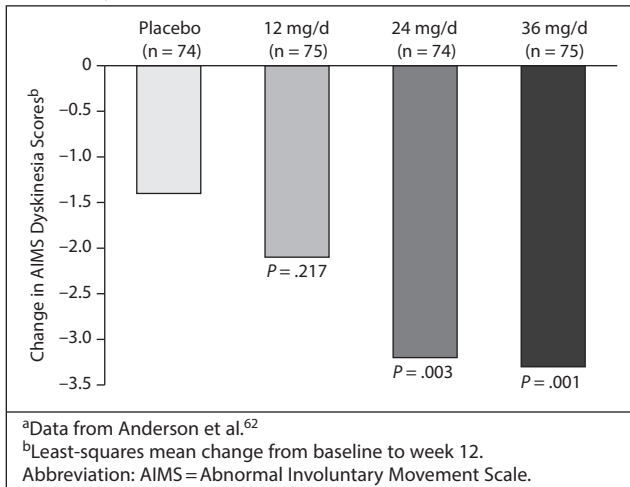
**Deutetrabenazine.** Deutetrabenazine is related to tetrabenazine in that deuterium is substituted for hydrogen at the sites of primary metabolism, with improvements in tolerability aided by slower drug metabolism.<sup>61</sup> Deuterium is a stable, nonradioactive, nontoxic, naturally occurring isotope of hydrogen and has the same size and shape as a hydrogen atom, differing only in forming stronger chemical bonds. Deutetrabenazine does not require genotyping. Efficacy of deutetrabenazine for TD was shown in placebo-controlled studies as outlined below.

In a 12-week, double-blind, phase 2 trial,<sup>61</sup> 117 patients with TD were randomly assigned to take twice-daily placebo or twice-daily deutetrabenazine. Dose was started at 6 mg twice daily and titrated weekly by 6 mg/d,

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**Figure 3. Phase 3 Fixed-Dose Trial Results for Deutetrabenazine Versus Placebo in Patients With Tardive Dyskinesia<sup>a</sup>**



if required, for up to 6 weeks until TD was controlled, a significant adverse event occurred, or the maximum dose (48 mg/d) was achieved. At the end of the titration period, the mean total daily dose was 38.8 mg/d. By endpoint, least-squares mean change from baseline in AIMS scores was significantly greater for the deutetrabenazine group versus the placebo group (-3.0 vs -1.6, respectively;  $P = .019$ ). Fewer patients discontinued because of an adverse event with deutetrabenazine than with placebo (1.7% vs 3.4%, respectively). In addition, the incidences of depression/depressed mood and suicidal ideation in the deutetrabenazine group were similar to or lower than those in the placebo group.<sup>61</sup>

In a 12-week phase 3 trial,<sup>62</sup> 298 patients with TD were randomly assigned to receive deutetrabenazine (12 mg, 24 mg, or 36 mg daily in 2 divided doses) or placebo. Patients taking deutetrabenazine started at 12 mg daily and then gradually increased over 4 weeks until the randomized dose was reached; the doses were maintained over 8 weeks. The AIMS improvement from baseline to endpoint was significantly ( $P < .05$ ) greater for those taking 24 or 36 mg/d of deutetrabenazine than for those taking placebo (Figure 3).<sup>62</sup> The percentages of patients discontinuing because of an adverse event were 4% for deutetrabenazine (all doses pooled) versus 3% for placebo.<sup>62</sup> Low incidences of depression and suicidal ideation were observed.<sup>62</sup>

Per product labeling,<sup>56</sup> deutetrabenazine dose is determined individually for each patient based on reduction of TD and tolerability. The recommended starting dose of deutetrabenazine for TD is 6 mg twice daily, administered with food, and the dose can be increased at weekly intervals in increments of 6 mg/d to a maximum recommended daily dosage of 48 mg. The most common adverse reactions in patients with TD (at  $\geq 4\%$  and greater than the rate of placebo) were nasopharyngitis and insomnia (4% vs 2%, and 4% vs 1%, respectively).

Dr Citrome noted that, while the efficacy and tolerability of these new VMAT2 inhibitors are encouraging, one consideration that clinicians have with the use of new agents is their cost.<sup>60</sup> Depending on insurance and health care setting, costs will vary for patients.

### Conclusion

Dr Citrome concluded that patients taking antipsychotics must be monitored as recommended using the AIMS and should be treated promptly if TD is present. Although the VMAT2 inhibitor tetrabenazine shows promise for alleviating TD, it has several limitations. Two novel VMAT2 inhibitors have been developed to retain the efficacy of tetrabenazine but offer improved safety and tolerability. These agents, valbenazine and deutetrabenazine, have been FDA-approved for the treatment of TD and could provide much-needed treatment options to alleviate TD in patients who require continued treatment with antipsychotics for their chronic conditions.

### Discussion of Case Practice Questions

#### Case 1.

##### Preferred response: b. Younger age

Older age is a very well established risk factor for TD while younger age is not. Because Casey is just 31, his age is not a risk factor. Bipolar disorder puts him at risk for TD since mood disorders are a risk factor. The dose of his antipsychotic medication is at the high end of indicated dosing, and his parkinsonian symptoms demonstrate early EPS, so these factors add to his risk for TD.

#### Case 2.

##### Preferred response: c. Consider Beverly to be at risk for TD and assess her again in 3 months

Beverly has an AIMS score of 2 (mild) in one body region. According to Schooler-Kane criteria, Beverly should not be diagnosed with probable TD because her cumulative antipsychotic use is less than 3 months and her involuntary movements are not severe enough or widespread enough. But, because she has a higher risk for TD (being elderly and female and having a mood disorder) and has developed early involuntary movements, the best option for the clinician is to reassess her when she has had 3 months of antipsychotic exposure.

#### Case 3.

##### Preferred response: d. An FDA-approved VMAT2 inhibitor

According to American Academy of Neurology Guidelines,<sup>36</sup> *Ginkgo biloba* has some evidence supporting its use. Vitamins E and B<sub>6</sub> do not have enough evidence to support or refute their efficacy in TD, while galantamine was not recommended. However, since the guidelines were published in 2013, novel VMAT2 inhibitors have been approved by the FDA for TD based on sufficient evidence of their efficacy.

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**Disclosure of off-label usage:** The authors have determined that, to the best of their knowledge, valbenazine and deutetabenazine are the only drugs approved by the US Food and Drug Administration for the treatment of tardive dyskinesia.

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## POSTTEST

To obtain credit, go to [PSYCHIATRIST.COM](http://PSYCHIATRIST.COM) (Keyword: October) to take this Posttest and complete the Evaluation.

1. Ms R is a 55-year-old, divorced woman who has experienced 2 major depressive episodes over several years. She was prescribed mirtazapine 3 years ago but only partially responded. Aripiprazole 10 mg daily was added, and she was able to return to her usual functioning. Three months ago, she noticed abnormal involuntary movements of her lips, tongue, and jaw, which were diagnosed as TD. What is the best next step to attempt to relieve Ms R's TD symptoms?
  - a. Discontinue mirtazapine
  - b. Discontinue aripiprazole
  - c. Add a VMAT2 inhibitor
  - d. Add electroconvulsive therapy
2. Mr J, a 45-year-old man, presents to the clinic with mild, involuntary movements of the tongue and jaw. He has been taking his current antipsychotic for 1 month, and he was not assessed for abnormal involuntary movements prior to starting treatment. Has Mr J had adequate cumulative antipsychotic drug exposure to meet Schooler-Kane research criteria for TD diagnosis?
  - a. Yes
  - b. No
3. Tardive dyskinesia may be caused by excess dopamine signaling where there has been an upregulation in post-synaptic dopamine receptors. Tardive dyskinesia may be able to be managed by modifying the activity of vesicular monoamine transporters (VMAT), which package dopamine into vesicles in the dopamine neuron. Both valbenazine and deutetrabenazine are:
  - a. VMAT1 and VMAT2 irreversible inhibitors
  - b. VMAT1 reversible inhibitors
  - c. VMAT2 reversible inhibitors
  - d. VMAT2 irreversible inhibitors

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