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GERIATRIC PSYCHIATRY (S LEHMANN, SECTION EDITOR)

"Evaluating and Managing Tardive Dyskinesia in the Older Adult"

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Abstract

Purpose of Review Tardive dyskinesia is an iatrogenic hyperkinetic movement disorder caused by chronic exposure to antidopaminergic agents. The older adult population is particularly vulnerable to developing TD. It is also more difficult to discern the condition given the confounding medical comorbidities that may present at this age including Parkinson's and other movement disorders that may mimic TD.

Recent Findings This paper reviews the most common risk factors, including both modifiable and non-modifiable risk factors. Additionally, the possible causes and proposed pathways of TD and how to correctly diagnose and evaluate TD are discussed. We then focus on how to prevent and manage TD given the current and evolving body of knowledge and evidence. Our stepwise management approach starts by frequent monitoring, discontinuing the culprit antipsychotic, decreasing the dose otherwise; followed by switching to less potent antipsychotics and prescribing VMAT-2 inhibitors. VMAT-2 inhibitors, initially approved for management of Huntington's disease, have been recently showing favorable results in treating other hyperkinetic movement disorders like Tourette's disease, quickly becoming the first line in the treatment of tardive dyskinesia. The properties of the three different agents belonging to this class: tetrabenazine, deutetrabenazine, and valbenazine will be examined, including side-effect profiles. Finally, recent investigational agents and treatment modalities, including neuromodulation (TMS and DBS) will be reviewed that can be considered when conventional treatment fails or is not tolerated.

Summary Older adults treated with antidopaminergic medications are at greatest risk for development of tardive dyskinesia. It is important to recognize risk factors and accurately diagnose TD early. New FDA-approved treatments and investigational agents are now available to manage the condition, however further research to optimally prevent and manage TD in the older adult population remains necessary.

Keywords Tardive dyskinesia · Antipsychotics · Movement disorder · VMAT-2 inhibitors · Geriatric psychiatry

Introduction

Tardive dyskinesia (TD) is an iatrogenic hyperkinetic movement disorder characterized by choreiform, athetoid, or rhythmically abnormal involuntary movements caused by chronic exposure to dopamine receptor blockers [1]. TD was first described in 1957, five years after the introduction of chlorpromazine, the first antipsychotic medication. Patients who had been exposed to chlorpromazine for two to eight weeks showed bucco-oral movements persisting after treatment cessation [2]. In the late 1960s, the term "tardive dyskinesia" appeared [3]. As the name implies, "tardive" refers to late onset as the syndrome is more common in individuals who have received dopamine blocking agents for an extended period. Dyskinesias are described as involuntary stereotyped movements, which can typically include movements of the face, trunk, and/or extremities.

Older adults are generally more vulnerable to developing TD. The prevalence rate is perhaps five to six times greater in older adults compared to younger adults [4]. A study found the mean cumulative annual incidence of tardive dyskinesia in older adults was 29 percent at one year, 50 percent at two years, and 63 percent at three years [4]. TD also develops earlier in the older adult's course of medication treatment. Antipsychotic medications, which are often the culprits for TD, are widely prescribed for older adults for a variety of reasons including psychotic spectrum and

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mood disorders as well as the behavioral and psychological symptoms of dementia (BPSD). Older adults residing in skilled nursing facilities are prescribed antipsychotic medications more often than community-dwelling older adults [5]. Although antipsychotic medications are not the first-line for treating BPSD, given the lack of FDA-approved medications for this indication and progressive severity of the illness, they are utilized off-label in 12.3 to 37.5 percent of patients for management of BPSD symptoms such as agitation, aggression, and psychosis [6].

Severe TD has potentially disruptive consequences for older adults. Orofacial movements can affect communication and oral intake, as well as lead to dental problems. Falls can occur with trunk and lower extremity affecting movements. Additionally, these movements can be uncomfortable and embarrassing for patients. In a large prospective study of individuals with schizophrenia, those with TD had more severe psychopathology, were less likely to achieve symptom remission, and had a lower quality of life compared with those without TD [7]. Currently, however, the literature is limited for TD in specifically older aged adults, as most studies are focused on the general population of adults with schizophrenia.

We will first discuss the causes and risk factors to further understand the basis of TD, followed by the evaluation and diagnosis of the condition in older adults. Then, we will focus on management including adjustment of antipsychotics, use of VMAT-2 inhibitors, and new research agents. Given the prevalent prescription of dopamine receptor blockers for older adults, and the vulnerability of this population to develop this adverse effect, it is important for clinicians to accurately assess, monitor, and manage TD.

Causes and Risk Factors

Although still inconclusive, it is likely that genetics plays a role in the propensity of an individual to develop TD. Antipsychotic naive patients with schizophrenia develop dyskinesia at a greater rate than matched controls [8]. This is termed spontaneous dyskinesia and unlike tardive dyskinesia, is not triggered by antipsychotic use. A review has suggested the spontaneous dyskinesia prevalence rate in adults over the age of 60 could be as high as 40 percent of all dyskinesia [9]. Siblings of patients with schizophrenia also have an increased prevalence of dyskinesia compared to matched controls [10]. Homogeneity for the Ser9Gly variant of the D3 dopamine receptor has been implicated, as 22 to 24 percent of patients with TD have the variant, compared to five percent of the control group [11].

Three pathogenetic hypotheses have been proposed for the development of TD:

1) Oxidative stress
2) Glutamate mediated toxicity in nigrostriatal circuits
3) Dopaminergic receptor hypersensitivity following receptor upregulation secondary to antipsychotic treatment [12•]

Risk factors for the development of TD include unmodifiable patient and diagnosis factors, as well as modifiable factors related to comorbidities and illness management (see table 1). The evidence has consistently demonstrated that age is a significant risk factor, with older adults most vulnerable [4, 13–15, 16•]. Schizophrenia and bipolar diagnoses and longer duration of mental illness are also illness related risk factors [10, 13, 16•]. The association of development of TD with extrapyramidal symptoms and recent use of anticholinergic medications may indicate that gene polymorphisms affecting individual variability in dopaminergic sensitivity could also play a role [4, 16•]. Other fixed characteristics that can be associated with increased risk include female sex, intellectual disability, brain damage, and white and African ethnicity [16•].

Modifiable factors relating to treatment highlight the important impact of prevention. Duration of antipsychotic use is considered the strongest risk factor [17]. In a study of older adults with a mean age of 65.5 years and a limited

Table 1 Risk factors for development of tardive dyskinesia

Modifiable risk factors	Non-modifiable risk factors
Use of anticholinergic medications in the past six months	Older age
Substance use (mainly alcohol and cannabis)	Ethnicity
Dose of antidopaminergic medication	Female sex
Duration of treatment with antidopaminergic medications	Longer duration of illness
Specific current antipsychotic treatment	Intellectual disability
Prior treatment with high potency first-generation antipsychotics	Brain damage
	Comorbid mood disorder
	Genetic susceptibility
	Early development of extrapyramidal symptoms

exposure to antipsychotics (median of 21 days total), 26.1 percent developed TD after one year of antipsychotic treatment and 51.7 percent after two years [18]. Higher medication dose, either current or cumulative, is also likely to affect TD risk [16•]. Although all antipsychotics are associated with increased risk of TD, second-generation antipsychotics appear to have less risk compared to first-generation antipsychotics. First-generation antipsychotics are characterized by higher dopamine-receptor activity compared to the latter. Moreover, it is the high potency first-generation antipsychotics like haloperidol and fluphenazine that have been associated with the highest risk of TD compared to low potency agents like chlorpromazine. The different second-generation antipsychotic medications also vary in risk profiles, with clozapine considered as the least likely for development of extrapyramidal symptoms and tardive dyskinesia, and lurasidone, risperidone, and paliperidone associated with higher risk [19]. Individual antipsychotics have unique receptor affinities which may explain these differences, with variations in degree of dopamine D2 receptor antagonism and dissociation and serotonin 5-HT2A receptor antagonism or partial agonism [20•]. In a recent meta-analysis, the mean TD prevalence was 25.3 percent, with a prevalence rate of 20.7 percent in current second-generation antipsychotic use and 30 percent in current first-generation antipsychotic use. Patients who were naive to first-generation antipsychotics had the lowest prevalence of TD at 7.2 percent, compared with 23.4 percent in those patients who likely had previous exposure [21].

In addition to antipsychotics, other agents that also have D2 blocking properties, like the anti-emetics metoclopramide and prochlorperazine, also have dose-dependent effects in causing TD [22]. Furthermore, chronic substance use has been linked to the development of TD. In a review of 284 psychiatric patients receiving antipsychotic treatment, the incidence of TD was significantly higher in patients who abused alcohol alone or alcohol and cannabis compared to abusers of sedatives, opiates, or stimulants with or without alcohol [23].

Diagnosis and Evaluation

Dopamine blocking medications can cause motor side effects which can be classified by time to onset in relation to medication initiation- acute, subacute, or delayed. Drug-induced parkinsonism has a subacute onset and is typically reversible with either decreasing or discontinuing the inciting medication [24]. Anticholinergic medications, which are commonly used to treat drug-induced parkinsonism and other acute and subacute extrapyramidal symptoms caused by antipsychotics, do not have a role in managing tardive dyskinesia [25]. Drug-induced movement disorders with delayed onset are called tardive syndromes, which include TD and also tardive dystonia, tardive akathisia, and tremor [1]. Dyskinesia can also be a manifestation of other serious medical conditions, including Parkinson's disease, Huntington's disease, Sydenham's chorea from infection, hyperthyroidism, and Wilson's disease [1]. Spontaneous dyskinesia is also a possibility in the elderly adult [9].

Per the DSM-5, tardive dyskinesia should be distinguished from neuroleptic withdrawal-emergent dyskinesia, the latter of which may emerge after discontinuation, or after change or reduction in dosage of neuroleptic medications, usually lasting less than four to eight weeks. If symptoms persist for longer than eight weeks, then the diagnosis becomes Tardive Dyskinesia [26].

Screening for TD should occur at least every six months [27]. The Abnormal Involuntary Movement Scale (AIMS) is a 12-item anchored clinician administered and scored scale used to evaluate for and track TD. It assesses orofacial movements, extremity and truncal dyskinesia, objective and subjective global severity, and distress [28]. It also assesses problems with teeth and dentures, as these can lead to a mistaken diagnosis of dyskinesia [29]. If the patient has mild TD in two areas or moderate movements in one area, then he or she should be given a diagnosis of TD [28].

Prevention and Management with Antipsychotic Adjustment

When starting antidopaminergic agents in older adults, we follow the adage "start low, go slow" to reduce the risk of side effects, which includes TD. The clinician should aim to achieve the lowest effective dose, routinely re-evaluate whether antipsychotic medication is necessary for patients who do not have a primary psychotic disorder diagnosis, and regularly monitor for signs of TD [20•].

When a diagnosis of TD is apparent, that inciting medication should be reduced gradually, and patients should be warned that TD symptoms may worsen transiently during this period. Rapid withdrawal of antidopaminergic medications may cause a phenomenon known as withdrawal emergent dyskinesia [30]. In these situations, reinstating a higher dose of the medication may mask the symptoms temporarily, however they will invariably return after a short time [20•].

Unfortunately in some cases, even with the tapering off of a suspected drug, the signs of TD may take months to years to remit, and in some cases may never resolve. A recent Cochrane review has concluded there is currently insufficient evidence to recommend dose reduction as a treatment for TD [31]. However, clinically this is often still the initial approach to management.

For patients who continue to warrant treatment with an antipsychotic medication, switching to a lower-risk less

strongly antidopaminergic antipsychotic is reasonable. Quetiapine and clozapine are considered the least risky for causing TD as well as extrapyramidal symptoms [22]. Some case studies have also suggested that clozapine may have effect in ameliorating TD [32].

Management with VMAT-2 Inhibitors

Hypersensitivity of postsynaptic dopamine receptors is a main hypothesis of TD development. Inhibiting Vesicular Monoamine Transporter 2 (VMAT-2) results in less dopamine being transported from the cytoplasm into presynaptic vesicles, which leads to less dopamine release from the presynaptic neurons into the synaptic cleft. This reduced dopamine release results in less stimulation of postsynaptic dopamine receptors in the nigro-striatal pathway, which is thought to subsequently decrease dyskinetic movements [33].

Tetrabenazine is the first VMAT-inhibitor, initially developed in the treatment of schizophrenia. In 2008, the FDA approved it for treatment of the involuntary movements (chorea) of Huntington's disease. Off-label, tetrabenazine was anecdotally shown to be effective with other hyperkinetic movement disorders like Tourette's disease and tardive dyskinesia. Tetrabenazine's short serum half-life however, requiring three times divided daily dosing, resulted in large peak to trough variations in plasma levels, which have been associated with off-target adverse effects, such as akathisia, somnolence, and even depression and suicidality [34]. The FDA shortly after issued a black box warning for depression and suicidality in patients with Huntington's disease using tetrabenazine [35].

This prompted the development of newer VMAT inhibitors, deutetrabenazine and valbenazine, both with more favorable pharmacokinetic profiles. As of 2017, deutetrabenazine and valbenazine are both FDA approved for treatment of TD and have at present the best high-quality evidence supporting their efficacy for TD, at the dose of 24–36 mg/day for deutetrabenazine and 40–80 mg/day for valbenazine, likely with a positive dose–response relationship [12•]. In KINECT 3, the phase 3 randomized control trial of valbenazine, the number needed to treat for the AIMS-based response was four for 80 mg/day and seven for 40 mg/day in patients with mood disorders and schizophrenia/schizoaffective disorder [36••]. Deutetrabenazine should be taken with food and its bioavailability after oral administration is 80 percent. The half-life of deutetrabenazine is about 9–10 h, thus twice-daily dosing is required [37]. Valbenazine can be taken with or without food, although the Cmax is decreased by high-fat meals [38]. It also has a more favorable pharmacokinetic profile with once-daily dosing.

Both deutetrabenazine and valbenazine appear to be safer alternatives as well. In fact, neither depression nor suicidality emerged as a concern with deutetrabenazine or valbenazine. Nevertheless, despite the current absence of a signal for depression and suicidal behavior in the deutetrabenazine and valbenazine studies, clinicians are still recommended to monitor mood status and suicidality, be it illness related or as part of an adverse effect [12•]. In a comparison of valbenazine tolerability in older (age ≥ 55) to younger adults, the older participants generally tolerated the medication, experiencing greater incidence of headaches and urinary tract infections, however did not experience worsening of underlying psychiatric disorder, suicidality, or other movement disorders [39]. Preliminary results suggest that older adults may be more likely to achieve a maximal response from valbenazine treatment than the general population [40••].

Other Investigational Agents and Clinical Implications

Multiple agents have been investigated as potential treatments for TD. A systematic review evaluated eleven poorly reported randomised trials (comprising 427 patients) studying vitamin E as possible treatment for TD. The analysis suggested vitamin E may be able to protect against TD deterioration, but no evidence was found that it can improve established symptoms of TD [41]. Vitamin B6 and amantadine have been separately evaluated in small trials. No serious adverse events were reported, and a limited clinical improvement was shown. Further studies are needed to validate such effects and to clarify dosages and duration of treatment. Currently, vitamin B6 or amantadine can be considered off-label if more established treatments are contraindicated or ineffective [24].

Extract of ginkgo biloba was shown to reduce the severity of TD in patients with schizophrenia in a recent meta-analysis consisting of three randomized control trials. Ginkgo biloba is an antioxidant and generally safe and well-tolerated. More studies are necessary to substantiate its role in treating TD [42]. In the case of tardive dyskinesia with severe tongue protrusion, botulinum toxin injections can be considered. Cases have been reported with botox injections in the genioglossal area have led to practical disappearance of the embarrassing tongue protrusion. Injections need to be repeated periodically for sustained effect [43].

A few small low-quality studies have examined the use of benzodiazepines and GABA-agonists and have shown no evidence of benefit. Given known acute and long-term harmful consequences (sedation, worsening of cognitive functions, tolerance, dependence, and risk of falls especially in elderly people), it is recommended to avoid their use in management of TD [44]. Long-term administration

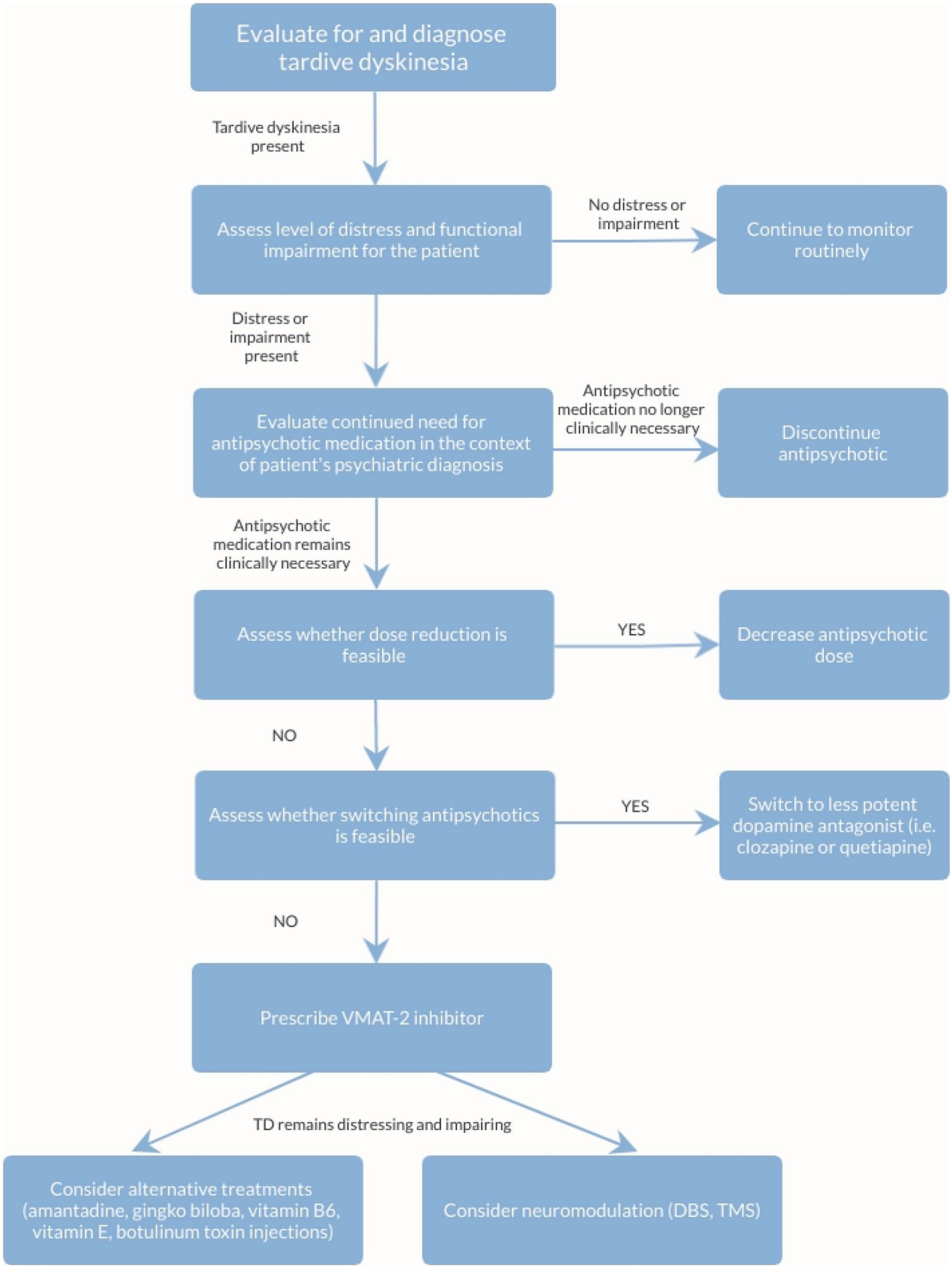

Fig. 1 Management of tardive dyskinesia caused by use of antipsychotic medications in older adults

of anticholinergic medications as a possible risk factor for TD has been described, but no convincing evidence for such claims exists. A randomized control trial of ten individuals with schizophrenia and TD, treated with antipsychotics and anticholinergics reported a significant improvement of TD in nine out of ten patients specifically in the oral region. Rebound drug-induced parkinsonism was seen however in three of ten patients [25].

Neuromodulation techniques have also been investigating management of TD, including deep brain stimulation (DBS) and transcranial magnetic therapy (TMS). Neuromodulation may be considered when oral pharmacotherapy is not tolerated or contraindicated, movements remain extremely distressing or impairing, and psychiatric conditions have been stabilized. Deep brain stimulation of the globus pallidus interna has shown limited evidence of success and can be considered as a last resort [45]. TMS has the advantage of not requiring surgery or general anesthesia, and may have an important role in treatment if further evidence of success and larger studies are completed. In one recent study of 26 patients comparing rTMS versus sham treatment, 2000 rTMS pulses for ten consecutive days showed greater improvement on AIMS exam in bilateral hemispheric rTMS compared with the sham (average 8.3 point decrease for rTMS versus 1.2 point decrease in the sham group) [46].

Conclusions

Age is a significant risk factor for development of TD, a condition that can cause notable distress and impairment in functioning for this population. As many older adults are prescribed antipsychotic medications for psychotic spectrum illnesses, as well as for mood disorders and behavioral disturbances of major neurocognitive disorder, we need to be careful in early recognition and management of TD. When recommending the use of antipsychotic medications, physicians have a responsibility to inform patients and their families of both the recognized short-term likelihood of developing TD and the indeterminate degree of risk associated with prolonged use. Routine assessment for abnormal movements concerning for TD, including at initiation of antipsychotic treatment, should be a standard component of clinical practice. Discontinuing and switching antipsychotic medication is usually the first step in management, however can be limited by the underlying condition being treated and the inadequate response to improvement in the TD movements. The advent of VMAT-2 inhibitors has provided promise in treating TD, and we have only recently begun use in routine clinical practice given cost. Additional investigational treatments including neuromodulation and off-label uses of other agents currently have limited and mixed evidence. Further research is necessary to more cohesively understand TD to both improve prevention techniques and facilitate new treatments.

Compliance with Ethical Standards

Human and Animals Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interests Omar Ghosn declares that he has no conflict of interest. Enstin Ye declares that she has no conflict of interest. Steven Huege declares that he has no conflict of interest.

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•• Of major importance

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