Tardive Dyskinesia: Spotlight on Current Approaches to Treatment

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Tardive dyskinesia (TD) is a debilitating, iatrogenic, and potentially severe movement disorder characterized by involuntary, repetitive, purposeless movements that are present throughout the body. The authors present a review of studies of past, current, and possible future treatment approaches to the management of TD; consider the phenomenology, assessment, and putative pathophysiological mechanisms of TD, early pharmacological trials, a focus on the newer vesicular monoamine transporter 2 inhibitors, and other evidence-based approaches, such as clozapine; and present preliminary evidence for newer approaches, such as deep brain stimulation and repetitive transcranial magnetic stimulation. On the basis of the evidence presented here, the authors highlight the importance of early recognition and assessment of TD, as well as how to best approach management of these often incapacitating symptoms.

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Tardive dyskinesia (TD) is an iatrogenic, irreversible, and potentially severe movement disorder characterized by involuntary, repetitive, purposeless movements, typically of the orofacial muscles but also often affecting muscles of the trunk, limbs, and head. The term *tardive dyskinesia,* originally coined in 1964 by Faurbye et al. (1), refers to the dyskinetic movements witnessed among those with long-term exposure to antipsychotic medications. However, TD can occur among patients exposed to any dopamine receptor blocking agent (DRBA), including nonpsychiatric medications such as metoclopramide. These hyperkinetic movements are often not only burdensome but also lead to psychological stress and impaired quality of life during a patient's recovery efforts (2).

Multiple scales have been developed to assess the severity of TD, as well as that of other drug-induced movement disorders. The Extrapyramidal Symptoms Rating Scale is a seven-item scale that addresses four types of drug-induced movement disorder: parkinsonism, akathisia, dystonia, and TD (3). The Simpson Rating Scale is a 15-item scale that focuses on movements in the orofacial region, neck, trunk, and extremities (4). The most frequently used scale, in terms of both research and clinical use, is the Abnormal Involuntary Movement Scale (AIMS), which allows providers to track a patient's symptoms over time and determine the appropriate course of action. The AIMS is a 12-item scale; items 1–7 measure involuntary movements across regions, scored on a scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia), resulting in a maximum score of 28 (5). Items 8–10 measure the severity of the involuntary movements, the level of incapacitation resulting from them, and the patient's awareness of these movements, respectively. Items 11–12 are related to the patient's mental status. According to the Schooler-Kane criteria (6), an AIMS score of at least 2 in two or more body regions or a score of 3 or 4 in at least one region for a patient with at least three months of cumulative antipsychotic exposure defines a probable diagnosis of TD. Per *DSM-5,* older adults may develop symptoms after a shorter period of antipsychotic use.

TD usually appears after long-term (months to years) exposure to DRBAs, but it has in certain cases been shown to occur after only a brief exposure (7). Second-generation antipsychotics (SGAs) are historically considered a lower risk for the development of TD, with a reported cumulative annual incidence of 0.8%−3.0% compared with 5.4%−7.7% for first-generation antipsychotics (FGAs) (8, 9). A 2017 meta-analysis (10) of 41 studies and 11,493 patients exposed to antipsychotics found a pooled TD prevalence of 25.3%, with a lower frequency among those with current SGA treatment (20.7%) than with FGA treatment (30.0%). Patients currently prescribed an SGA with no lifetime history of FGA treatment had the lowest prevalence of TD at 7.2%. In addition to antipsychotic medication exposure (dose, duration, or type), older age is another well-established risk factor. Elderly patients (defined as those with a mean age of 65 years) have a five to six times greater risk of developing TD (11). Other risk factors include African American ethnicity, female sex, history of alcohol or other substance abuse disorders, HIV-positive

status, diabetes, and use of lithium or antiparkinsonian agents, in particular anticholinergic medications (12).

The pathophysiology of TD is not fully elucidated, and it is postulated to have a multifactorial etiology. Several mechanisms have been proposed, with the prevailing hypothesis implicating postsynaptic dopamine receptor upregulation following chronic blockade of dopamine receptors in the nigrostriatal pathway. This, in turn, may lead to permanent receptor hypersensitivity and increased affinity for dopamine, resulting in the characteristic hyperkinetic movements (13). This model would explain the "masking" of TD that temporarily occurs with greater dopamine blockade through an increase in the dosage of the DRBA.

However, this mechanism alone does not account for the variability in development of TD. Given that all antipsychotic medications are DRBAs to some extent, and yet approximately one in four patients taking these medications develops TD, this suggests that other factors, genetic vulnerability, or both are also involved. Oxidative stress—through brain injury, aging, or even neuroleptic exposure (14)—has been implicated in the development of TD. DRBAs induce a secondary increase in the synthesis and metabolism of dopamine (15), and this increased metabolism is associated with increased free radical production via monoamine oxidase. Particular antipsychotics, including haloperidol, have been shown to be directly harmful through the production of free radicals. One in vitro study showed that haloperidol caused apoptotic cell death when administered to cell cultures of murine neurons, an effect that was attenuated by antioxidants such as vitamin E (16).

Damage to striatal gamma-aminobutyric acid (GABA)-containing neurons may also contribute to pathogenesis of TD. In studies of animals after chronic exposure to antipsychotic medication, decreased activity of glutamic acid decarboxylase in the substantia nigra, globus pallidus, and subthalamic nucleus has been reported (17). However, GABA agonist treatments in humans have not had robust effects, with two recent Cochrane reviews finding inconclusive evidence to support the use of either benzodiazepine or nonbenzodiazepine GABA agonists in the treatment of antipsychotic-induced TD (18, 19).

This article highlights the varying treatment options for TD with a specific focus on the newer vesicular monoamine transporter 2 (VMAT2) inhibitors. We also provide some historical context for older approaches to TD treatment as well as for medications such as clozapine that continue to be effective yet underused for TD. Last, we review a growing literature on novel neurostimulation techniques that appear to offer some potential benefit for more refractory TD cases.

INTERVENTIONS

Ideally, TD would be preventable, although among patients with a primary psychotic disorder, the long-term use of DRBAs is typically necessary. However, SGAs are now frequently used with patients with numerous other diagnoses, including bipolar disorder, autism spectrum disorder, and major depressive disorder, expanding the population at risk for development of TD. Therefore, it is essential that this potential risk be thoroughly discussed and that antipsychotic medications only be prescribed when clinically necessary. Close monitoring for development of symptoms is also key.

Once TD symptoms are observable, cessation of the medication may not lead to resolution. In fact, this is one method of differentiating between TD and parkinsonism. Although parkinsonism is typically improved by either complete cessation or decreasing the dosage of the offending agent, the same is not true for TD. In addition, anticholinergic agents frequently used to treat parkinsonism are considered ineffective for TD and potentially deleterious (20). In studies examining the natural history of TD, remission rates have been highly variable, largely because of heterogeneity in rates of continued antipsychotic exposure, supporting the ability of these medications to mask ongoing TD. Although an older study found remission of TD in 37% of patients after cessation of antipsychotic medication (21), this finding has not been replicated. In a retrospective study of patients with TD resulting from DRBA use for nonpsychotic conditions (N=108), 13% experienced symptom resolution, although only 2% achieved this without the addition of various therapeutic agents (22).

Although it has been postulated that switching from an FGA to an SGA may lead to improvement in TD, the American Academy of Neurology has reported insufficient evidence for switching (23). This was supported by a naturalistic study of 223 patients with severe mental illness and TD (mean baseline AIMS score 9.1) for whom switching from an FGA to an SGA or from a high D_2 affinity antipsychotic to one with lower affinity had no significant impact on AIMS score (24). Adding an SGA to an existing FGA resulted in a 2- to 3-point reduction, and switching to an FGA led to a three-point reduction, consistent with the masking theory.

Early Medication Trials

No medication carried Food and Drug Administration (FDA) approval for treatment of TD before 2017, although multiple agents have been tried off-label. In 2013, the American Academy of Neurology published treatment guidelines for TD (23). At that time, results indicated limited evidence for any treatment, listing only two drugs with level B evidence (clonazepam and Gingko biloba) and two with level C evidence (tetrabenazine and amantadine).

Given the hypothesis that striatonigral GABAergic pathways reduce dopaminergic activity in the substantia nigra via negative feedback, various GABA agonists have also been trialed for the treatment of TD. In a small (N=19) double-blind, randomized crossover trial assessing the effect of clonazepam versus placebo, clonazepam treatment decreased dyskinesia scores by 37.1% versus placebo, an effect that was quickly reversed with placebo administration (25). Of note, clonazepam was more effective among patients with dystonic symptoms than among those with choreoathetoid symptoms.

Amantadine, a noncompetitive N-methyl-D-aspartate receptor antagonist and dopamine releaser, has also been used to treat drug-induced dyskinesias, including TD, although results have been varied and, even in positive trials, of debatable clinical significance. An 18-week double-blind crossover study of 16 patients with a baseline mean AIMS score of 8.375 randomized to placebo or amantadine administration (up to 300 mg/day) reported a slight improvement in follow-up AIMS scores for the amantadine group over the placebo group (7.312 versus 8.188, respectively) (26). In this trial, patients were continued on their existing antipsychotic regimen, although anticholinergic medications were held. In a double-blind randomized controlled trial (RCT) comparing amantadine and placebo among patients with antipsychotic-induced TD (N=22), results demonstrated slight improvement in the average AIMS total score for those randomized to amantadine (21.8% versus 0% in the placebo arm) at 2 weeks (27). In an older double-blind crossover RCT comparing amantadine and biperiden (an older anticholinergic medication), a similar, though modest, improvement in TD was reportedly found for both amantadine and biperiden, but the full text of this article was not available (28).

In the early 1980s, propranolol was reported to be effective for the treatment of TD, primarily in case series (29, 30). Propranolol, a beta-adrenergic receptor antagonist, has antidyskinetic properties postulated to be the result of its modulation of dopaminergic activity through presynaptic attenuation of dopamine efflux (31). However, when thioridazine serum levels were reported to be increased by the addition of propranolol, the question was then whether propranolol was simply masking TD through the same mechanism as an increase in the antipsychotic dosage (32). Although no additional trials have investigated the role of propranolol in TD treatment, a 2012 case series reported improvement in AIMS scores for two patients prescribed low-dose propranolol for TD after the offending agents (metoclopramide and risperidone) had been discontinued, suggesting that propranolol may be efficacious on its own in treating TD (33).

VMAT2 Inhibitors

Recent studies have focused on the efficacy of reversible VMAT2 inhibitors in the treatment of TD. VMAT2 is a vesicular protein that transports monoamines, including dopamine, noradrenaline, and serotonin from the cytosol into the membrane, where they are sequestered into vesicles before release into the synaptic cleft. VMAT2 inhibitors block this monoamine transport into vesicles, leading to their degradation in the cytosol (34). This reduction in dopamine release in particular, leading to less activation of postsynaptic dopamine receptors in the nigrostriatal pathway, is believed to decrease dyskinetic movements. The VMAT2 inhibitors discussed here are reversible, in contrast to reserpine, which is an irreversible, nonselective VMAT inhibitor at both VMAT1 and VMAT2. The pharmacokinetic and pharmacodynamic profiles of each of the three VMAT2 inhibitors—tetrabenazine (TBZ), deutetrabenazine (DBZ), and valbenazine (VBZ)—and evidence for their use in treatment of TD are summarized in Table 1. Of note, all three VMAT2 inhibitors are metabolized by cytochrome P450 2D6 (CYP2D6) and have the potential to cause Qtc prolongation, particularly in poor metabolizers (35).

Tetrabenazine. TBZ, a VMAT2 inhibitor that was FDA approved for Huntington's disease in 2008, has long been used off-label in the treatment of TD. The first randomized trial for TBZ in treating TD was published in 1972 and demonstrated significant improvement in frequency of abnormal movements, with resolution of TD in 33% of the 24 enrolled patients (36). An open-label trial (N=20) published in 1999 reported a 54% improvement in AIMS scores (37). However, there are several limitations to the use of TBZ. Due to its short serum half-life, tetrabenazine requires three times daily dosing. The associated high peak concentrations and fluctuations in plasma levels are believed to be responsible for its poor tolerability, including reports of somnolence and depression. TBZ also carries an FDA black box warning for suicidality in patients with Huntington's disease.

Deutetrabenazine. Since the advent of TBZ, two newer VMAT2 inhibitors have been developed to enhance tolerability via pharmacokinetic and pharmacodynamic improvements. DBZ and VBZ were both FDA-approved for the treatment of TD in 2017. DBZ is a highly selective VMAT2 inhibitor containing deuterium. The addition of deuterium slows the metabolism of DBZ, leading to reduced serum-level fluctuations compared with TBZ, thereby decreasing the potential for adverse effects associated with peak concentrations. This longer half-life also enables twice daily dosing.

There have been two randomized, double-blind, placebo-controlled trials of DBZ with published results (38–40) (summarized in Table 2). Both included 12 weeks of follow-up. In the Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD) study, (38), patients (N=117) were randomized to placebo versus escalating doses of DBZ, titrated until symptoms were adequately controlled or an adverse event occurred, to a maximum dose of 48 mg/day. A 6-week maintenance period at the final dosage followed. Although AIMS scores were significantly reduced in the treatment group, results were modest (−3.0 versus −1.6, p=0.019). Similarly, the secondary outcome of Clinical Global Impression (CGI) score was rated as "much improved" or "very much improved" for 48.2% of the DBZ group versus 40.4% for the placebo group. There were low rates of adverse events in the DBZ and placebo groups, including depression (1.7% versus 1.7%) and suicidal ideation (0% versus 1.7%). In addition, no worsening of parkinsonism or akathisia was observed in either group.

Similar positive results were also found in the Addressing Involuntary Movements in Tardive Dyskinesia (AIM-TD) trial (39). After 8 weeks of maintenance following a 4-week titration to a lower target dose (12, 24, or 36 mg/day), the change in least-squares mean AIMS score was significantly improved in the two higher dosage DBZ groups, with a

TABLE 1. Comparison of VMAT2 inhibitors[a]

Drug	Affinity for VMAT–2 (Ki)	Half-life (hours)	Time to peak concentration, Cmax (hours)	Dosage range (mg/day)	Dosing frequency	Need to take with food?	Metabolism
Tetrabenazine	100	5–7	1–1.5	12.5–150	3 times daily	No	Hepatic; CYP2D6
Deutetrabenazine	Multiple metabolites; range, 4.2–690	9–10	3–4	12–48	2 times daily	Yes	Hepatic; CYP2D6
Valbenazine	150	15–22	4–8	40–80	Once daily	No (although high-fat meals lower Cmax)	Hepatic; CYP3A4, CYP2D6

[a]VMAT2, vesicular monoamine transporter 2; Cmax, maximum concentration recorded; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4.

treatment difference of −1.9 points (p=0.001) in the 36 mg/day group and of −1.8 (p=0.003) in the 24 mg/day group, compared with placebo. The 12 mg/day group did not reach a statistically significant treatment difference (−0.7 points, p=0.217). The proportion of patients who experienced at least a 50% improvement from their baseline AIMS score was greater in the two higher dosage groups (24 mg/day: 35%, p=0.005; 36 mg/day: 33%, p=0.007) compared with placebo (12%), but this was not true for the 12 mg/day group (13%). Treatment success defined as "much improved" or "very much improved" on the CGI was also significantly higher in the 24 mg/day and 36 mg/day groups (49% and 44%, respectively) versus placebo (26%). The rate of adverse events was similar in all treatment and placebo groups, with high mean adherence to the study drug (98%). Two deaths from cardiac events were reported in the DBZ groups, but these were not deemed to be related to study drug exposure.

Participants who completed either AIM-TD or ARM-TD were eligible to enter an open-label extension trial of a 6-week dose-escalation phase followed by a long-term maintenance phase of up to 106 weeks (40) in order to evaluate the tolerability and long-term efficacy of DBZ maintenance treatment. Of the 368 patients who successfully completed the phase 3 trials, 343 patients rolled over into this open-label extension study (DBZ, N=232; placebo, N=111). After a 1-week washout period from the phase 3 study drug, DBZ was titrated in a similar fashion as in the AIM-TD trial, to a maximum of 48 mg/day (36 mg/day if on concurrent strong CYP2D6 inhibitors), with more robust improvement reported. The mean change in AIMS score was −4.9 points at week 54 (N=146) and −6.3 points at week 80 (N=66). The most common neuropsychiatric adverse events reported included headache, somnolence, depression, and anxiety, with rates that were comparable to or lower than those reported in the shorter-term ARM-TD and AIM-TD phase 3 trials. This study therefore supported the long-term safety and efficacy of DBZ treatment. Although DBZ carries a black box warning for suicidality among patients with Huntington's disease, the data have not showed an increased risk for suicidality during its use for TD treatment, and therefore DBZ does not have a regulatory warning for this population.

Valbenazine. VBZ is a highly selective, reversible VMAT2 inhibitor with metabolites that have affinity strictly for VMAT2 receptors, thereby minimizing adverse effects. A prodrug of DBZ, its activation is via hydrolysis and therefore not dependent on hepatic metabolism. Multiple double-blinded, placebo-controlled trials have demonstrated significant improvement in TD among patients randomized to VBZ versus placebo. Although three studies have shown acute improvement in trials carried out for between six and 12 weeks, others have been conducted for up to a maximum of 52 weeks to analyze long-term effects.

The KINECT series of trials (41–45), summarized in Table 3, has provided the majority of the evidence. In the initial 6-week KINECT trial, neither AIMS nor Clinical Global Impression of Change–Tardive Dyskinesia (CGI-TD) scores improved with VBZ over placebo (41). In the larger KINECT2 trial, participants were randomized to either placebo or VBZ, titrated to a maximum dosage of 75 mg/day, depending on tolerability and response (42). After 6 weeks of follow-up, there was a mean 3.6-point decrease in AIMS severity score for VBZ compared with a 1.1-point decrease in that score for placebo (p<0.001). A significantly greater percentage of responders (>50% reduction in AIMS from baseline) was present in the VBZ group versus the placebo group (48.9% versus 18.2%, p<0.001).

Similar results were found in KINECT 3, both for short-term (43) and long-term (44) trials. In the 6-week trial, participants were equally randomized to placebo, VBZ 40 mg/day, or VBZ 80 mg/day. The difference in the least-squares mean change between baseline and week 6 was −3.2 points in the VBZ 80 mg/day group, −1.9 points in the 40 mg/day group, and −0.1 in the placebo group, equating to a number needed to treat (NNT)of 3.2 (rounded up to 4) for the 80 mg/day VBZ group.

The KINECT3 extension study (44) had a 42-week VBZ extension period, followed by a 4-week washout period, for a total of 52 weeks of follow-up. Those receiving placebo earlier in the study were randomized to 40 mg/day or 80 mg/day, and those receiving 40 or 80 mg VBZ were continued on these doses. During follow-up, AIMS and CGI-TD score improvements were maintained, indicating sustained improvement in TD. At week 48, mean changes in AIMS scores were −4.8 (80 mg/day group) and −3.0 (40 mg/day group) (p<0.001). As expected, these improvements were reversible, with scores returning toward baseline after VBZ discontinuation.

KINECT 4 (45) further evaluated the long-term effects of VBZ over 48 weeks of follow-up. In this open-label trial (N=167), treatment was initiated at 40 mg/day and increased

TABLE 2. Efficacy and safety analysis data for DBZ[a]

Study	Study design	Population	Exposure	Primary endpoint	Efficacy results	Adverse events
ARM-TD trial (38) N=117 (70% with schizophrenia or SCAD), mean baseline AIMS score=9.6	12-week, randomized, double-blind, parallel-group study at 46 sites in the United States and Europe. Randomized 1:1 for DBZ versus PBO. Stratified by use of DRBA at baseline.	TD diagnosis for >3 months and history of DRBA use >3 months (>1 month if age >60). Total AIMS motor score >6.	DBZ started at 12 mg/day (6 mg BID) and titrated weekly by 6 mg/day, if required, for up to 6 weeks until adequate dyskinesia control was achieved, a significant AE occurred, or the maximal allowable dose (48 mg/day) was reached; this was followed by maintenance (6 weeks) and a 1-week washout.	Change in AIMS score from baseline to week 12	DBZ reduced least-squares mean AIMS scores from baseline to week 12 vs. PBO (−3.0 vs.−1.6, p=0.019). Improvement in AIMS score significantly differed between the DBZ and PBO groups by week 4.	Low rates of anxiety in DBZ vs. PBO groups (3.4% vs. 6.8%), depressed mood (1.7% vs. 1.7%), and suicidal ideation (0% vs. 1.7%, respectively).
AIM-TD trial (39) N=298 (60% with schizophrenia or SCAD), mean baseline AIMS score ranged from 9.4 to 10.1 (reported per treatment arm)	12-week randomized, double-blind study, patients randomized in a 1:1:1:1 pattern to receive 1 of 3 fixed-dose regimens of DBZ (12, 24, or 36 mg/day) or PBO.	TD diagnosis for >3 months and history of DRBA use >3 months (>1 month if age >60). Total AIMS motor score >6.	DBZ at a dosage of 36, 24, or 12 mg/day. Target dose maintained for 8 weeks.	Change in AIMS score from baseline to week 12	Change in least-mean squares AIMS score improved by −3.3 in the DBZ 36 mg/day group, −3.2 in the 24 mg/day group, and −2.1 in the 12 mg/day group, versus −1.4 in the PBO group. This equated to a significant treatment difference of −1.9 (p=0.001), −1.8 (p=0.003), and −0.7 (p=0.217) for the 3 groups respectively, compared with PBO.	No increased risk of akathisia or parkinsonism was found in the DBZ groups vs. the PBO group. Rates of depression, suicidal ideation, and anxiety were not significantly different among DBZ treatment groups vs. PBO group.
AIM-TD/ARM-TD extension trial (40) N=343, mean baseline AIMS score=8.8	Open-label dose-extension trial (6 weeks) followed by maintenance follow up phase (≤106 weeks)	Participants who had successfully completed AIM-TD or ARM-TD	DBZ at a dosage of 36, 24, or 12 mg/day	Safety assessment, plus change in AIMS score from baseline to each follow-up visit	Mean change in AIMS score was −4.9 at week 54 (N=146) and −6.3 at week 80 (N=66).	Exposure-adjusted incidence rates of adverse events (most common including depression, anxiety, and somnolence) were comparable to that of the short-term ARM-TD trial, indicating no evidence of cumulative toxicity or tolerability findings associated with long-term DBZ treatment

[a] DBZ, deutetrabenazine; ARM-TD, Aim to Reduce Movements in Tardive Dyskinesia study; TD, tardive dyskinesia; SCAD, schizoaffective disorder; AIMS, Abnormal Involuntary Movement Scale; PBO, placebo; DRBA, dopamine receptor blocking agent; AIM-TD, Addressing Involuntary Movements in Tardive Dyskinesia study; BID, twice a day; AE, adverse event.

TABLE 3. Efficacy and safety analysis data for VBZ[a]

Study	Study design	Population	Exposure	Primary endpoint	Efficacy results	Adverse events
KINECT 2 (42) N=100 (58% with schizophrenia or SCAD), mean baseline AIMS score=8.0	6-week randomized, double-blind study of VBZ vs. PBO	Moderate to severe TD diagnosis at study entry (assessed via video by movement disorder specialists) among patients with psychiatric stability (BPRS<50) and history of DRBA use	NBI–98854 (VBZ) at a starting dosage of 25 mg once daily, increased by 25 mg every 2 weeks until reaching maximum dosage of 75 mg/day	Change in AIMS score from baseline to week 6	AIMS score improved by −3.6 in the VBZ group vs. −1.1 points in PBO group. A significantly greater percentage of responders (>50% reduction in AIMS from baseline) present in VBZ vs. PBO group (48.9% vs. 18.2%, p<0.001)	Most common adverse events in VBZ vs. PBO group were fatigue (9.8% vs. 4.1%), headache (9.8% vs. 4.1%), constipation (3.9% vs. 6.1%) and urinary tract infection (3.9% vs. 6.1%), respectively.
KINECT 3 (43) N=227 (65% with schizophrenia or SCAD), mean baseline AIMS score=10.0	6-week double-blind study, randomized 1:1:1 to PBO, VBZ 80 mg/day, or VBZ 40 mg/day	Moderate to severe TD diagnosis at study entry (assessed via video by movement disorder specialists), history of DRBA use >3 months	VBZ at 40 mg/day or 80 mg/day	Change in AIMS score from baseline to week 6	Mean least-squares AIMS score improved by −3.2 in the VBZ 80 mg/day group, −1.9 in the 40 mg/day group, and −0.1 in PBO group. NNT=4 for the VBZ 80 mg/day group.	Most common adverse events VBZ 40 mg/day group vs. VBZ 80 mg/day group vs. PBO group were somnolence (5.6%, 5.1%, and 3.9%), akathisia (4.2%, 2.5%, and 1.3%), and dry mouth (6.9%, 0%, and 1.3%), respectively.
KINECT 3 42-week extension trial (44) N=198, mean baseline AIMS score=9.6 for 40 mg/day group vs. 10.4 for 80 mg/day group	42-week VBZ extension trial of KINECT3 participants	Same as KINECT 3 initial study	Participants randomized to PBO in 6-week trial rerandomized 1:1 to VBZ 40 or 80 mg. Those on VBZ in initial study continued at current dose.	Change in AIMS score from baseline to week 48	AIMS improvement sustained throughout the extension period. At week 48, mean changes in AIMS score of −4.8 for the 80 mg/day group and −3.0 for the 40 mg/day group. Mean percentage of improvement from baseline was 30.4% (80 mg/day group) and 23.7% (40 mg/day group). AIMS scores worsened from weeks 48–52 after VBZ discontinuation, with evidence of TD returning toward baseline levels.	Most common adverse events in 80 mg/day group vs. 40 mg/day group were headache (6.9% vs. 7.2%), urinary tract infection (6.9% vs. 7.2%), diarrhea (7.9% vs. 3.1%), and dizziness (6.9% vs. 4.1%). Syncope occurred in 3 patients. There was no worsening of akathisia or parkinsonism.

continued

TABLE 3, *continued*

Study	Study design	Population	Exposure	Primary endpoint	Efficacy results	Adverse events
KINECT 4 (45) N=167 (73% with schizophrenia or SCAD), mean baseline AIMS score=10.0	48-week open-label treatment period followed by a 4-week washout	Moderate to severe neuroleptic-induced TD for >3 months at study entry, stable psychiatric status, medical stability	Participants started on VBZ 40 mg/day, then changed to 80 mg/day after 4 weeks on the basis of efficacy and tolerability	Long-term safety assessment, plus change in AIMS score from baseline to endpoint	TD improvement was sustained throughout treatment, with AIMS mean total score changes from baseline to week 48 of −10.2 (40 mg/day group) and −11.0 (80 mg/day group). AIMS scores trended back toward baseline during washout period.	The most common TEAEs (≥5% after week 4) were urinary tract infection (8.5%) and headache (5.2%).

[a] VBZ, valbenazine; SCAD, schizoaffective disorder; AIMS, Abnormal Involuntary Movement Scale; PBO, placebo; BPRS, Brief Psychiatric Rating Scale; DRBA, dopamine receptor blocking agent; NNT, number needed to treat TEAE, treatment-emergent adverse event.

to 80 mg/day at week 4 on the basis of individual tolerability and response, in order to simulate real-world clinical situations. Mean AIMS score improvement for the 40 mg/day group was 10.2 points, compared with 11.0 points for the 80 mg/day group. Among all participants, treatment response (>50% improvement on AIMS) was found to be 90%. During the extension period, 69.2% of patients reported at least one adverse event, with headache being the most common (7.2% versus 6.9% for the 40 mg/day versus 80 mg/day groups, respectively). Discontinuation rate due to any adverse event was 15.7%.

Serious adverse events were observed among 14.6%, although the only serious event occurring for more than two participants was syncope (N=3). VBZ treatment did not induce or worsen parkinsonism or akathisia, as measured by the Simpson-Angus Scale and the Barnes Akathisia Rating Scale. No clinically meaningful changes were reported in vital signs or electrocardiogram parameters during the extension trial. Suicidal ideation was reported among 5.1% of participants, and suicidal ideation or behaviors led to treatment discontinuation by five people, although these were judged by site investigators to be unlikely to be related to VBZ. It is noted that few participants had worsening of scores on the Columbia Suicide Severity Rating Scale for suicidal ideation, despite nearly a third having a lifetime history of suicidality. This study further supported the long-term safety and efficacy of VBZ, even among older patients. When patients were dichotomized at age 55, no significant differences were found between older and younger groups in regard to either efficacy or adverse events.

Clozapine

Clozapine is an SGA and the only FDA-approved antipsychotic medication for treatment-resistant schizophrenia. Although there have been reports of clozapine worsening or inducing TD (46), the majority of evidence supports its use as an effective treatment for TD. An early 2001 meta-analysis evaluated the effectiveness of SGAs among patients with treatment-resistant schizophrenia on outcomes related to symptoms as well as side effects, including TD (47). The meta-analysis found a significant decrease in TD among patients treated with clozapine, although the effect was nonsignificant when compared with other SGAs.

Since that initial study, a more recent meta-analysis investigating the effect of switching from a nonclozapine antipsychotic to clozapine for TD demonstrated that in studies of patients with schizophrenia, switching to clozapine resulted in a significant reduction in symptoms of TD (effect size of 0.4, indicating a small to moderate effect) (48). Although there was significant heterogeneity in the studies included in the meta-analysis in regard to baseline severity of TD, the meta-analysis demonstrated the most significant reductions in those studies of individuals (N=4 studies, 48 patients) with moderate to severe TD.

These findings were further supported by a larger recent systematic review demonstrating effectiveness for switching from either FGAs or SGAs to clozapine across 13 studies (46). The review also demonstrated a negative association between duration of clozapine use and severity of TD symptoms, with variability among studies regarding time to significant reduction in symptoms that ranged from four to 12 weeks. Moreover, longer trials have supported a sustained effect over time (49–51). This review also found a significant negative relationship between TD severity and mean clozapine dose, which suggests that improvements in TD symptoms may be found early in the course of clozapine titration even before achieving a meaningful antipsychotic effect.

One possible explanation for the role of clozapine in the treatment of TD may be supported by the hypothesized mechanisms of TD. Postsynaptic D_2 receptor upregulation or potential hypersensitivity of these receptors may be mitigated by the low affinity of clozapine for the dopamine D_2 receptor as opposed to other antipsychotics that have greater affinity for that receptor (52, 53). Moreover, because of its quick dissociation from the D2 receptor, it is unlikely that the effect of clozapine on TD symptoms is due to a masking effect but is rather likely due to other mechanisms that warrant further investigation.

Neurostimulation

In severe, refractory cases of TD, neurostimulation via deep brain stimulation (DBS) or repetitive transcranial magnetic stimulation (rTMS) has been studied. A recent meta-analysis described cases of 117 patients who underwent elective DBS (for the majority, the bilateral posteroventral globus pallidus pars interna was targeted) to treat refractory tardive syndromes (54). Whereas most cases were open label, four studies (N=31) reported on assessments that were done in a double-blind fashion (55–58). Of note, the majority of cases (N=113) were patients with tardive dystonia. All but two cases in this analysis were patients treated with antipsychotic medications. Patients showed significant improvement on the AIMS (mean±SD 62±15%) and the Burke-Fahn-Marsden scale (76±21%) after DBS. Although the included data were heterogeneous in terms of recruitment, severity, assessment, and so forth, the data from these case studies suggest that DBS may be an effective option for severe treatment-refractory cases with significant disruption in quality of life.

One RCT of pallidal DBS versus sham treatment has been conducted with patients with tardive syndromes (dystonia and dyskinesia) (59). Although patients in the active DBS condition showed a 22.8% improvement in their symptoms at 3 months, this was not statistically significantly different from the sham group, who showed a 12.0% improvement. Patients went through an open-label extension phase for 6 months and demonstrated an overall improvement of 41.5%. Adverse events occurred in 10 of 25 cases and included DBS lead discomfort, gait disorders, dysarthria, confusion, skin erosion (DBS lead), pulmonary embolism, and in one case aggravation of dyskinesia as a result of a gastrointestinal infection. All adverse events resolved, suggesting that DBS for tardive syndromes may be a safe option. Further RCTs will be important to provide evidence that DBS is an effective treatment option for patients with severe TD.

Given these DBS findings, Khedr et al. (60) suggested that tardive syndromes may result from a distributed corticostriatal network that may be modulated by rTMS. The authors conducted a double-blind RCT of rTMS versus sham over the motor cortex with 26 patients for 10 consecutive days. The active rTMS group showed a significantly greater reduction in AIMS scores (8.3±1.7 points), as tardive symptoms compared with the sham group (1.2±3.3). It is important to interpret this finding with caution, given that it represents one single-site study whose findings will need to be replicated in multiple larger trials across sites. If replicated, rTMS may be an effective option for medication-refractory patients who do not want to progress to DBS.

Miscellaneous Treatments

Agents often used in the treatment of Alzheimer's disease that have cholinergic properties (e.g., cholinesterase inhibitors), such as galantamine, donepezil, and rivastigmine, have been proposed as putative therapeutic agents for TD because some of the older cholinergic drugs were found to have some benefit (61). Systematic reviews of these older agents in addition to the newer Alzheimer's drugs have found limited overall benefit across studies with nonsignificant trend-level benefit for active drug compared with placebo (62). Although one small randomized, placebo-controlled clinical trial showed no difference for donepezil compared with the control (63) several case reports (64, 65) and open-label trials (66, 67) have demonstrated benefit for donepezil in the treatment of TD. One randomized placebo-controlled clinical trial for galantamine (68) that used a crossover trial design has been published. It did not find an overall significant benefit for galantamine in reducing TD symptoms compared with placebo, although when patients who were initially randomized to galantamine were crossed over to placebo, they had worsening of both dyskinesia and parkinsonism.

Limited evidence exists for the efficacy of branched-chain amino acids, with two open-label trials demonstrating benefit for the treatment of TD symptoms (69, 70). There have been three RCTs of Gingko biloba, whose purported mechanism is via the antioxidant, free-radical scavenging properties of the extract. A meta-analysis of these trials showed benefit for Gingko biloba compared with placebo (71), although larger trials are warranted, as well as further studies that provide greater mechanistic understanding. Vitamin E has also been studied, and whereas a recent meta-analysis of 15 studies showed benefit for vitamin E over placebo (72), a recent Cochrane Review of the literature showed no evidence for vitamin E compared with placebo over 13 RCTs (73). Of note, studies of vitamin E demonstrated significant publication bias in the meta-analysis, which may explain the discrepancy in these reviews.

CONCLUSIONS AND FUTURE DIRECTIONS

TD remains a challenging clinical concern for patients treated with antipsychotic medications. Although the incidence has decreased since the advent of SGAs, the risk of TD even after treatment with SGAs remains significant. The impact on quality of life, treatment adherence, and recovery should not be underestimated. Not only is it important for prescribing physicians to discuss the risk of TD with patients who are treated with antipsychotic agents (in addition to medications such as metoclopramide), but physicians must be aware of the different treatment options available to treat these debilitating symptoms.

Clozapine remains an underused treatment option for TD. It is already underprescribed for patients with persistent symptoms of psychosis, with barriers such as the need for regular blood monitoring and significant risks of neutropenia and myocarditis, in addition to more common but concerning side effects (i.e., weight gain, tachycardia, sialorrhea, and constipation). More education on how to safely and effectively manage these barriers may lead to greater access to clozapine for patients for whom other antipsychotic medications fail. Should psychiatrists feel more competent and comfortable prescribing clozapine, its use as a treatment for TD may be considered. In fact, some have

recommended switching to clozapine monotherapy as an initial approach to treating TD (35).

The newer VMAT2 inhibitors appear to have the strongest evidence for nonclozapine treatment of TD. Tolerability and cost appear to be the most common barriers to the use of these agents. Concern for Qtc prolongation must be considered, especially if given with antipsychotics or in conjunction with CYP2D6 inhibitors because all three VMAT2 inhibitors are metabolized via this method. Nevertheless, these medications appear to offer significant benefit to patients with debilitating TD.

Other medications that have been studied and reviewed herein (i.e., clonazepam, amantadine, Gingko biloba) have limited evidence, although they may have some benefit for individual patients, especially if those patients cannot tolerate or have other contraindications to clozapine or the VMAT2 inhibitors. Finally, for particularly refractory cases, surgical and neurostimulatory approaches may be considered, although most evidence thus far comes from case reports, primarily of tardive dystonia, and thus its benefit for patients with TD remains unclear.

Future studies are needed to advance our understanding of the mechanisms underlying TD in order to both develop new, effective treatment agents and, ideally, discover preventive approaches. Although progress has been made in recent years with the current medications, ultimately these medications target only improvement, which is reversible when medication is discontinued, as opposed to discovering mechanisms that may lead to reversal of these debilitating symptoms. Moreover, greater understanding of underlying risk factors for TD may lead to predictive algorithms to identify those at greater risk and help inform physicians' choice of antipsychotic medication. Despite these gaps in our understanding of these symptoms, the current pharmacological options, especially with the more widespread use of the VMAT2 inhibitors, offer some hope for greater symptomatic improvement that may lead to greater quality of life and recovery for patients.

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