Treatment of Tardive Dyskinesia

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KEYWORDS

• Tardive dyskinesia • Tardive syndrome • VMAT2 inhibitors • Deutetrabenazine • Valbenazine

KEY POINTS

- Tardive dyskinesia is a common movement disorder caused by treatment with antipsychotics ('neuroleptics') and other dopamine receptor blocking agents.
- The judicious use of dopamine receptor blocking agents is key to the prevention of tardive dyskinesia, reduction of disease burden, improvement in quality of life, and maintenance of remission.
- Deutetrabenazine and valbenazine are vesicular monoamine transporter 2 inhibitors approved by the FDA for the treatment of tardive dyskinesia, supported by high level evidence from pivotal clinical trials.
- Although evidence is limited, other treatment options can be considered in those who cannot tolerate or do not respond to vesicular monoamine transporter 2 inhibitors.
- Botulinum toxin or trihexyphenidyl can be considered for tardive dystonia and deep brain stimulation or electroconvulsive therapy can be considered for disabling symptoms refractory to other therapies.

INTRODUCTION AND OVERVIEW

The term, *tardive dyskinesia* (*TD*), originally was coined by Faurbye and colleagues[1] in their description of delayed-onset, persistent, rhythmic, stereotyped movements after exposure to dopamine receptor blocking agents (DRBAs). Initial studies focused on exposure to antipsychotics (or neuroleptics) but the DRBAs also include drugs used in the treatment of nausea (antiemetics), gastroparesis (promotility agents), and cough (antitussives). The original phenomenological descriptions focused on involuntary movements involving chiefly face, mouth, and tongue (orobuccolingual [OBL]), later classified as stereotypies; however, the phenomenology of TD gradually expanded to include other motor and nonmotor features.[2–4] This led to the concept of the tardive syndrome (TS), an umbrella term representing the full spectrum of hyperkinetic

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and hypokinetic movement disorders that include stereotypy, dystonia, akathisia, chorea, myoclonus, tics, tremor, parkinsonism, and gait disorders as well as ocular deviations, respiratory dyskinesia, and various sensory symptoms.[5,6] The use of the term, *extrapyramidal syndrome*, particularly popular among psychiatrists, is now strongly discouraged by experts for lack of clarity.[7]

The presentation of TS can vary from a mild, barely perceptible, orofacial movement or a feeling of irritation or a burning sensation in the mouth or genital area to a disabling and potentially even life-threatening condition that causes severe impairment in physical, mental, and social functioning.[8] Among the most serious forms of TS is status dystonicus as a complication of TD[9,10] and neuroleptic malignant syndrome.[11] TD has been associated with higher mortality among psychiatric patients.[12]

Epidemiologic studies have shown that TD is a common problem, associated with almost all DRBAs, except possibly clozapine.[13] Early studies of TD estimated prevalence rates among patients exposed to DRBAs ranging from 24% to 56% with an average closer to 20% to 30%.[14–16] In the era of typical (first-generation) antipsychotics, the risk of TD after exposure for 5 years was estimated to be 32%, 57% after 15 years and 68% after 25 years.[17] At first, the arrival of atypical (second-generation or third-generation) antipsychotics appeared to be associated with a lower risk of TD[18] (13.1% vs 32.4%); however, later studies did not confirm these findings.[19] The well-known Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a large randomized clinical trial comparing effectiveness of typical and atypical antipsychotics in schizophrenia, failed to show decrease in TD with atypical antipsychotics.[20] A recent meta-analysis comparing typical and atypical antipsychotics across 41 studies between 2000 and 2015, estimated a mean prevalence of 25.3% for all treatment groups that was somewhat greater with typical antipsychotics (30%) versus atypical (20%) although the significance of this difference could not be determined because TD severity data were considered insufficient.[21] Unfortunately, prescribing rates for approved and off-label indications remain high and even may be increasing worldwide.[22] Antipsychotics are used frequently and inappropriately by physicians and allied professionals as an off-label treatment of depression, anxiety, insomnia, and other conditions.[23,24] This concerning trend highlights the importance of education about judicious use of antipsychotics.

Although the relationship of TD and antipsychotics is well established, drugs with the potential to cause TD also include antiemetics (metoclopramide, prochlorperazine, and promethazine), lithium, serotonin reuptake inhibitors (duloxetine and citalopram), tricyclic antidepressants (amoxapine and amitriptyline), and calcium channel blockers (cinnarizine and flunarizine).[3] Except for the antiemetics that act by blocking dopamine receptors, the other drugs appear to work through other mechanisms in causing TD. Compared with antipsychotics, however, the evidence for these drugs causing TD mostly are limited to case reports or case series.[25] A recent review of the literature found that rather than cause TD, both tricyclic antidepressants and selective serotonin reuptake inhibitors may unmask or exacerbate TD from prior or concurrent use of DRBAs, a possible priming effect.[26]

The exact cause of TD remains unknown although several theories have been proposed.[27] The mostly widely accepted theory is dopamine receptor supersensitivity, whereby chronic blockade of dopamine receptors leads to receptor up-regulation with subsequent postsynaptic supersensitivity. This theory is supported by the observation of reduction in TD when DRBA doses are increased and the exacerbation of TD with abrupt withdrawal of DRBAs (including a severe, potentially life-threatening variant known as withdrawal emergent dyskinesia).[28–32] This theory, however, does not explain the enduring symptoms of TD because the receptors would be expected

to eventually down-regulate after DRBA discontinuation. It also does not explain the incidence of non-DRBAs causing TD. Alternatively, genetic factors, free radical damage, and aberrant, maladaptive synaptic plasticity also have been implicated in the pathophysiology of TD.[27]

Many risk factors have been identified for the development of TD.[33] Broadly, these are classified into modifiable and nonmodifiable factors. The modifiable include choice of DRBA, higher cumulative antipsychotic dose, prior acute dystonic reaction, diabetes, smoking, and alcohol/substance abuse, among others. The nonmodifiable include older age, female sex, white and African descent, intellectual disability, mood disorders, and genetic differences in antipsychotic metabolism.[27,33] An analysis of 189,415 patients treated with antipsychotics found the following predictors for the development of TD: age, diagnosis of schizophrenia, dosage of antipsychotic, and the presence of bipolar and related disorders.[34] Anticholinergics (eg, benztropine) frequently are coprescribed with antipsychotics by psychiatrists in an effort to reduce or prevent the onset of TD.[35] This practice is not supported, however, by evidence and even may precipitate or worsen TD.[36,37]

TD is an insidious, complex, and potentially devastating iatrogenic complication that has an impact on a substantial proportion of vulnerable patients; 2017 was a crucial year because it saw the approval of the first 2 medications to treat TD by the US Food and Drug Administration (FDA),[38] bringing renewed interest and much-needed investment in educating physicians, especially psychiatrists, in the diagnosis and treatment of TD. This article aims to provide the practicing neurologist with a succinct review of the treatment options for TD, with emphasis on recent developments.

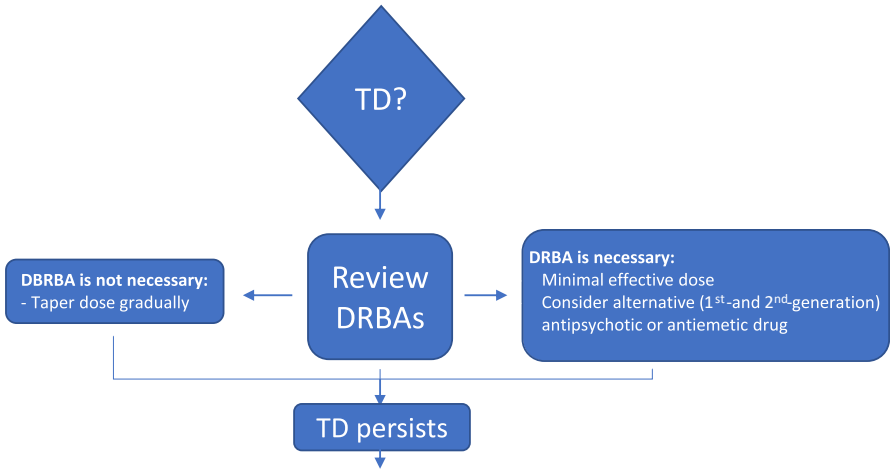
MANAGEMENT GOALS

- Recognizing TD and effectively utilize rating scales, such as the Abnormal Involuntary Movement Scale (AIMS) to determine severity and monitor treatment response
- Initiating therapy with the highest level of evidence to reduce the signs and symptoms of TD
- Reducing deficits in physical, mental, and social functioning that are either a direct or indirect result of TD
- Minimize adverse effects (AEs) and the financial burden of treatment
- Emphasizing and promoting the judicious use of DRBAs
- Maintaining regular follow-up with frequent reassessments of the patient

GENERAL APPROACH

From the outset, the prevention of TD is of paramount importance. DRBAs should be avoided whenever possible by choosing alternative medication with lower or no risk of TD. If the use of a DRBA is necessary, then long-term treatment should be avoided whenever possible. Frequent reassessments must be utilized to determine if ongoing DRBA use is indicated and to remain vigilant for early symptoms and signs of TD. When TD is identified, DRBAs should be withdrawn slowly in patients who can tolerate it because abrupt withdrawal may worsen or precipitate TD (as well as the underlying psychiatric disorder when present).[29,39,40] Frequently, neurologists and psychiatrists must work together to provide multidisciplinary care to balance the risk of TD and management of underlying psychiatric illness. If patients require continued treatment, then every effort should be made to switch to medication with lower risk of TD. In the cases of antipsychotics, switching to clozapine or quetiapine may be considered because they have lower dopamine receptor affinity and relatively low risk of TD.[41,42] Pimavanserin, a nondopaminergic inverse serotonin

agonist, is a novel antipsychotic approved for Parkinson disease psychosis[43] that also can be considered as an alternative, off-label treatment.[44] In cases of antiemetics, those without dopamine receptor blocking activity should be considered first line (eg, ondansetron and trimethobenzamide). Even when the offending agent is withdrawn, remission rates may be as low as 13%.[45] This combination of increasing exposure rates and low remission rates highlights the need for effective treatment of TD. It also has led to the increased use of off-label treatments. Despite best efforts to minimize the risks of TD, a substantial proportion of patients will develop TD and require pharmacologic and/or surgical treatment. **Fig. 1** outlines a general approach to treatment of TD.



Treatment option	Level of evidence
VMAT2 inhibitor - Deutetrabenazine - Valbenazine - Tetrabenazine	 Level A Level A Level C
Clonazepam	Level B
Ginkgo biloba	Level B
Amantadine	Level C
Bilateral GPi DBS (refractory TD)	Level C
Botulinum toxin	Level U
1st and 2nd generation antipsychotics	Level U
Acetazolamide, baclofen, levetiracetam, vitamins B_6 and E, zonisamide, zolpidem, ECT.	Level U

Fig. 1. Treatment algorithm for TD. Levels of evidence according to AAN 4-tiered scheme = level A (established as effective), level B (probably effective), level C (possibly effective), and level U (data inadequate)[55] (updated and modified).(*Adapted* from Bhidayasiri R, Jitkritsadakul O, Friedman JH, Fahn S. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. J Neurol Sci. 2018;389:67-75; with permission.)

PHARMACOLOGIC TREATMENTS

Vesicular Monoamine Transporter Type 2 Inhibitors

Although the pathogenesis of TD is not fully understood, the finding that increased dopamine signaling plays an important role led to the pursuit of agents that could modulate signaling without directly blocking receptors. The vesicular monoamine transporters (VMATs) are transport proteins integrated into the synaptic vesicles of presynaptic neurons and exist as 2 isoforms, VMAT1 and VMAT2.[46] VMATs facilitate the transport of cytoplasmic monoamines (dopamine, histamine, norepinephrine, and serotonin) into presynaptic vesicles. In contrast to VMAT1, which is localized in both the central and peripheral nervous system, VMAT2 is found only in central presynaptic neurons.[46,47] Inhibition of VMATs thus reduces presynaptic storage and release of monoamines, particularly dopamine, which then are degraded by monoamine oxidase in the cytoplasm, resulting in presynaptic dopamine depletion.[13] Selective VMAT2 inhibition is preferred, because VMAT1 inhibitors, such as reserpine (a nonselective VMAT inhibitor used to treat hypertension and hyperkinetic movement disorders), are associated with multiple peripheral AEs such as bronchospasm, nausea, vomiting, hypotension, and nasal stuffiness.[47] Three selective VMAT2 inhibitors currently are available for the treatment of TD: tetrabenazine (TBZ), deutetrabenazine (DTBZ), and valbenazine (VBZ). **Table 1** provides a summarized comparison of these medications.

Tetrabenazine

TBZ originally was developed in the 1950s to treat psychosis and in 1971 it was introduced in the United Kingdom for the treatment of hyperkinetic movement disorders.[48] It was not until 2008 that it was approved in the United States for the treatment of Huntington chorea; however, it frequently is prescribed for off-label indications, including TD.[49]

Kazamatsuri and colleagues[50] reported the first clinical trial of TBZ in TD in 1972. This prospective, single-blind study of 24 chronic psychiatric patients with TD at

Table 1
Comparison of vesicular monoamine transporter type 2 inhibitors

Characteristic	Tetrabenazine (Xenazine)	Deutetrabenazine (Austedo)	Valbenazine (Ingrezza)
Mechanism of action	Reversible VMAT2 inhibitor	Reversible VMAT2 inhibitor	Reversible VMAT2 inhibitor
US FDA approval (y)	HD chorea (2008)	HD chorea (2017), TD (2017)	TD (2017)
Pivotal trials	TETRA-HD	First-HD, AIM-TD, ARM-TD	KINECT 2, KINECT 3
Active metabolites	Yes	Yes	Yes
Half-life	5–7 h	9–10 h	15–22 h
Dose range (recommended)	12.5–100 mg/d	6–48 mg/d	40–80 mg/d
Safety data	>40 y	>2 y	>2 y
AE profile	1. Sedation 2. Parkinsonism 3. Depression	1. Sedation 2. Insomnia (similar to placebo)	1. Sedation 2. Headache 3. Fatigue

Abbreviation: HD, Huntington disease.

Boston State Hospital began with a 4-week baseline period in which medications were not changed (14 patients were taking DRBAs) followed by 4 weeks on placebo where all DRBAs were discontinued; then, a 6-week treatment period with TBZ starting at 50 mg/d titrated to 100 mg/d to 150 mg/d. It ended with a 2-week TBZ washout period on placebo. The primary outcome measure was mean frequency of dyskinetic movements per minute as reported by a blinded rater; 8 patients (33%) had complete resolution of TD, 6 (25%) had marked improvement; another 6 had little or no change; and 4 patients did not complete the study (2 developed severe malaise, 1 withdrew due to exacerbation of psychosis, and 1 was lost to follow-up).[50] Compared with placebo, TBZ was found to significantly reduce TD by 64%. Ondo and colleagues[51] reported a prospective, single-blind study of 20 patients with TD (mean duration 43.7 months) who were videotaped before and after treatment with TBZ. One patient withdrew from the study due to sedation. Videotapes were randomized and scored using the motor subset of the AIMS by a blinded rater. The average improvement on the AIMS score was 54.2% (from 17.9 to 8.2; $P<.0001$) after an average treatment period of 20.3 weeks on a mean daily dose of 57.9 mg/d, 11 patients rated themselves as markedly improved, 6 as moderately improved, and 2 as moderately improved.[51]

Two large, retrospective reports of TBZ in hyperkinetic movement disorders have supported its beneficial role in TD.[52,53] Combined, they report greater than 84% of TD patients (a total of 242 patients) that rated their improvement as either moderate or marked. These 2 studies also shed light on the most common AEs of TBZ, which included sedation (25.0%–36.5%), parkinsonism (15.4%–28.5%), depression (7.6%–15.0%), insomnia (4.9%–11.0%), anxiety (5.1%–10.3%), and akathisia (7.6%–9.5%).[52,53] Essentially, all TBZ-related AEs have been shown to be dose related and decrease with dose reduction. They also can be managed with antidepressants, stimulants, and other pharmacologic strategies if patients otherwise benefit from TBZ. Both the 2013 American Academy of Neurology (AAN) guideline and a recently published systematic review gave TBZ a level C (possibly effective) recommendation in the consideration of treatment of TD, based on lack of double-blind, placebo-controlled studies.[54,55]

TBZ is quickly metabolized into α-dihydrotetrabenazine and β-dihydrotetrabenazine (half-life 5–7 h) via hepatic isoenzyme CYP2D6. Because of its short half-life, TBZ typically is dosed 3 times a day.[56] TBZ should be started at low doses (12.5–25 mg/d) with careful titration (typical therapeutic dose, 50–75 mg/d) and monitoring for AEs. It is recommended by the FDA that patients receiving more than 50 mg of TBZ per day be genotyped for CYP2D6, but the various genotypes do not reliably predict the frequency of AEs.[56] With this need for frequent dosing and a side-effect profile restricting its use, a strong interest grew in the development of novel VMAT2 inhibitors. Although TBZ has been approved for the treatment of chorea associated with Huntington disease, it has not been approved for the treatment of TD.

Deutetrabenazine

DTBZ is a deuterated version of TBZ, incorporating 6 atoms of the naturally occurring and nontoxic isotope deuterium or heavy hydrogen in its molecule.[47] Deuterium-carbon bonds are stronger than hydrogen-carbon bonds, thus more resistant to metabolizing cytochrome P450 enzymes like CYP2D6.[57] This provides significant pharmacokinetic advantage (ie, longer half-life) over TBZ without altering target pharmacology. DTBZ is dosed twice a day versus 3 times daily (half-life 9–10 h), with a lower dose per administration to achieve similar clinical effect (6 mg of DTBZ is approximately the equivalent of 12.5 mg TBZ).[58] DTBZ first obtained FDA approval for the treatment of Huntington chorea in April 2017 after the pivotal First-HD trial

demonstrated safety and efficacy.[59,60] This was followed by approval for the treatment of TD in August 2017 based on the results of 2 pivotal trials, Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD) and Addressing Involuntary Movements in Tardive Dyskinesia (AIM-TD).[61,62]

ARM-TD was a phase 3, double-blind, multicenter trial of 177 patients with moderate to severe TD (AIMS $\geq$6) that were randomized 1:1 to either placebo or DTBZ.[61] Patients were allowed to continue DRBAs provided there was no recent change in medications. The DTBZ group was started at 12 mg/d, with weekly titration of 6 mg/d until either adequate TD control was achieved, a significant AE occurred, or the maximal allowable dose of 48 mg/d was reached. This was followed by a 6-week maintenance period and 1-week washout. The primary endpoint was the change in AIMS score from baseline to week 12 as assessed by 2 blinded video raters who were movement disorder specialists. Secondary endpoints included treatment success at week 12 on the Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC). The mean daily dose was 38.8 mg at the end of the study period. There was a mean 3.0-point reduction in AIMS score for DTBZ versus 1.6 in the placebo group (P = .019), a treatment difference of 1.4. Although the percentage of patients who achieved treatment success on the CGIC (48.2% vs 40.4%) and PGIC (42.9% vs 29.8%) favored DTBZ, these differences did not reach statistical significance. Most common AEs for DTBZ versus placebo were somnolence (13.8% vs 10.2%), insomnia (6.9% vs 1.7%), and akathisia (5.2% vs 0%). Discontinuation rates because of AEs were 1.7% versus 3.4%, respectively. Neither DTBZ nor placebo group experienced any worsening in parkinsonism and rates of psychiatric AEs were low: anxiety (3.4% vs 6.8%), depressed mood/depression (1.7% vs 1.7%), and suicidal ideation (0% vs 1.7%).

AIM-TD was a second-phase 3, double-blind, multicenter trial of 298 patients randomized 1:1:1:1 to receive fixed doses of DTBZ 12 mg/d, 24 mg/d, 36 mg/d, or matching placebo for 8 weeks after a 4-week titration period.[62] The primary endpoint was change in AIMS score from baseline to week 12 based on blinded video assessments. From baseline to week 12, change in least squares mean AIMS score improved by $-$3.3 points in the DTBZ 36 mg/d group, $-$3.24 in the 24 mg/d group, and $-$2.1 points in the 12 mg/d group, with a significant treatment difference of $-$1.9 points (P = .001), $-$1.8 points (P = .003), and $-$0.7 points (P = .217), respectively, compared with placebo.[62] The investigators defined treatment success as "much improved" or "very much improved" on the CGIC, which was accomplished in 49% of patients receiving 24 mg/d (P = .014) and 44% of those receiving 36 mg/d (P = .059) compared with 28% with 12 mg/d and 26% with placebo. There was no significant difference in PGIC outcomes between DTBZ and placebo. The most common AE was headache (5%). There were no other single AEs for DTBZ (all doses pooled) with incidence greater than or equal to 5% or greater than that observed for placebo. Discontinuation rates because of AEs were 4.1% for DTBZ (all doses pooled) versus 2.8% for placebo. 2 patients (1%) died, 1 each in the 24 mg/d and 36 mg/d groups; neither death was deemed related to study drug.[62]

Pooling the data across both trials,[63] the number needed to treat (NNT) for greater than 50% reduction of the AIMS score at the therapeutic doses of DTBZ versus placebo was 7 (95% CI, 4–18). DTBZ was well tolerated, with low rates of AEs in both ARM-TD and AIM-TD. AE-related discontinuation occurred among 3.6% of patients randomized to DTBZ (at any dose) versus 3.1% for placebo, yielding a number needed to harm of 189 (not significant). A recently published open-label extension study, analyzing 331 patients treated for a mean of 352.9 days, confirmed safety outcomes of both trials, demonstrating that DTBZ is well tolerated for long-term use in TD

patients.[64] DTBZ has received a level A (established as effective) recommendation for the treatment of TD.[55]

Valbenazine

The metabolites of TBZ possess several chiral centers that generate isomers with different VMAT2 binding affinity.[65] Once characterized, VBZ was developed as a purified parent drug of TBZ that metabolizes into an isomer of α-dihydrotetrabenazine with a combined half-life of 15 hours to 22 hours.[66] This allowed for a convenient once-daily dosing. VBZ also was designed to metabolize slowly, minimizing high peak plasma concentrations thereby improving tolerability.[66] Its limited range of metabolites reduces the likelihood of off-target effects that can occur with TBZ metabolites.[47,66] These pharmacokinetic and pharmacodynamic advantages made VBZ an attractive agent for further study in TD.

KINECT 2 was a phase 2, 6-week, double-blind, placebo-controlled dose-titration study that randomized 102 patients with moderate or severe TD to placebo or VBZ, 25 mg/d, with titration to a maximum of 75 mg/d; 76% of the VBZ group reached this maximum allowed dose.[67] The primary efficacy endpoint was change in AIMS from baseline at week 6 scored by 2 blinded video raters. Secondary efficacy endpoint was CGIC. At week 6, least squares mean AIMS scores were reduced by −2.6 points for the VBZ group compared with −0.2 for placebo ($P = .0005$).[67] CGIC and PGIC results also favored VBZ versus placebo as a rating of "much improved" or "very much improved" occurred in 66.7% versus 15.9% ($P<.0001$) and 57.8% versus 31.8% ($P = .001$), respectively. Treatment-emergent AE rates were 49% in the VBZ and 33% in the placebo subjects. The most common AE (VBZ vs placebo) were fatigue and headache (9.8% vs 4.1%) and constipation and urinary tract infection (3.9% vs 6.1%). These results supported further study in a phase 3 trial.

KINECT 3 was a phase 3, randomized, double-blind, placebo-controlled trial of VBZ in TD.[68] It was designed similarly KINECT to 2. This 6-week study randomized 234 patients (of whom 86% received concomitant DRBAs) 1:1:1 to once-daily placebo or VBZ (40 or 80 mg/d). Least squares mean AIMS scores improved by −1.9 points for VBZ, 40 mg/d ($P = .002$); −3.2 for VBZ, 80 mg/d ($P<.001$); and only −0.1 for placebo. In a pooled analysis of both trials, 36.5% of patients receiving VBZ (both doses) versus 12.4% receiving placebo had a greater than 50% reduction of AIMS scores, yielding an NNT of 5 (95% CI, 3–7).[69] The most common AEs reported (VBZ vs placebo) were somnolence (5.4 vs 3.2%), headache (4.5 vs 3.2%), fatigue (4.0 vs 2.4%), dry mouth (4.0 vs 0.8%), vomiting (3.0 vs 0%), and urinary tract infection (2.5 vs 4.8%).[69] KINECT 3 did note that 4.2% of VBZ patients reported akathisia and suicidal ideation versus 1.3% and 5.3% in placebo, respectively.[68] The 1-year KINECT 3 extension study of 198 patients supported long-term efficacy, safety, and tolerability of VBZ in TD.[70] The recently published data from KINECT 4 (clinicaltrials.gov, NCT02405091), which included 48 weeks of open-label treatment with VBZ followed by a 4-week washout, demonstrated sustained and clinically meaningful improvement of TD, and VBZ generally was well tolerated without notable changes in the psychiatric status of patients.[71]

Based on these data, VBZ received FDA approval for the treatment of TD in April 2017. VBZ has a level A recommendation for the treatment of TD.[55]

Non–vesicular Monoamine Transporter Type 2 Pharmacologic Agents

Benzodiazepines

The ϒ-aminobutyric acid (GABA)ergic system has been implicated in the pathophysiology of TD.[72] Benzodiazepines are allosteric $GABA_A$ agonists that hyperpolarize neurons by increasing Cl^- influx and frequently are used in the treatment of TD.[73]

Clonazepam was evaluated in a 12-week, double-blind, randomized, crossover trial of 19 chronically ill patients with TD taking DRBAs.[74] Overall, a 37.1% reduction ($P<.001$) in dyskinesia was noted from baseline after 12 weeks using the Maryland Psychiatric Research Center movement disorders scale. Patients with dystonic symptoms (n = 6) showed greater benefit (41.5% reduction) than the remainder with choreoathetoid dyskinesia (n = 13; 26.5% reduction).[74] The investigators followed 5 patients for an additional 9 months and noted they developed tolerance to clonazepam; however, an antidyskinetic effect was recaptured after a 2-week drug holiday. Clonazepam has a level B recommendation (probably effective) for the treatment of TD.[55]

Diazepam and alprazolam are shorter-acting benzodiazepines for which the effectiveness in TD remains unclear. An open-label study of 21 patients with TD demonstrated improvement in AIMS scores with diazepam.[75] A 24-week, randomized, placebo-controlled, crossover study of 13 patients using blinded rating did not find improvement with diazepam.[76] A small study comparing alprazolam, diazepam, and placebo showed no benefit for TD.[77] Alprazolam has not been studied in a randomized trials; only case reports have been described.[78]

Ginkgo biloba

Ginkgo biloba extract (EGb-761) is obtained from the fan-shaped leaves and seeds of the Ginkgo biloba tree (or maidenhair tree) and has antioxidative properties.[79] It is among the most sold medicinal plants in the world and commonly used in traditional Chinese medicine. In a 12-week, double-blind, randomized, placebo-controlled trial of 157 patients with schizophrenia and TD, EGb-761 reduced AIMS scores by an average of 2.13 ($P<.001$) compared with 0.1 for placebo[80]; 51.3% of patients in the EGb-761 group experienced greater than 30% reduction in AIMS score compared with just 5.1% of placebo ($P<.001$). Although additional studies are needed to confirm these data, Gingko biloba has been given a level B recommendation for the treatment of TD.[55]

Amantadine

Amantadine, initially developed as an antiviral agent, is a noncompetitive *N*-methyl-D-aspartate antagonist with antiglutamatergic properties, now commonly used in the management of levodopa-induced dyskinesias.[81] It was first reported to improve TD in 1971 after 2 small case series.[82,83] The investigators subsequently performed 2 double-blind, crossover studies of amantadine 100 mg 3 times and twice daily versus matching placebo for 10 days (14 patients and 10 patients, respectively) that were negative.[84] More recently, 2 small studies evaluated amantadine in TD patients taking DRBAs and noted positive results.[85,86] Angus and colleagues[85] reported a double-blind, randomized, placebo-controlled, 7-week-per-arm, crossover trial of amantadine initiated at 100 mg/d and titrated to 300 mg/d maintained for 3 weeks. The mean AIMS score was significantly lower in the amantadine group than placebo (7.312 vs 8.188; $P<.05$). Pappa and colleagues[86] reported a double-blind, randomized, placebo-controlled, 2-week-per-arm, crossover trial of amantadine up to 400 mg/d. Patients receiving amantadine exhibited a reduced mean AIMS score (13.5–10.5; $P = .000$) whereas the placebo group showed no reduction. These studies supported the short-term use of amantadine; however, given the mixed results and small study sizes, amantadine has a level C recommendation for the treatment of TD.[55]

Other Pharmacologic Treatments

There are several other oral agents for which there is insufficient evidence to support their use in TD.[54,55] These include cholinergic agents (eg, donepezil, physostigmine, choline, and galantamine),[87,88] anticholinergics (eg, benztropine),[37] antioxidants other than Ginkgo biloba (eg, vitamin B_6 and vitamin E), baclofen, buspirone, eicosapentaenoic

acid, calcium channel blockers, acetazolamide, melatonin, zonisamide, and propranolol.[55]

Trihexyphenidyl, an anticholinergic, showed improvement in TD from data of 2 retrospective studies using 10 mg/d to 32 mg/d in 3 of 8 patients[89] and 6 mg/d to 12 mg/d in 8 of 21 patients.[90] This is consistent with the observation that anticholinergics are useful in primary dystonia.[91] The risk of cognitive AEs and worsening of OBL stereotypies, however, limit their use and it is generally discouraged in TD.[92,93]

Zolpidem, a nonbenzodiazepine hypnotic, has been reported to be effective for the treatment of TD and tardive akathisia in a small series of 3 patients.[94] Placebo-controlled study is needed to further document effectiveness of zolpidem in TD.

Levetiracetam is an antiepileptic that targets synaptic vesicle glycoprotein 2A and may modulate vesicle release.[95] Two small open-label trials[96,97] and a small randomized trial[98] demonstrated reduced severity of TD. The latter was a 12-week, double-blind study of 50 patients receiving levetiracetam (500–3000 mg/d) versus placebo. AIMS scores declined 43.5% from baseline in the levetiracetam group compared with 18.7% for placebo ($P = .022$); however, there was a high dropout rate because of psychiatric disorientation, nonadherence, loss to follow-up, and unrelated stressors.[98] Although the results were somewhat promising, further studies have not been done and levetiracetam has been given a has been given a level U (inadequate evidence) recommendation for the treatment of TD.[55]

Lastly, although there is some evidence that initiating or switching to atypical antipsychotics can help reduce TD,[99,100] based on the knowledge that all atypical antipsychotics (with the possible exception of clozapine) can cause TD, both the 2013 AAN guidelines and a recent systematic review do not recommend the use of these agents to treat TD.[54,55]

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is a well-recognized and widely used treatment option for many movement disorders, including Parkinson disease, essential tremor, and dystonia.[101] DBS in TD typically is reserved for severe, disabling, medically refractory cases (level C recommendation).[55] A recent systematic review and metanalysis found that the majority of DBS studies in TD to date are open-label case reports or part of open-label case series of dystonia of various etiologies.[102] All cases were related to use of neuroleptics, except those of 2 patients, which were a result of metoclopramide exposure.[103,104] A majority of cases target bilateral posteroventral globus pallidus internus (GPi), although a few cases of subthalamic nucleus DBS also have been successfully reported with long-term follow-up.[105,106] Across 51 cases of DBS in classical TD, in which the outcome measure was change in AIMS score, the mean percentage of AIMS score improvement was 62 $\pm$ 15% after DBS surgery (median 58%; range 33%–90%).[102] In cases of TD, the Burke-Fahn-Marsden (BFM) scale has been most widely used. The BFM motor score improvement across 67 cases was 76 $\pm$ 21% after DBS (median 82%; range 7%–100%).[102] The limitations of these data are the differences across case reports, including phenomenology, severity, clinical assessments, frequency of follow-up, and the lack of prospective, controlled trial.

OTHER TREATMENT OPTIONS

Botulinum Toxin

Botulinum neurotoxin (BoNT) is derived from *Clostridium* bacteria and acts on presynaptic vesicular release complex proteins to reduce neurotransmission.[107] It has emerged as one the most versatile therapeutic options in medicine. Within movement

disorders, BoNT type A (onabotulinumtoxinA) is approved for the treatment of blepharospasm, craniocervical dystonia, and limb spasticity.[107] There have been no controlled trials studying the effects of BoNT in the treatment of TD. Several case reports, case series, and open-label reports, however, have shown promising results.[108–110] A majority of reports include patients with focal symptoms, such as OBL stereotypies or TD that had failed other pharmacologic treatments. Slotema and colleagues[111] performed a single-blind (raters only) 33-week study of 12 patients with orofacial TD receiving BoNT every 3 months for 3 treatments. Although there was a nonsignificant ($P = .15$) reduction in TD severity overall, in the patients with no change in their antipsychotic medication (ie, stable doses; n = 8), the reduction was significant (AIMS score 4.81–3.0; $P = .035$). After the study, 50% of the patients preferred to continue treatment with BoNT. Notable limitations of BoNT in the treatment of TD are the need for technical expertise (which can vary significantly between injectors), need for reinjection, and the potential for perioral, lingual, or neck injections to cause dysarthria and dysphagia. In the absence of controlled trials, BoNT currently has a level U recommendation for the treatment of TD.[55]

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) uses a small electric current to produce a generalized cerebral seizure under general anesthesia, primarily used for the management of severe, treatment-resistant psychiatric conditions.[112] Multiple case reports have described improvement of TD after ECT in patients treated for depression or schizophrenia.[113–115] Yasui-Furukori and colleagues[116] reported a retrospective series of 18 patients receiving ECT that demonstrated a mean AIMS score improvement from 19.1 $\pm$ 4.7 to 9.6 $\pm$ 4.2. These findings contrast with reports (albeit quite dated) of worsening TD,[117] emergence of TD,[118] or no change in TD[119] with ECT. Overall, the 2013 AAN guidelines concluded that there is insufficient evidence (level U) for the efficacy of ECT in treating TD.[54]

SUMMARY

The aim of this review is to provide a summary of the current treatment options for TD with emphasis on recent developments; 2017 was a pivotal year for TD with the approval of 2 new drugs, VBZ and DTBZ, bringing with them renewed interest and attention to the condition. The management of TD remains challenging, however, given the heterogeneity of cases and limited treatment options. There are many important areas of research specifically addressing those patients who remain refractory to treatment despite recent developments. As discussed previously, many other agents with different mechanisms and tolerance profiles have shown promise but need to be studied in large, controlled, multicenter trials. In an era of precision medicine, better understanding the pathophysiology and underlying genetics of TD will lead to new, targeted treatments. The development of patient registries to provide long-term data will be essential for such endeavors. Conceivably, the development of newer antipsychotics that do not cause TD may reduce disease burden significantly. Physician education, however, regarding the judicious use of current DRBAs remains central to the prevention and management of TD.

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