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Current treatment of tardive dyskinesia

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ABSTRACT

Tardive dyskinesia (TD) is a common, iatrogenic movement disorder affecting many individuals treated with dopamine-receptor blocking agents (DRBAs). Studying treatment of TD can be complex, as the symptoms can be affected by changes in either dosage or type of DRBA, as well as by the variable natural course of the disease. Historically many pharmacological therapies have been studied in TD, finding varying degrees of treatment success. Most recently, the VMAT2 inhibitors valbenazine and deutetrabenazine were rigorously studied in TD in large, phase III clinical trials, and were shown to be beneficial in this population. In this article, we will review various treatments of TD, including manipulation of the offending agent, VMAT2 inhibitors, other non-VMAT2-inhibiting medications, and non-pharmacological approaches.

1. Introduction

A variety of neurologic disorders secondary to exposure to dopamine-receptor blocking agent (DRBAs) have been described. The term “tardive syndrome” (TS) refers to any of the variety of neurologic symptoms that result from use of DRBAs and that persist despite cessation of the offending agent [1]. The most common TS is characterized by frequent, involuntary, relatively rhythmic movements of the oral-buccal-lingual (OBL) and masticatory muscles, sometimes accompanied by comparable movements of the trunk, limbs, or pelvis [2]. The term “tardive dyskinesia” (TD) has been used by previous authors variably to refer to this common type of TS, or to refer to TSs as a whole [3]. In keeping with the recently proposed nosology of these syndromes by Frei et al. [2], we will refer to the afore mentioned syndrome (involving predominantly OBL muscles) as TD.

TSs can be distinguished from a variety of other drug-induced movement disorders secondary to DRBAs, including drug-induced parkinsonism, acute dystonic reaction, acute akathisia, etc., as these typically resolve shortly after discontinuing the offending agent [4]. In addition to the previously mentioned TD, other common TSs include tardive dystonia and tardive akathisia. Other less common TSs that have been described include tardive tremor, tardive myoclonus, tardive chorea, and tardive tics, among others [1]. The pathophysiology of these syndromes is not clearly understood, but it is most commonly attributed to increased post-synaptic dopamine receptor number and sensitivity [5].

A recent meta-analysis by Carbon et al. [6] found the prevalence of TD in patients exposed to antipsychotics to be 25.3%, although there was significant variation in the studies analyzed, depending on the study population and the methodology used to diagnose TD. While previously felt only to be a complication of ‘typical’ antipsychotic use, TD secondary to atypical antipsychotics is now a well-established phenomenon [7,8].

Risk factors for developing TD can be divided into modifiable and non-modifiable factors, as in the recent review by Solmi et al. [9]. Non-modifiable risk factors include older age, female sex, and a variety of genetic variants involving drug metabolism or the dopaminergic system. The modifiable risk factors are predominately treatment-related, including DRBA type (higher risk with first generation antipsychotics), dose, and duration of exposure. There is also evidence to suggest that comorbid diabetes, alcohol use, smoking, and cocaine use may be independent risk factors for the development of TD [9]. Given the presence of these treatment-related, modifiable risk factors, strategies to prevent the development of TD have been emphasized. American Psychological Association guidelines recommend periodic monitoring for TD; every 6 months for patients on first-generation antipsychotics and every 12 months for patients on second-generation antipsychotics [10]. In general, efforts should be made to maintain the patient on the lowest necessary DRBA dose, for the shortest possible period of time, especially in high-risk patients [9].

The natural course of TD and other TSs is variable, but in general the rate of spontaneous resolution appears to be low. In a retrospective cohort of 108 patients with TSs (45.4% with “mixed” TS, 25.9% with TD) in whom DRBA was discontinued, Zutshi et al. [11] found that only 13% of the patients experienced resolution of symptoms. Only 2.8% of patients experienced resolution with cessation of DRBA alone (i.e.

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without other treatment for TS). The average time to resolution (in the 13% of patients whose symptoms resolved) was 2.3 years (range 0.10–6.34 years, median 1.49 years). The authors did not find any patient characteristics that predicted resolution of symptoms.

The presence of TD has been correlated with poorer quality of life [12], emphasizing the value of effective management of the condition. While many medications have been studied in TD, it wasn't until recently that the first medications were approved for this condition; the VMAT2 inhibitors valbenazine and deutetrabenazine. In this article, we review various treatment approaches to TD, with special attention given to valbenazine and deutetrabenazine.

2. Manipulation of the offending agent

2.1. Discontinuing the offending agent

Discontinuing or decreasing the dose of the offending agent is often the first consideration when encountered with a patient with TD. This approach is difficult to rigorously study for several reasons. The highly variable natural course of TD, as discussed above, makes it so that study outcomes may be highly dependent on the duration of the study, amongst other factors. Drug withdrawal must be done cautiously, as symptoms of TD may worsen transiently with abrupt discontinuation of DRBAs. Abrupt withdrawal may also precipitate withdrawal emergent syndrome – a syndrome characterized by choreiform movements in the limbs and trunk, occurring in the setting of DRBA cessation, typically self-limited and resolving after a few days [1]. Furthermore, there is a risk of psychiatric relapse with reduction or cessation of DRBAs [13], therefore only a sub-population of TD sufferers are candidates for this approach. At this time no large, placebo-controlled randomized trials have been done evaluating the efficacy of this treatment strategy. A recent Cochrane review by Bergman et al. [14] deemed the existing evidence studying dose reduction in the treatment of TD to be "*very low quality*" mostly due to small sample sizes.

It is no surprise that the available data provide an unclear picture. As an example, no significant difference in TD severity was seen between treatment groups in a small study (N = 31) of outpatient schizophrenic patients on fluphenazine decanoate randomized to continuing their medication versus placebo [15]. Moreover, several other studies [16,17] have shown a significant worsening of TD, perhaps reflecting the tendency for short-term exacerbation of symptoms after DRBA cessation that is often seen in clinical practice.

Nonetheless, due to the inherent difficulty of conducting a randomized, controlled trial of DRBA withdrawal, along with the universal rationale that the best strategy to alleviate any side effect is to discontinue the offending agent, the majority of clinicians first attempt to wean DRBAs to the minimum necessary dose, before adding any other dyskinesia-suppressing drugs, despite a lack of overwhelming evidence. Not uncommonly, TD patients may have been initiated on a DRBA primarily for the short-term relief of nausea, gastroparesis, agitation, insomnia, depression, or even acute psychosis in the inpatient setting, rather than for a chronic disorder that truly necessitates long-term treatment. Therefore, a review of the necessity of the continued use of a DRBA may increase the subset of TD patients where this initial approach is most optimal. The speed of weaning off DRBAs largely depends on the severity of TD and the clinician's impression of the patient's likelihood of psychiatric (or gastrointestinal) relapse.

2.2. Increasing the dose of the offending agent

Increasing the dose of the offending DRBA can temporarily mask the symptoms of TD, but this approach is generally not pursued as the benefits are often not sustained, and it also increases the risk of developing other neurologic side effects such as drug-induced parkinsonism, tremors, and dystonia [5]. This tendency of masking TD symptoms at the expense of parkinsonism was illustrated in a longitudinal study by Fernandez et al. [18] where 53 psychiatric inpatients were followed over 14 years, while doses of DRBAs were largely maintained. Indeed while TD symptoms surprisingly diminished (average Abnormal Involuntary Movement Scale (AIMS) score decreased by 4.0), this was at the expense of parkinsonism, with a mean increase in the Rating Scale for Extrapyramidal Signs of 3.5. Therefore, although use of typical antipsychotics such as haloperidol [19], pimozide [20], and thiopropazate [21] are possibly effective for the short term treatment of TD (most randomized studies ranging 2–8 weeks), they are generally not recommended for this use [22].

3. VMAT2 inhibitors

Vesicular monoamine transporter 2 (VMAT2) is a membrane protein, located only in the central nervous system, which helps to sequester dopamine (and other monoamines) into the synaptic vesicle in presynaptic neurons [23]. VMAT2 inhibitors therefore reduce synaptic dopamine concentration by depleting dopamine storage in these vesicles [24]. In recent years, this class of medications has become the hallmark of treatment of TD. The only two medications with FDA approval to treat TD are the VMAT2 inhibitors valbenazine and deutetrabenazine (both approved in 2017, though of note these drugs are not yet readily available outside of the US).

3.1. Tetrabenazine

The VMAT2 inhibitor tetrabenazine is FDA-approved to treat Huntington's chorea, and has been used as an off-label treatment of TD. Tetrabenazine is rapidly converted via first-pass metabolism to two primary pharmacologically active metabolites, α-HTBZ and β-HTBZ (each with two enantiomers, (+)α-HTBZ and (−)α-HTBZ, and (+)β-HTBZ and (−)β-HTBZ). Half-lives for these compounds are approximately 7 h for α-HTBZ and 5 h for β-HTBZ. The compounds are then further metabolized by the cytochrome P450 system into renally excreted metabolites [23].

A non-randomized, single-blind study of tetrabenazine in 20 patients with TD showed a significant decrease in symptoms as measured by AIMS score [25]. One of the 20 patients was not able to complete the study due to sedation, which was felt to be secondary to tetrabenazine, while the other 19 patients continued to take the drug after study completion. Doses ranged from 12.5 mg twice per day up to 50 mg three times per day in this study, with mean dose 57.9 mg/day. Tetrabenazine has not been studied in large, randomized trials in this population. Furthermore, its use is limited by side effects including sedation (13–36.5%), depression (1.7–15%), and parkinsonism (2.5–28.5%) [26]. Tetrabenazine's adverse side effect profile is felt to be in part related to high peak plasma concentration and serum fluctuations of active metabolite levels, as a consequence of their short half-lives [23,27]. It should be noted that tetrabenazine was not found to be associated with an increased risk of depression or suicidality in a recent retrospective study of greater than 4000 patients with Huntington disease, suggesting the risk of worsening depression may not be as high as previously thought [28].

3.2. Deutetrabenazine

Deutetrabenazine is a VMAT2 inhibitor similar to tetrabenazine, but with the insertion of deuterium - a naturally occurring, non-toxic form of hydrogen [27]. Carbon-deuterium bonds are stronger than carbon-hydrogen bonds, and as a result the metabolism of the deuterated forms of α-HTBZ and β-HTBZ is attenuated, leading to longer half-lives and less serum variability of these pharmacologically active compounds, as compared to their non-deuterated counterparts [23].

Deutetrabenazine was shown to be safe and efficacious in two large, randomized, double-blind placebo controlled trials in the TD population [29,30]. The ARM-TD study was a flexible-dose design, multi-

center, multi-national, Phase III clinical trial in which 117 patients with TD were randomized to 6 mg twice daily of deutetrabenazine or placebo. Dose increases up to a maximum of 24 mg twice daily were allowed in order to achieve adequate dyskinesia control via dose increases of 6 mg/day each week. To be eligible the patients were required to have moderate-severe TD as defined by total AIMS score (items 1–7) of greater than or equal to 6. The patients were allowed to remain on DRBAs but the dose must have been stable for at least 30 days, and must have remained so throughout the study. The primary outcome was change in AIMS score at 12 weeks, as assessed by 2 central video raters. The patients who received deutetrabenazine had an average improvement in AIMS score at 12 weeks of 3.0 points, compared to 1.6 points in the placebo group ($p = 0.019$). However, the secondary outcome measures of treatment success on the Clinical Global Impression of Change (CGIC) and the Patient Global Impression of Change (PGIC) scales showed only a trend toward favorability of deutetrabenazine compared to placebo. The lack of significant change on the PGIC scale may be due to variable symptom appreciation by the patient, and the lack of significant change on the CGIC scale may be in part because many recruiting clinicians in the trial were psychiatrists, who may be less familiar with the motor nuances of TD. The mean daily dose at the end of the titration period in the deutetrabenazine arm was 38.8 mg/day. Depression or depressed mood was seen in only 1.7% of patients in the treatment arm, identical to that of the placebo group. Akathisia was noted in 5.2% of patients in the treatment arm, compared to 0% in the placebo arm. Sedation was encountered in 13.8% of patient's receiving deutetrabenazine versus 10.2% receiving placebo. Notably, there was no worsening of parkinsonism in the study in patients receiving deutetrabenazine from baseline to week 12, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [29].

The AIM-TD study is a fixed-dose design, multi-center, multi-national, Phase III clinical trial in which 298 patients with TD were randomly assigned to deutetrabenazine 12 mg/day, 24 mg/day, 36 mg/day, or placebo in 1:1:1:1 fashion. Patients who received deutetrabenazine were started on 12 mg/day, and then increased in weekly increments of 6 mg/day until randomization dose was reached. Patients who remained on DRBAs were eligible for the study, provided there was no change in dose for at least 30 days prior to screening. The primary outcome of the study was also the change in AIMS score (items 1–7) from baseline to week 12, as assessed by central video raters. Both the 36 mg/day group and the 24 mg/day group showed significant improvement as compared to placebo in AIMS score at 12 weeks (improvement of 3.3 points and 3.2 points, respectively, compared to improvement of 1.4 points in the placebo group). Significant benefit for these two groups was seen as early as 2 weeks after initiation of treatment. There was a significantly higher proportion of treatment success on the CGIC (defined as responses of “much improved” or “very much improved”) in the 24 mg/day group compared to placebo ($p = 0.014$) and a trend toward significance in the 36 mg/day group as compared to placebo ($p = 0.059$). Patients in these groups also showed numerical (but not significant) improvement in PCIG scale score compared to placebo. There was a similar rate of adverse events in the placebo group versus the treatment groups, as seen in the ARM-TD study [30].

Patients in both the ARM-TD and AIM-TD were invited to continue taking deutetrabenazine as part of an open label single-arm study. The majority of patients chose to continue to take the medication. At 54 weeks, the drug continued to be efficacious and well-tolerated, with no worsening of parkinsonism, and suicidal behavior only seen in < 1% of patients. Patients were able to remain on their DRBAs, suggesting that deutetrabenazine use did not interfere with concomitant use of these medications over this period of time (Fernandez et al., submitted).

3.3. Valbenazine

The VMAT2 inhibitor valbenazine has also been studied in TD, and now has FDA approval for the treatment of this condition. Valbenazine is a parent drug of the tetrabenazine metabolite with the highest affinity for VMAT2, (+)α-HTBZ [31]. Of note, this compound has virtually no off-target interactions at serotonin or dopamine receptor sites, unlike the other major metabolites of tetrabenazine [32]. Valbenazine has a half-life of approximately 20 h, leading to less pharmacokinetic variability (as compared to tetrabenazine), and allowing for once daily dosing [32,33].

The KINECT 3 trial was a randomized, double-blind, placebo-controlled, multi-center, Phase III study comparing valbenazine to placebo in the treatment of TD [34]. Patients were randomized to valbenazine 40 mg/day, valbenazine 80/day, or placebo in 1:1:1 fashion. The study protocol allowed for a one-time dose reduction for tolerability; the 80 mg/day group could receive a new study drug kit with 40 mg/day dosing, whereas placebo and 40 mg/day patient would receive a new study drug kit remaining at their current dosage. The primary endpoint was change in AIMS score (items 1–7) at 6 weeks as compared to baseline. Two hundred and five of 234 participants (87.6%) who were randomized completed the study; with withdrawal of consent (10 participants) and adverse events (8 participants) being the most common reasons for dropout. At the 6-week endpoint both the 80 mg/day and the 40 mg/day groups showed significant reduction in AIMS score (reductions of 3.2 and 1.9, respectively) compared to placebo (reduction of 0.1). Similar to the deutetrabenazine ARM–TD trial (but unlike the AIM-TD trial), no significant difference was seen in the secondary outcome of CGIC scores at 6 weeks between placebo and any treatment group. Side effects seen in the treatment groups included somnolence (5.3% in the combined treatment groups versus 3.9% for the placebo group), dry mouth (3.3% and 1.3%, respectively), and akathisia (3.3% and 1.3% respectively). Psychiatric symptoms remained stable during the study period [34]. Similarly, the results of a 42-week extension study showed that valbenazine remains safe and efficacious with longer-term use, with no worsening of parkinsonism, and no apparent increased risk of suicidal ideation [35].

In conclusion, the VMAT2 inhibitors deutetrabenazine and valbenazine have the most rigorous evidence of treatment efficacy and safety in the TD population today. Although antipsychotics also can mask symptoms of TD, VMAT2 inhibitors have an advantage over that class of medications in that they do not appear to cause troublesome neurologic side effects of acute dystonic reactions, or to cause tardive dyskinesia themselves. It should be noted that, technically, VMAT2 inhibitors may also cause TD, but this would be difficult to detect or interpret in a patient with pre-existing TD. If and when this occurs, it would likely be interpreted as “loss of efficacy”, or attributed to the original DRBA.

Although not compared head-to-head, the side effect profiles of valbenazine and deutetrabenazine are likely to be more favorable compared to that of conventional tetrabenazine, perhaps due to longer half-lives and therefore more stable serum drug levels. Due to differences in trial design, comparisons between deutetrabenazine and valbenazine are speculative. However, valbenazine has the advantage of ease of dosing, given that there are only two dosing options, while deutetrabenazine has the advantage of several dosing options, which provides greater flexibility in carefully balancing side effects versus efficacy. The ARM-TD and AIM-TD (deutetrabenazine) trials, and the KINECT 3 (valbenazine) trial have shown that TD symptoms can be improved without needing to adjust the DRBA. Therefore these medications are ideal options for TD patients who are unable to withdraw their DRBA due to the nature of their primary psychiatric or gastrointestinal condition.

4. Other treatment approaches

4.1. GABA-ergic compounds

A wide variety of medications have been studied in the treatment of

TD. Damage to striatal neurons utilizing the neurotransmitter γ-aminobutyric acid (GABA) has been hypothesized to play a role in the pathogenesis of TD [36], and as such a number of GABA-ergic medications have been studied as possible treatments for TD, including clonazepam, diazepam, and baclofen. A small, crossover design study failed to show significant benefit in TD symptoms with diazepam treatment at 24 weeks [37]. A double-blinded, randomized trial with 19 psychiatric patients comparing clonazepam to placebo found a significant reduction in symptoms with clonazepam as measured by the Maryland Psychiatric Research Center Movement Disorder Scale [38]. However, loss of benefit due to drug tolerance was noted after several months in the patients who continued treatment open label [38]. Baclofen appears to provide some benefit in TD treatment, but efficacy often wanes over time and there may be significant side effects [39–41].

Bhidayasiri et al. [42] recently conducted a systematic review of the treatments for TSs including TD, and classified treatments using the American Academy of Neurology (AAN) therapeutic classification scheme. Clonazepam was determined to be *probably effective* in the treatment of TD, while data were *insufficient* to support or refute baclofen as a treatment for TD. Overall, GABA-ergic medications may possibly provide short-term improvement of TD symptoms, but may also have significant side effects and are unlikely to be effective long term.

4.2. Anti-oxidants

Vitamin E has been studied as a treatment for TD, as it is hypothesized that the antioxidant effect may be helpful in protecting from damage from free radicals from rapid dopamine metabolism [43]. Previously, multiple small placebo-controlled randomized trials showed improvement in TD symptoms with vitamin E administration [44,45]. However, a large, multicenter, double-blinded trial done by Adler et al. comparing vitamin E (1600 IU/day) to placebo failed to show improvement of TD symptoms with vitamin E [46]. This has been the largest randomized trial of vitamin E in TD to date. Therefore, overall data are *insufficient* to support or refute treatment with vitamin E for TD symptoms [42]. Another compound with antioxidant properties, Ginkgo biloba extract (EGb-761), did demonstrate significant improvement in symptoms in a randomized placebo-controlled trial of 157 patients with TD [47], and was determined by Bhidayasiri et al. based on the positive results of this large, randomized controlled trial, to be *probably effective* for this use [42].

4.3. Atypical antipsychotic agents

Numerous second-generation antipsychotics have been studied in TD, though high-quality evidence is limited. Quetiapine showed greater reduction of dyskinesia at 12 months when compared to haloperidol in an investigator-blinded randomized study [48]. Significant separation between the two groups did not occur until 6 months, suggesting a more “passive” treatment effect, similar to the natural healing that occurs in some patients with TD when off of their DRBAs. A randomized trial comparing olanzapine and risperidone found no significant difference in TD symptoms between the two groups, though both groups showed significant improvement as compared to baseline at 24 weeks [49]. It is unclear if this was simply a reflection of the short-term improvement typically seen when DRBA are increased in the setting of TD. It should be noted that the likelihood of developing parkinsonism or other neurologic side effects over time is difficult to determine with a short study duration. Clozapine has been observed to be effective in treating TD in several single-arm (non-placebo-controlled) studies [50,51]. A series by Simpson et al. [52] showed improvement in TD symptoms with clozapine, and relapse of symptoms after the drug was discontinued, suggesting active suppression of TD symptoms. Clozapine showed greater benefit than haloperidol at 12 months in a trial in TD comparing the two mediations [53]. There is a 0.5–0.9% risk of agranulocytosis with clozapine [54,55]; its use is thus limited by requirements of both frequent laboratory monitoring, and of dispensation of only a one week's supply at a time. Bhidayasiri et al. determined in their review that switching from a typical antipsychotic to risperidone *probably improved* TD symptoms, while switching to olanzapine *possibly improved* TD symptoms, and that there was *insufficient evidence* to support or refute switching from a typical antipsychotic to quetiapine or clozapine [42].

4.4. Amantadine

There is evidence to suggest that NMDA-receptor activity contributes to the pathogenesis of TD [56]. Amantadine is an antagonist at these receptors, and has been studied as a possible treatment for TD [56]. In a randomized trial of amantadine versus placebo in patients continued on DRBAs, the amantadine group had an AIMS score 15% lower than that of the placebo group ($p = 0.05$) [57]. A second more recent double blind, placebo-controlled trial showed a similar small but significant improvement in TD symptoms with amantadine [58]. Overall, amantadine was determined to be *possibly effective* in treating TD [42].

4.5. Botulinum toxin injections and non-pharmacologic treatments

Other treatments that have been studied in the treatment of TD include botulinum toxin injections, electroconvulsive therapy (ECT), and deep brain stimulation (DBS). There are no large, randomized trials studying these approaches. Botulinum toxin has been studied more extensively in tardive dystonia; data in TD (lingual-facial-buccal dyskinesia) is limited to case series. An open label study of botulinum toxin injections with twelve patients conducted by Rapaport et al. [59] demonstrated significant improvement in TD symptoms at eight weeks as compared to baseline, with minimal adverse effects. A smaller but more recent series [60] produced similar benefit, including improvement in tongue protrusion with genioglossus injection. ECT was studied in a retrospective study of 18 patients with TD conducted by Yasui-Furukori et al. [61] which found 7/18 (39%) showed greater than 50% average improvement on AIMS scores compared to pre-intervention baseline. The data supporting both botulinum toxin injections and ECT are limited due to the lack of placebo-controlled, randomized trials.

DBS previously has shown promise in case reports [62,63] and case series [64] for treatment of severe TD. Recently, stimulation of bilateral globus pallidus interna (GPi) in patients with severe TD was found to be efficacious in a double-blind evaluation (stimulation on versus stimulation off) 6 months following the procedure [65]. Based on these data, GPi DBS was determined to be *possibly effective* in treatment of TD, and may be a reasonable treatment strategy in some patients whose symptoms are resistant to pharmacotherapy [42].

4.6. Other treatments

In this review, we have covered medications and non-pharmacologic treatments that have been shown to be at least *possibly effective* in TD, or have been commonly used in clinical practice in treating TD. Other medications reviewed by Bhidayasiri et al. that were found to have *conflicting* or *insufficient evidence*, include but are not limited to bromocriptine, buspirone, levetiracetam, melatonin, reserpine, selegiline, vitamin B6, and zonisamide [42]. There is *insufficient evidence* to support the use of anticholinergic medications in treatment of TD; there are no controlled trials examining benztropine, trihexyphenidyl, or other medications in this class [22]. Medications that were found to be *possibly* or *probably ineffective* include diltiazem, eicosapentaenoic acid, and galantamine.

5. Conclusion

A wide variety of medications and non-pharmacologic treatments have been studied in the TD population. While rigorous evidence on the withdrawal of the offending agents is wanting, whenever possible, it should probably be the "first line treatment" to alleviate TD symptoms. However, for patients unable to discontinue their DRBA, or for those whose TD symptoms persists despite the discontinuation of the offending DRBA, the VMAT2 inhibitors deutetrabenazine and valbenazine have the most rigorous scientific evidence supporting their use. Both have been shown to be effective and well tolerated. These medications should be considered the mainstay treatments for TD. The other treatment approaches reviewed above may be indicated in select patients.

In their recent review, Bhidayasiri et al. presented a useful treatment algorithm for TD [42]. In patients with troublesome TD symptoms despite being on lowest effective dose of DRBAs, treatment with valbenazine or deutetrabenazine (or tetrabenazine if the newer VMAT2 inhibitors are unavailable) is recommended. If this does not sufficiently improve symptoms, then clonazepam or ginkgo biloba can be considered. If symptoms are still not controlled, a trial of amantadine may be indicated. Finally, if TD is refractory to pharmacologic therapy, then DBS may be considered. We are in general agreement with, and feel that the evidence reviewed here supports this approach.

Author contributions

AM and HHF drafted the manuscript, with HHF making critical revisions.

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