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MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Tardive Dyskinesia: Treatment Update

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Abstract

Purpose of Review Tardive dyskinesia (TD) is caused by exposure to medications with dopamine antagonism, mainly antipsychotics. It often distresses individuals, physically and emotionally and affects their quality of life. We evaluated peer-reviewed recently published articles with a goal of providing a critically appraised update on the latest advancements in this field.

Recent Findings In 2017, FDA approved VMAT2 inhibitors, deutetrabenazine and valbenazine. They have demonstrated efficacy in several class 1 studies. Also there have been update in the evidence-based guidelines for treatment for tardive dyskinesia.

Summary Various medication classes are being used for treatment of TD with VMAT2 inhibitors to be first FDA-approved medications. Their use should be tailored to the individual patient. Long-term studies will further guide us in how to optimize treatment, especially in the real-world setting. As clinicians, we need to take into consideration all aspects of symptomatology, etiology, potential side effects of the medications, to find the best possible "match" for our patients.

Keywords Tardive dyskinesia · Antipsychotics · VMAT2 inhibitors · Antioxidants · Vitamins · Neuroleptic-induced movements disorders

Introduction

Tardive dyskinesia (TD) is the sum of two words "tardive" meaning that appears late, and "dyskinesia" meaning abnormal involuntary movements. It is defined as a late onset, involuntary, purposeless movement disorder that affects the face, mouth, trunk, and limbs often with rhythmic, choreiform, and athetoid movements [1]. This condition was first described by Sigwald et al. [2] in 1959, and the term was later coined by Faurbye et al. in 1964 [3]. Patients on antipsychotic medications, for at least 3 months, are at risk of developing TD with prevalence of 20 to 35% [4]. Its tendency to often be irreversible despite the withdrawal of the offending medication baffles the patients and physicians alike. Recently proposed nosology by Frei et al. places TD, the oro-buccal-lingual form, as a subtype of tardive syndromes (TSs), with TSs being inclusive of all other movement disorders which develop secondary to the prolonged use of dopamine-receptor blocking agents (DRBAs). Other TSs include tardive dystonia, tardive tremor, tardive akathisia, tardive tourettism, tardive tics, tardive myoclonus, tardive chorea, and controversially, tardive parkinsonism [5].

This article is part of the Topical Collection on *Movement Disorders*

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Pathophysiology

Various mechanisms are hypothesized to cause TD such as increased post-synaptic sensitivity of dopamine receptors from chronic dopamine receptor blockage by neuroleptics; free radical associated burden resulting in oxidative stress effecting the basal ganglia and subcortex; imbalance of GABA neurotransmitter; excitotoxicity of NMDA receptors; and, degeneration of cholinergic striatal interneurons [6–11].

Antipsychotic agents are, indeed, the major subgroup known to cause TD with prevalence of 32.4% with typical

antipsychotics and 13.1 with atypical antipsychotics [12]. In addition, various other medications other than antipsychotics are listed in Table 1 that have been found to be associated with TD (Table 1).

Risk factors for tardive dyskinesia can be classified into modifiable and non-modifiable. Old age, female sex, African race, genetic variations regarding drug metabolism, and dopaminergic systems are some of the reported non-modifiable risk factors. Modifiable risk factors include the use of typical and atypical antipsychotics, higher dosages of DRBAs, long duration of DRBA exposure, comorbid conditions like diabetes, HIV, dementia, mood disorders, and substance use (e.g., alcohol use, smoking, cocaine) [14, 24–26].

Various measuring scales have been developed to quantify the severity of TD. The most widely utilized are the Abnormal Involuntary Movement Scale (AIMS), Simpson Dyskinesia Scale, and the Extrapyramidal Symptoms Rating Scale (ESRS) [27–29]. These scales attempt to provide objective parameters to detect and follow progression of symptoms in naturalistic studies as well as clinical trials. However, they may not truly capture the totality of motor and psychological impairment that patients suffer from various forms of TSs.

Management

The American Academy of Neurology published an evidence-based guideline for treatment of TD in 2013. These guidelines were more recently revisited by Bhidayasiri et al. in 2018. Treatment options were tiered into different levels: A (established efficacy), B (probable efficacy), C (potential efficacy), U (data insufficient) [30••, 31••]. These levels will be mentioned as we go through this review. Treatment options for each level A, B, and C are summarized in Fig. 1.

Table 1 Medications other than antipsychotics associated with tardive dyskinesia

Anticholinergic agents [13]
Lithium [14]
Antidepressants—trazadone, clomipramine, doxepin, amitriptyline [15, 16]
SSRI-SSRI—fluoxetine and sertraline [17, 18]
MAOI [6]
Antiemetics—metoclopramide, prochlorperazine [19, 20]
Anticonvulsants—carbamazepine and lamotrigine [21]
Antihistamine—hydroxyzine [22]
Antimalarial—chloroquine, amodiaquine [23]
Anxiolytics—GABA agonist and barbiturates [9]

I—Managing the DRBAs

Adherence to guidelines regarding antipsychotic utilization plays an important role in the prevention of TD. Some of the measures include avoiding off-label use, using the lowest efficacious dose, medication reconciliation at each patient visit, limiting chronic use whenever possible, and informing patient and caregiver to be mindful of the symptoms of TD, in order to facilitate early detection [32, 33].

Once TD has been recognized, tapering down the causative medication (which must be done slowly to avoid withdrawal emergent syndrome) has possibly been shown to result in resolution of TD (level U) [34, 35]. However, in many cases this cannot be done safely, as evidenced by a cohort study published in 2018 that analyzed medical claims from six US states during a six-year period, which showed that dose reduction in antipsychotics increased all cause- and mental health-related admissions [36].

Switching to an atypical antipsychotic (level U) could be tried as they have a lesser tendency to cause TD [37]. A meta-analysis published in 2018 on role of clozapine in the management of TD, which included 16 studies, showed that the severity of TD was reduced by transitioning to clozapine, with and even greater improvement seen in patients with moderate to severe TD [38]. Current guidelines from the American Psychiatric Association state that switching to clozapine can be considered after a partial response to 2 other antipsychotics with at least one being a second-generation antipsychotic [39].

II—Pharmacological Agents

VMAT2 Inhibitors

Two selective vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine (both with level A evidence), recently became the only medications with FDA approval to treat tardive dyskinesia. The VMAT2 protein helps in transporting neurotransmitters such as dopamine, serotonin, histamine, and norepinephrine into the presynaptic vesicles for neuronal function [40]. The mechanism of action is attributed to depletion of presynaptic dopamine levels without risk of over sensitizing post-synaptic receptors.

Valbenazine Valbenazine was approved by FDA in April 2017. The KINECT 3 trial was a 6-week, double-blinded, placebo-controlled randomized (1:1:1 to placebo: valbenazine 40 mg/day: 80 mg/day) phase III trial of 234 participants. The primary outcome of the study was the mean change in AIMS score after 6 weeks of the therapy. In the valbenazine 80-mg group, this score was reduced by 3.2 points, as compared with baseline, while in the placebo group, mean AIMS score was reduced by 0.1 points ($P = 0.001$). In the 40-mg daily dosing group, the mean AIMS score reduced by 1.9 points ($P =$

Anticholinergic agents (13)
Lithium (14)
Antidepressants - trazadone, clomipramine, doxepin, amitriptyline (15, 16)
SSRI -SSRI - fluoxetine and sertraline (17,18)
MAOI (19)
Antiemetics - metoclopramide, prochlorperazine (20, 21)
Anticonvulsants - carbamazepine and lamotrigine (22)
Antihistamine – hydroxyzine (23)
Antimalarial - chloroquine, amodiaquine (24)
Anxiolytics- GABA agonist and barbiturates (25)

Fig. 1 Summarizes the level A, B, and C medications, as per Bhidayasiri et al. updated guidelines [30, 31]

0.002, when compared with placebo) [41•]. Somnolence (5%), dry mouth (3%), and akathisia (3%) were the most common side effects seen in the valbenazine treatment groups. The drug was well-tolerated with only 4% discontinued due to the adverse events in valbenazine group, as compared with 3% in the placebo group [41•]. Continued efficacy and tolerability were demonstrated in the 1-year extension of the same study that included 198 participants. Headache and urinary retention were the main side effect reported (7% each); 16% stopped the treatment because of adverse drug event [42•] over the study period.

The recommended starting dose for valbenazine is 40 mg once per day, which can then be increased to 80 mg once daily in 1 week, if needed. Patients with moderate to severe hepatic impairment or taking strong CYP3A4 or CYP2D6 inhibitors should limit the dose to 40 mg daily. Valbenazine is not advised to be taken together with monoamine oxidase inhibitors or strong inducers of CYP3A4, or in the setting of severe renal impairment. It is also important to note that valbenazine can result in digoxin toxicity by reducing its renal tubular secretion [43•].

Deutetrabenazine Deutetrabenazine was approved by FDA for the treatment of TD in August 2017. It is the deuterated (non-toxic form of hydrogen) form of tetrabenazine, that increases the half-life of the active metabolite, allowing for both reduced total daily dose, reduced dosing frequency, thus achieving better tolerability.

There were two phase III trials of deutetrabenazine for the treatment of TD—ARM-TD and AIM-TD [44•]. AIM-TD was a 12-week, randomized (1:1:1:1 to placebo: deutetrabenazine 12 mg/day: 24 mg/day: 36 mg/day with deutetrabenazine dose increased over 4 weeks) double-blind, placebo-controlled phase III trial of 298 patients. At week 12, the mean AIMS score decreased by 1.4 points in the placebo group, by 2.1 points in the 12-mg total daily group ($P = 0.217$ when compared with placebo), by 3.2 points for 24 mg per day ($P = 0.003$ when compared with placebo), and by 3.3 in the 36 mg per day group ($P = 0.001$ compared with placebo) [45•]. Headache (5%), anxiety (4%), and diarrhea (4%) were the most common side effects in the deutetrabenazine treatment groups, with a discontinuation rate of 4%, in comparison with 3% of the placebo group [44•].

The ARM TD trial was a 12-week, double-blinded, placebo-controlled, randomized trial (1:1: placebo: deutetrabenazine) that included 46 sites and enrolled total of 117 patients. Dosing for deutetrabenazine group was started at 12 mg/d (6 mg twice daily) and was weekly increased by 6 mg/day with maximum limit of 48 mg/day. At the end of 12 weeks, AIMS score was reduced by (least squares mean [standard error]) − 3 [0.45] vs −1.6 [0.46], $P = 0.019$. 48.3% in deutetrabenazine group had treatment-related adverse events (AE) as compared with 35.6% in placebo group. One patient had depressed mood in the deutetrabenazine group as compared with 1 having depression and 1 with suicidal ideation in the placebo group. Somnolence, insomnia, and akathisia were seen more in the deutetrabenazine group as compared with placebo. Overall, AE did not result in study withdrawal [45•].

Initial dosing for deutetrabenazine is 6 mg twice daily, which can be increased by 6 mg weekly to a maximum dose of 24 mg twice daily, if indicated based on patient response [46•]. In recently published results of open-label extension of the ARM-TD and AIM-TD trials, deutetrabenazine continued to be efficacious and well-tolerated, with dosages up to 48 mg/day [47•].

CYP2D6 also plays role in deutetrabenazine metabolism so total daily dose should not exceed 36 mg/day in patients taking CYP2D6 inhibitors or who are known poor CYP2D6 metabolizers. Deutetrabenazine is contraindicated in patients with hepatic impairment, suicidal ideation, untreated or ineffectively treated depression, or in patients taking reserpine, MAOIs, or tetrabenazine. Deutetrabenazine has no impact on the renal function and can be safely taken in the setting of impaired renal function [46•]. Valbenazine and deutetrabenazine should not be prescribed in patients with congenital long QT syndrome or arrhythmias related to QT prolongation, or in pregnant or breast-feeding patients [43•, 46•].

In a recently published systematic review and meta-analysis of recently published randomized trials, valbenazine and deutetrabenazine were reported to be effective for acute as well as long-term treatment of TD without any clear signal for increased risk of depression or suicide [48•].

Table 2 Treatment options summarized

Treatment options for TSs/TD		
Managing the DRBAs	Reassessing the need of antipsychotics Reducing or switching the DRBAs to newer generation agent (only if tolerated by the patient)	
Pharmacological agents	Most effective treatment—VMAT2 inhibitors	Valbenazine Deutetrabenazine Tetrabenazine
	Less effective—other agents	GABA-ergic compounds—diazepam, clonazepam, baclofen Antioxidants—vitamin E, *Ginkgo biloba* NMDA receptor antagonist—amantadine
	Insufficient evidence [29, 30]	Bromocriptine, buspirone, levetiracetam, melatonin, r eserpine, selegiline, vit B6, zonisamide, trihexyphenidyl
Chemodenervation treatment	Most evidence is for tardive dystonia	
Surgical therapy	Bilateral Globus pallidus interna DBS stimulation for severe TD/TSs refractory to other treatments	

There has been no head-to-head comparison studies among these two VMAT2 inhibitors.

Other Medications

Antioxidants such as *Ginkgo biloba* (level B evidence) and vitamin E (level U evidence) have been studied and are sometimes used for the treatment of TD. EGb-761 extract of *Ginkgo biloba* was studied in a randomized, double-blind, placebo-controlled trial in China, comprised of 157 patients. *Ginkgo biloba* extract was found to significantly decrease total AIMS score as compared with placebo at 12 weeks [49].

Similarly, vitamin E was studied in a multicenter, randomized, placebo-controlled, prospective 2-year trial, with a dose of 1600 IU/Day. This study of 158 patients failed to show improvement in TD symptoms [50]. However, the data from other studies reveal somewhat of an unclear picture, as evidenced by a Cochrane review suggesting that vitamin E may prevent the worsening of TD symptoms [51].

The GABA agonist clonazepam (level B evidence) showed some reduction in orofacial dyskinesia in a study done in 1981 [52]. In 1990s, a double-blind, placebo-controlled, randomized crossover study of 19 patients showed that clonazepam treatment reduced dyskinesia scores by 37% compared with placebo. However, the effect was reversed during placebo period and 5 patients developed tolerance to the medication [53]. Baclofen (level U evidence) has been shown to likely reduce hyperkinetic movements of TD, but may cause significant side effects, including sedation and confusion, which limit its use [54].

Amantadine (level C evidence) is a non-competitive inhibitor of NMDA receptors that was shown to reduce the average total AIMS score by 21.81% in a double-blind, placebo-controlled crossover design (2 weeks each) study of 22 patients. Patients with unstable medical, neurological, or psychiatric illness, and those with renal insufficiency were excluded. Insomnia [3], constipation [2], and dizziness [2] were the most common side effects seen [55].

Bergman and Soares published a systemic review on usage or discontinuation of anticholinergic medications, in treatment of tardive dyskinesia associated with antipsychotics. Review failed to show any effectiveness of anticholinergic in regard to TD [56].

III—Surgical Treatment

The long-term efficacy of pallidal deep brain stimulation (DBS) (level C evidence) was studied in a double-blind trial in France, and published in 2016. All 19 patients were followed for 1 year and 14 of them were followed for 6–11 years. This study showed a reduction of Extrapyramidal Symptom Rating Scale (ESRS) scores by 40% after 6 months. For 12 months, improvement among the ESRS and AIMS score was maintained. Main side effects were divided into four categories: equipment-related adverse events (6 patients) needing re-intervention, perioperative complications (2 patients), mental illness-related adverse events (8 patients), and miscellaneous side effects, such as falls, balance, or gait disorders (14 patients). These adverse events were taken care of by supportive measurements; thus, no DBS device was discontinued. In 14 patients who were followed from 6 to 11 years, the ESRS and AIMS scores were decreased by 60% and 63%, respectively, when compared with baseline. Three patients had behavioral changes. Two patients had replacement of the lead, one due to infection related and other for displacement. Symptoms came back in 9 patients, when DBS came to a standstill [57].

IV—Chemodenervation Treatment

Several case reports have been published using botulinum toxin (level U evidence) injection as treatment for TD

symptoms. Perioral muscle groups were injected for orofacial TD without tongue protrusion, and genioglossal muscle was injected when significant tongue protrusion was present [58–60].

Table 2 summarizes all the treatment options by grouping them in their particular category.

Conclusion

The management of TD has to be individualized and the process starts once the patient is placed on the medications that are known to cause TD. As we highlighted above, these medications are not limited to neuroleptics, as other drug exposures have been described and reported to cause similar phenomenology. Explaining the risks, including the development of TD and other extrapyramidal side effects, to the patient and a close follow-up is the key, especially when the risk-benefit ratio of prescribing DRBAs favors its utilization. In general, patients should be exposed to the lowest dosage and the shortest duration of DRBAs, and thus its continued utilization should be reassessed periodically. When the patient's psychiatric disorder makes it impractical or dangerous to discontinue the offending agent, one advantage of the most recently approved medications for TD (the VMAT2 inhibitors) is their ability to potentially control TD symptoms without making changes with the DRBA and thus preventing all cause- and mental health-related admissions. Finally, standard scales used to evaluate TD may not consistently evaluate the entire spectrum of TSs, nor capture the total motor and psychological impairment imposed by the disorder. Digital technology might provide more reliable and sensitive TD monitoring in the real life setting.

Compliance with Ethical Standards

Conflict of Interest Divya Arya, Tarannum Khan, and Adam J. Margolius each declare no potential conflicts of interest. Hubert H. Fernandez has received research support from Acorda Therapeutics, Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, Parkinson Study Group, Sunovion, but has no owner interest in any pharmaceutical company. Dr. Fernandez has received honoraria from American Osteopathic Association, Cleveland Clinic, South Alabama Medical Science Foundation Thoraxx Clinical Communications, UMA Education, as a speaker in CME events. Dr. Fernandez has received honoraria from Acorda Therapeutics, Denali Therapeutics, Pfizer, Partners Healthcare System(Parkinson Study Group), Sunovion Research and Development Trust as a consultant. Elsevier as the Editor-In-Chief of Parkinsonism and Related Disorders Journal. Dr. Fernandez has received royalty payments from Demos Publishing and Springer for serving as a book author/editor. The Cleveland Clinic has a contract with Teva for Dr. Fernandez' role as a Co-Principal Investigator in SD-809/Austedo Tardive Dyskinesia global studies. Dr. Fernandez also serves as a member of the publication committee for Acorda Pharmaceuticals, Sunovion Pharmaceuticals but does not receive any personal compensation for this.

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

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