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Advances in Tardive Dyskinesia:
A Review of Recent Literature

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In the past three years, the US Food and Drug Administration (FDA) has approved two medications for tardive dyskinesia (TD): valbenazine and deutetrabenazine. These approvals have contributed to a resurgent interest in the recognition, management, and treatment of this important phenomenon. Although the precise causes of TD are still unclear, Schonecker[1] first reported cases of antipsychotic-associated involuntary and persistent abnormal (perioral) movements in 1957. Faurbye and colleagues[2] introduced the term "tardive dyskinesia" in 1964.

This supplement provides a brief review of primarily recent literature on TD, including signs and symptoms, risk factors and epidemiology, potential mechanisms, and screening and treatment. Each section provides an overview followed by key recent or seminal articles, including concise summaries of selected studies.

Signs and symptoms

Although DSM-5 defines TD as following at least a few months of antipsychotic exposure, symptoms of TD may emerge more rapidly in some patients, especially the elderly. Specifically, DSM-5 defines TD as

> Involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphrag-matic, or trunk muscles), developing in association with the use of a neuroleptic (antipsychotic) medication for at least a few months.

For research purposes, the Schooler-Kane criteria define TD as:[3]

- At least 3 months of cumulative antipsychotic treatment;
- Mild dyskinesias in two or more body areas or moderate dyskinesias in one body area;
- Persistence of movements for at least 3 months; and
- The absence of other conditions causing involuntary dyskinesias.

The functional disability associated with TD can range from mild to moderate to severe. Potential functional domains associated with TD include physical (eg, medical complications such as aphasia, aspiration, respiratory distress, falls), psychiatric (eg, worsening of psychopathology such as increased depression or anxiety due to abnormal movements), social (eg, social isolation due to embarrassment of going out in public by the patient, family, and/or caregivers), and occupational (eg, movements interfering with job functioning).

Risk factors and epidemiology

Spontaneous dyskinesias are abnormal involuntary movements in antipsychotic-naïve patients that are indistinguishable from TD. Thus, spontaneous dyskinesias are an important consideration in the differential diagnosis of TD. A review of studies of antipsychotic-naïve patients with schizophrenia from the pre-antipsychotic era or developing countries found that the prevalence of spontaneous dyskinesias ranges from 4% to 40% and increases with age.[4]

TD remains highly prevalent in patients with schizophrenia treated with antipsychotics. A review of 56 studies from 1959 through 1979 found a mean 20% prevalence of TD.[5] Similarly, in their meta-analysis of 41 studies (N = 11,493 patients), Carbon and colleagues[6] found a mean 25% prevalence of TD. Rates of TD were lower with second-generation antipsychotics than with first-generation antipsychotics (21% versus 30%).

Evidence from both prevalence and incidence studies shows that TD risk may be lower (but not negligible) in patients treated with second-generation antipsychotics versus first-generation antipsychotics.[6–8] For example, a recent study in a large community-dwelling sample of patients with schizophrenia from France (N = 674), of whom over 90% were taking second-generation antipsychotics, found an overall 8.3% prevalence of TD. The cumulative duration of antipsychotic exposure, however, is an important consideration in these estimates.[9]

Meta-analyses have identified several risk genes for TD with modest effect sizes, including *COMT* (catechol-O-methyltransferase), *DRD2*

(dopamine receptor D2), *CYP1A2* and *CYP2D6* (cytochrome P450 1A2 and 2D6), and *MnSOD* (manganese superoxide dismutase).[10,11] Other potential candidate genes associated with TD include *DRD3* (dopamine receptor D3), *HTR2A* and *HTR2C* (serotonin 2A and 2C receptors), and *SLC18A2* (*vesicular monoamine transporter 2* [*VMAT2*]).[12] A recent meta-analysis found that the G allele of the Perlecan (*HSPG2* [heparan sulfate proteoglycan 2]) rs2445142 polymorphism was associated with risk of TD.[13]

Nongenetic risk factors for incident TD have also been identified in qualitative reviews and meta-analysis. These factors may be classified as nonmodifiable or modifiable, as well as being patient, illness, or treatment related. Nonmodifiable risk factors for TD include older age, female sex, race (white and African descent), illness duration, intellectual disability, and negative symptoms.[14,15] Modifiable risk factors include diabetes, smoking, substance use, cumulative lifetime exposure to antipsychotics, treatment with first-generation antipsychotics, and early extrapyramidal symptoms.

Interactions between genetic and nongenetic risk factors for TD are not well characterized and warrant further investigation. Evidence also shows that patients with TD have greater health care resource utilization and costs, medical comorbidity (evidenced by a higher Charlson Comorbidity Index score and medical hospitalizations), and increased mortality.[16-18] An interesting recent case report also described a patient with new-onset abnormal movements associated with aspartame consumption following discontinuation (and later reinstitution) of treatment with a second-generation antipsychotic.[19] Risk factors for TD are summarized in **Table 1**.

Table 1: Risk factors for tardive dyskinesia

- Genetics
- Diabetes
- Increasing age
- Smoking
- Females
- Substance use
- Race (African descent > Caucasian > Asian)
- Cumulative antipsychotic exposure
- Illness duration
- Treatment with first-generation antipsychotics
- Intellectual disability
- Early extrapyramidal symptoms
- Negative symptoms

Mechanisms of action

The causes of TD remain unknown, but they are likely to be complex and multifactorial. As detailed previously, evidence exists for a polygenic contribution to TD risk, which may interact with other nongenetic factors to moderate risk. Several animal models have been developed to increase our understanding of potential mechanisms contributing to TD. One such model is the use of long-term antipsychotic treatment in nonhuman primates. Another key model is antipsychotic-induced vacuous chewing movements (VCM) in rodents.

Leading hypotheses for the etiopathophysiology of TD involve dopamine receptors and oxidative stress; however, there is conflicting evidence regarding each theory.[20,21] Other neurotransmitter systems that may be implicated in the pathophysiology of TD include gamma-aminobutyric acid (GABA), glutamate, and opioids.

Prevailing theories of TD pathogenesis involve dopamine-2-receptors. The "dopamine-2-receptor upregulation" hypothesis theorizes that the chronic exposure to increased D2 receptor blockade results in an actual increase in the postsynaptic number of D2 receptors. The "dopamine D2 receptor hypersensitivity" theory hypothesizes that the D2 receptors themselves become hypersensitive to their response to dopamine and not related to upregulation. It is likely that both phenomena are involved to differing degrees (D2 receptor hypersensitivity and upregulation). Findings broadly consistent with these hypotheses include data from rodent VCM models, associations between genes involved in the dopaminergic system (eg, *COMT*, *DRD2*, *VMAT2*) and TD, and the efficacy of VMAT2 inhibitors in patients with TD.

By contrast, the "oxidative stress" hypothesis posits that antipsychotic treatment is associated with increased production of reactive oxygen species and/or free radicals that overwhelm the endogenous antioxidant defense system in the metabolically active, dopamine-rich striatum, which contributes to neurotoxicity and subsequent cell death. Findings consistent with this theory include an association between the *MnSOD* gene (antioxidant enzyme) and TD, and evidence (albeit modest) for efficacy of agents with antioxidant properties, including Ginkgo biloba and vitamin B6.

Several recent animal model studies have investigated novel potential prophylactic agents with antioxidant properties against the development of TD. A study of fluphenazine-induced VCMs in rats found that cotreatment with resveratrol, a phytoalexin found in grapes with antioxidant and neuroprotective properties, reduced orofacial dyskinesias and that monoamine oxidase B (MAO-B) activity in the striatum was negatively correlated with the number of VCMs.[22]

Two studies by the same research group found that treatment with L-theanine, a potent antioxidant found in green tea, protected against haloperidol- and reserpine-induced orofacial dyskinesias in rats, with evidence implicating the nitric oxide pathway in the induction of these movements.[23,24] Another study found that haloperidol-induced VCMs were not reduced with low-dose lipoic acid and the movements were increased with high-dose lipoic acid.[25]

Screening and treatment

As previously described, spontaneous dyskinesias are an important consideration in the evaluation of TD. Withdrawal-emergent dyskinesias are another important consideration in the differential diagnosis of TD. Antipsychotic withdrawal-emergent dyskinesias are TD-like movements that may also appear after changes in dose or discontinuation of antipsychotics. Because this phenomenon is usually time limited (< 4–8 weeks), dyskinesia persisting for a longer duration suggests probable TD.[26] Although both TD and spontaneous dyskinesias are more common in patients with schizophrenia, they are also found in the general population without psychosis. TD may occur in the general population for patients exposed to dopamine-2-receptor blocking agents for medical or nonpsychotic conditions (eg, metoclopramide for gastroesophageal reflux disease, diabetic gastroparesis, nausea and vomiting, augmentation of nonpsychotic major depressive disorder, and other off-label psychiatric uses).[27]

> ***"For patients at increased risk for TD, assessments should be done every 3 months (first-generation antipsychotics) or every 6 months (second-generation antipsychotics)."***

Two of the most commonly used instruments for the assessment of TD in both clinical practice and research are the Abnormal Involuntary Move-

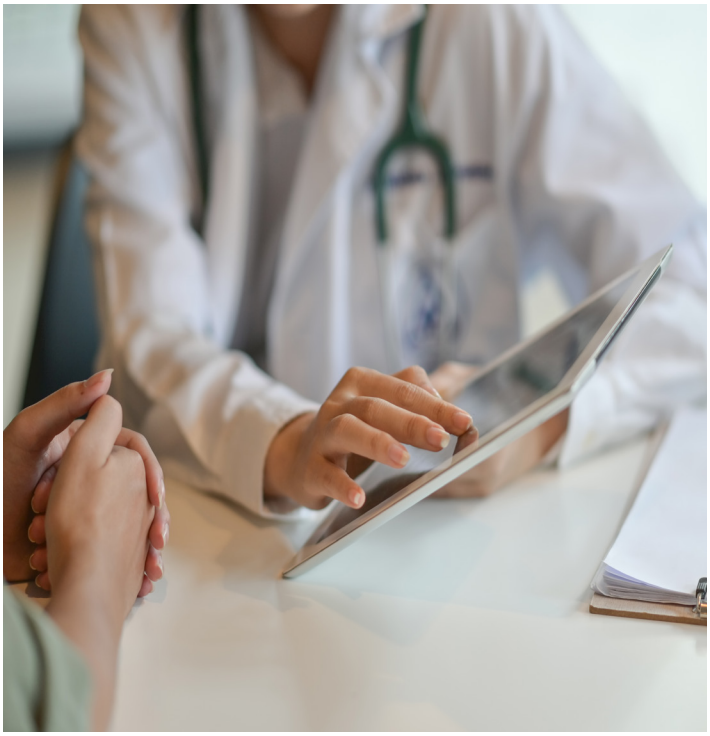
Table 2: Adjunctive treatment options for tardive dyskinesia

Agent	MOA	Dose	Comments
Valbenazine	VMAT2 inhibitor	40–80 mg/d	FDA approved for TD
Deutetrabenazine	VMAT2 inhibitor	6–48 mg/d	FDA approved for TD and chorea associated with Huntington disease
Tetrabenazine	VMAT2 inhibitor	25–100 mg/d	FDA approved for chorea associated with Huntington disease
Clozapine	SGA	25–900 mg/d	Switching, when indicated, may reduce TD
Ginkgo biloba	Antioxidant	240 mg/d	3 RCTs
Melatonin	Antioxidant	2–20 mg/d	4 RCTs
Vitamin E	Antioxidant	400–1600 IU/d	May help with deterioration of TD symptoms

MOA, mechanism of action; SGA, second-generation antipsychotic; RCTs, randomized controlled trials; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

ment Scale (AIMS) and the Extrapyramidal Symptom Rating Scale (ESRS).[28,29] The AIMS is an observer-rated, 12-item scale that takes approximately 5 to 10 minutes to administer. The ESRS was developed to assess TD and other drug-induced movement disorders.

The American Psychiatric Association practice guidelines for the treatment of schizophrenia recommend the clinical assessment of abnormal involuntary movements at baseline and every 6 months in patients taking first-generation antipsychotics and every 12 months in patients taking second-generation antipsychotics.[30] For patients at increased risk for TD, assessments should be done every 3 months (first-generation antipsychotics) or every 6 months (second-generation antipsychotics).



Early screening for and recognition of TD based on risk factors and regular AIMS exams is paramount, because this leads to earlier intervention and potentially better outcomes. A reasonable first step in the treatment of new-onset TD, whenever possible (based on a discussion of risks and benefits with the patient), is to discontinue (or lower the dose of) the presumed causative antipsychotic. A slow taper of the offending agent may also prevent antipsychotic withdrawal-emergent dyskinesias. Given that most patients with schizophrenia require chronic antipsychotic treatment, switching to a different agent with lower risk of TD is recommended.

> ***"Early screening for and recognition of TD based on risk factors and regular AIMS exams is paramount, because this leads to earlier intervention and potentially better outcomes."***

For patients with chronic, established TD, treatment with a myriad of different adjunctive agents has been investigated (**Table 2**). To date, only two agents—valbenazine and deutetrabenazine, both (reversible) VMAT2 inhibitors that decrease presynaptic dopamine release are FDA approved for adults with TD. Recent trials of valbenazine and deutetrabenazine support their efficacy and safety.[31-39] Treating TD with either agent allows patients to remain on their antipsychotic regimens.

Several recent meta-analyses and Cochrane Schizophrenia Group systematic reviews have investigated a variety of other potential pharmacologic treatment strategies for TD. All found inconclusive and/or unconvincing evidence for GABA agonists, calcium channel blockers, buspirone, ergot alkaloids, pemoline, promethazine, insulin, branched-chain amino acids, and isocarboxazid, as well as benzodiazepines and vitamin B6.[40–44] Although not associated with improvement in the symptoms of TD, some evidence indicates that adjunctive vitamin E may be associated with significantly less deterioration of TD symptoms compared with placebo.[45] There is also a positive meta-analysis of three randomized controlled trials (RCTs) for Ginkgo biloba for reduction in TD symptoms.[46] A recent meta-analysis found that switching to clozapine was associated with a significant reduction in TD severity, and therefore, when clinically indicated, may be a beneficial treatment approach.[47] Another meta-analysis found a nonsignificant trend for improvement in TD with melatonin.[48]

In addition to pharmacologic approaches, one recent study investigated the potential efficacy of neurostimulation for TD. Khedr and colleagues[49] reported a significant reduction in AIMS scores with real (versus sham) repetitive transcranial magnetic stimulation. This finding piques interest for further investigation of neurostimulation approaches for the treatment of TD.

Conclusion

TD is a serious and potentially disabling movement disorder that affects approximately one-quarter of patients with schizophrenia. In patients treated with antipsychotics, it is critical to regularly screen for TD via clinical assessment (ie, using AIMS). Several genetic variants are associated with increased risk for TD. Other replicated risk factors for TD include older age and early extrapyramidal symptoms.

The etiopathophysiology of TD remains unknown, although leading theories involve abnormalities in dopaminergic and antioxidant defense systems that are being investigated in nonhuman primate and rodent models.

When symptoms of TD manifest, it is recommended to discontinue the offending medication (or lowering the dose) via slow taper or switch to a different, lower-risk antipsychotic (if clinically an option). If the patient requires continued antipsychotic treatment for symptom control, adding a VMAT2 inhibitor may reduce the severity of the abnormal movements to a degree acceptable to the patient.

In 2017, the FDA approved the first two medications for TD: the VMAT2 inhibitors valbenazine and deutetrabenazine. In 2018, the American Academy of Neurology guidelines recommended VMAT2 inhibitors as first-line therapy for the treatment of TD. Many other treatment approaches are being vigorously investigated. Future research in this area is clearly warranted to elucidate mechanisms and other novel treatment strategies.

Summaries of key articles

Lower prevalence of TD with second-generation antipsychotics

Results of a meta-analysis of 41 studies (N = 11,493) on the prevalence of TD with second-generation antipsychotic use found a 25% prevalence of TD, with significant variation in individual studies.6 Findings from this study indicate that rates of TD were lower with second-generation antipsychotics compared with first-generation antipsychotics (21% versus 30%, respectively).

> ***"The researchers concluded that TD remains highly prevalent, with a higher incidence with first-generation antipsychotics."***

This association was moderated by older age, geography (lower rates in Asia), longer illness duration, and higher frequency of parkinsonism. The researchers concluded that TD remains highly prevalent, with a higher incidence with first-generation antipsychotics. Information was insufficient, however, on the severity of TD to allow interpretation of its clinical impact.

Prevalence of TD in schizophrenia cohort

Misdrahi and colleagues[9] report an overall 8.3% prevalence of TD in a community-dwelling large sample of patients with schizophrenia in France (N = 674). More than 90% of patients were being treated with second-generation antipsychotics. Using the Schooler-Kane criteria, patients were assessed for TD with AIMS.

Mean illness duration was 11 ± 8 years, but details on the duration of second-generation antipsychotic and first-generation antipsychotic exposure were not provided. TD was associated with higher Positive and Negative Syndrome Scale (PANSS) disorganized factor scores (odds ratio [OR], 1.1) after controlling for potential confounding effects of age, sex, negative symptoms, first-generation antipsychotic use, and benzodiazepine and anticholinergic drug use. Furthermore, extrapyramidal symptoms were associated with higher PANSS negative subscale scores (OR, 1.1) in the cohort.

> ***"These findings strengthen the evidence for a polygenetic component for the pharmacogenetic interactions underlying TD."***

COMT, DRD2, and MnSOD genes linked to antipsychotic-induced TD

Bakker and colleagues[10] undertook a meta-analysis to understand the association between polymorphisms in *COMT*, *DRD2*, *CYP1A2*, and *MnSOD* genes and TD. For the *COMT* Val158Met polymorphism, the researchers found a significant protective effect in Val-Met heterozygotes and Met carriers (OR, 0.63–0.66). For the Taq1A polymorphism in *DRD2*, a risk-increasing effect for the A2 variant (OR, 1.3) and the A2-A2 homozygotes (OR, 1.8) was seen. For the *MnSOD* Ala-9Val polymorphism, a significant protective effect was seen in Ala-Val heterozygotes and Val carriers (OR, 0.4–0.5). These findings strengthen the evidence for a polygenetic component for the pharmacogenetic interactions underlying TD.

Perlecan (HSPG2) gene associated with TD risk

The Perlecan (*HSPG2*) rs2445142 G allele has been associated with TD in several recent genome-wide association studies. Perlecan has been found in the neuromuscular junction and is required for synaptic acetylcholinesterase clustering, as well as the basement membrane extracellular matrix of part of the blood–brain barrier. Zai and colleagues[13] performed a meta-analysis that included 324 patients with TD and 515 controls without TD. The results showed that the *HSPG2* rs2445142 G polymorphism was associated with a significant 1.2-fold increased odds of TD. The largest effect of this gene was seen in a Japanese sample (OR, 2.2). These findings support further molecular genetic studies of *HSPG*[2].

Clinical risk factors for TD

Solmi and colleagues[14] reviewed clinical risk factors for TD, which they classified as being nonmodifiable or modifiable, as well as patient, illness, or treatment related. Nonmodifiable patient-related risk factors for TD include older age, female sex, race, and genetics (dopamine, cytochrome P450). Illness-related nonmodifiable risk factors include longer duration of severe illness, intellectual disability and brain damage, and negative symptoms.

Modifiable comorbidity-related risk factors include diabetes, smoking, and alcohol and other substance use disorders. Modifiable treatment-related risk factors include treatment with first-generation antipsychotics, extrapyramidal symptoms, high antipsychotic dose and plasma levels, intermittent antipsychotic treatment, and co-treatment with anticholinergic medications.

Resveratrol protects against VCMs in rats

Resveratrol found in grapes, cranberries, and peanuts is a phytoalexin with antioxidant and neuroprotective properties. Resveratrol may modulate dopaminergic proteins, including MAO. Busanello and colleagues[22]

exposed rats (n = 9) to the first-generation antipsychotic fluphenazine by intramuscular injection for 18 weeks and fluphenazine plus resveratrol (n = 8) 20 mg/kg daily in drinking water. Fluphenazine increased the prevalence and severity of VCMs, resulting in 8 of 9 rats with VCMs. VCMs were reduced by co-treatment with resveratrol (2 of 8 rats with VCMs).

The total number of VCMs was reduced by approximately one-third in the resveratrol group. They also found a significant negative correlation between number of VCMs and striatal MAO-B activity. Findings warrant further investigation of resveratrol in the prevention of TD.

L-theanine protects against VCMs in rats

L-theanine, a potent antioxidant found in green tea, also has neuroprotective effects. Tsai and colleagues[23] looked at the effects of L-theanine on first-generation antipsychotic-induced VCMs. Rats were exposed to treatment with 1 mg/kg haloperidol (n = 8) intraperitoneally for 21 days. Pretreatment with 100 mg/kg L-theanine (n = 8) orally for 35 days was started 14 days prior to haloperidol exposure. L-theanine prevented most of the haloperidol-induced orofacial dyskinesias.

Co-pretreatment with L-arginine (nitric oxide [NO] precursor) eliminated the protective effect of L-theanine, whereas L-NAME (NO synthase inhibitor) potentiated its protective effect. Findings raise the possibility of L-theanine in the prevention and/or treatment of TD and implicate the NO pathways in the pathophysiology of orofacial dyskinesias.

Valbenazine improves TD in adults

Hauser and colleagues[32] undertook a 6-week randomized, double-blind, placebo-controlled, fixed-dose study of once-daily valbenazine (40 mg or 80 mg) to further evaluate its efficacy, safety, and tolerability in adults with TD. The study included 234 participants who were randomized to active drug (40 mg or 80 mg) or placebo. A total of 205 (88%) participants completed the study.

At endpoint, valbenazine 40 mg and 80 mg were associated with significant reductions in TD symptoms compared with placebo on AIMS dyskinesia score (-1.9 and -3.1 points, respectively, versus -0.1 for placebo). Moreover, 24% of participants in the 40-mg valbenazine group and 40% of those in the 80-mg valbenazine group were AIMS responders (> 50% reduction from baseline) compared with 9% in the placebo group. Treatment-emergent adverse effects were reported in fewer than 5% of participants. The adverse effects were primarily somnolence and dry mouth. Valbenazine may be an effective treatment option for TD.

Long-term safety and tolerability of valbenazine

Factor and colleagues[35] undertook a 42-week valbenazine extension period and a subsequent 4-week washout period with participants of the KINECT 3 trial.[32] Those who received placebo in the earlier trial were re-randomized 1:1 to valbenazine 40 mg or 80 mg, and the other subjects were continued at their current dose. Initially, 198 patients were entered in the study; 124 (63%) participants completed 48 weeks of treatment and 121 (61%) completed the follow-up visit after washout. Due to treatment-related adverse events, 16% of participants discontinued valbenazine. Participants generally remained psychiatrically stable during the study. The AIMS assessment indicated sustained improvement in TD, with scores returning toward baseline after 4 weeks of valbenazine washout.

Long-term safety and tolerability of valbenazine

Marder and colleagues[36] undertook an extension KINECT 4 trial. The 48-week, open-label treatment study of valbenazine and a 4-week washout period included 163 patients. Dosing was initiated at valbenazine 40 mg daily and increased to 80 mg daily at week 4 based on tolerability and efficacy. After week 4, 12% of patients had a treatment-emergent adverse effect leading to discontinuation, most commonly a urinary tract infection and/or headache. The mean decrease from baseline to week 48 in AIMS total score was 10 points in the 40-mg group and 11 points in the 80-mg group. Approximately 90% of subjects in both groups had at least a 50% improvement that was classified as much or very much improved. Some evidence of loss of effect after valbenazine washout was found.

Deutetrabenazine significantly improved TD

Deutetrabenazine is a novel, selective VMAT2 inhibitor that contains deuterium, which attenuates metabolism and decreases plasma fluctuations of tetrabenazine levels. Fernandez and colleagues[37] undertook a 12-week RCT to evaluate the efficacy, safety, and tolerability of deutetrabenazine treatment of TD (N = 117). The mean deutetrabenazine dosage was 39 mg daily.

Results showed a significant reduction (-3 points) in AIMS scores compared with placebo. Moreover, the number of psychiatric adverse effects was low. Thus, deutetrabenazine significantly reduced TD and was well tolerated.

Deutetrabenazine improved TD with favorable safety and tolerability

Anderson and colleagues[38] undertook a 12-week, multisite RCT of deutetrabenazine (12, 24, or 36 mg per day) or placebo in 298 patients with TD aged 18 to 80 years. The mean improvement in AIMS total score was 3.3 points in the 36-mg daily group, 3.2 in the 24-mg daily group, and 2.1 in the 12-mg daily group compared with a 1.4-point improvement with placebo. These differences were statistically significant for the 24-mg and 36-mg groups. Rates of serious adverse events were low.

Long-term deutetrabenazine treatment safe, efficacious, and well tolerated

Patients with TD who completed the 12-week phase 3 trial of deutetrabenazine were eligible to enter an extension study undertaken by Fernandez and colleagues.[39] The open-label, single-arm, 2-year extension study included 343 patients. Patients were started at deutetrabenazine 12 mg daily, which was titrated based on tolerability and efficacy, with a maximum dose of 48 mg daily. Exposure-adjusted incident rates of adverse events were comparable to or lower than those observed in the past three trials. The mean decrease in AIMS total score was -4.9 at week 54, -6.3 at week 80, and -5.1 at week 106.

> *"They found that switching to clozapine was associated with a significant decrease in TD with a small-to-medium effect size (0.40), with greater effects in studies with TD severity as the primary outcome."*

Switching to clozapine may decrease symptoms of TD

Mentzel and colleagues[47] performed a meta-analysis of 16 studies on the effect of switching to clozapine on symptoms of TD. Inclusion criteria were a diagnosis of schizophrenia or related disorder, a switch to clozapine monotherapy, and TD rating scale scores before and after the switch. They found that switching to clozapine was associated with a significant decrease in TD with a small-to-medium effect size (0.40), with greater effects in studies with TD severity as the primary outcome. Effects were also greater in patients with moderate-to-severe TD.

Adjunctive melatonin may decrease symptoms of TD

Sun and colleagues[48] undertook a meta-analysis of the effect of adjunctive melatonin on symptoms of TD. They identified four RCTs (N = 130) for inclusion. There was a nonsignificant trend for improvements in TD with adjunctive melatonin (weighted mean difference of 1.5 points on AIMS total score). Larger RCTs of this agent may be warranted.

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