

Psychiatric Times

PUBLISHED AS A SUPPLEMENT TO



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TARDIVE DYSKINESIA

A REVIEW OF THE LITERATURE



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Tardive Dyskinesia: A Review of the Literature

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Recognizing Tardive Dyskinesia

Although the causes of tardive dyskinesia are still unclear, in 1957, Schonecker¹ first reported cases of antipsychotic-associated involuntary and persistent abnormal (perioral) movements. Faurbye and colleagues² introduced the term tardive dyskinesia (TD) in 1964. 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, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic (antipsychotic) medication for at least a few months.” The International Classification of Diseases (ICD) codes for TD are 333.85 (ICD-9), and G24.01 (ICD-10). 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; elderly patients are especially vulnerable.

A number of other movement disorders are part of the differential diagnosis of TD, including spontaneous dyskinesias (SDs) and withdrawal-emergent dyskinesias. SDs are abnormal involuntary movements in antipsychotic-naïve patients that are indistinguishable from TD. In some patients, TD-like movements may also appear after changes in dose or discontinuation of antipsychotics, referred to as antipsychotic withdrawal-emergent dyskinesia. Because this phenomenon is usually time-limited (< 4–8 wks), dyskinesia persisting for a longer duration suggests probable TD.³ Although both TD and SDs are more common in patients with schizophrenia, they are also found in the general population without psychosis.⁴

A number of different rating scales for the assessment of TD are used in both clinical practice and research. Two of the most commonly used instruments are the Abnormal Involuntary Movement Scale (AIMS)⁵ and the Extrapyramidal Symptom Rating Scale (ESRS).⁶ 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 (FGAs), and every 12 months in patients taking second-generation antipsychotics (SGAs).⁸ For patients at increased risk of TD, assessments should be done every 3 months (SGAs) or 6 months (FGAs).

For research purposes, TD is often defined by the Schooler-Kane criteria⁷:

1. At least 3 months of cumulative antipsychotic treatment
2. Mild dyskinesias in 2 or more body areas or moderate dyskinesias in 1 body area
3. Persistence of movements for at least 3 movements
4. The absence of other conditions causing involuntary dyskinesias

The purpose of this supplement is to provide a brief literature review of TD, including epidemiology and risk factors, potential mechanisms, and treatment. Each section provides an overview, followed by key recent or seminal articles, with concise summaries of selected studies. Readers are also referred to several recent review articles on this topic.^{3,9–11}

References

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Epidemiology and Risk Factors

As described above, SDs are an important differential diagnosis in the evaluation of TD. It has been argued that to find the true prevalence of TD, it is necessary to subtract the background prevalence of SDs. A review of studies of antipsychotic-naïve patients with schizophrenia from either the preantipsychotic era or developing countries found that the prevalence of SDs ranges from 4% to 40% and increases with age.¹ Another systematic review of antipsychotic-naïve patients with schizophrenia found a median 9% prevalence of SDs.² A large sample of Southeast Asian patients with first-episode psychosis (FEP) did not find any cases of SDs, suggesting ethnically based variation.³

TD remains highly prevalent in patients with schizophrenia treated with antipsychotics.⁴ 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, Kane and Smith⁶ found a mean 25% prevalence of TD, which was more common in patients treated with FGAs. There is evidence from both prevalence and incidence studies that TD risk is lower (but not negligible) in patients treated with SGAs versus FGAs.^{7–9}

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

ase), *DRD2* (dopamine receptor D2), *CYP1A2* and *CYP2D6* (cytochrome P450 1A2 and 2D6), and *MnSOD* (manganese superoxide dismutase).^{10,11} More recently identified promising candidate genes associated with TD include *SLC18A2* (vesicular monoamine transporter 2 [VMAT]) and *CNR1* (cannabinoid receptor 1).¹²

Other replicated nongenetic risk factors for incident TD identified in a meta-analysis are increasing age, non-white ethnic group, and early extrapyramidal symptoms, but not gender or current antipsychotic dose.¹³ The association between TD and increasing age may also reflect cumulative lifetime exposure to antipsychotics. Interactions between genetic and non-genetic risk factors for TD are not well characterized, although potential clinical correlates of TD have been investigated using baseline data from the CATIE schizophrenia trial.¹⁴ Interestingly, a quantitative review found that TD may also be associated with increased mortality.¹⁵ Replicated risk factors for TD are summarized in **Table 1**.

KEY LITERATURE

1. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *J Clin Psychiatry*. 2000;61(suppl 4):10-14.

The prevalence of SDs in antipsychotic-naïve patients with schizophrenia was 4% to 40% and found to be positively correlated with age

A review and pooled analysis of the prevalence of SDs across 14 studies was undertaken. The participants comprised 675 antipsychotic-naïve patients with schizophrenia, either from the pre-antipsychotic era or from developing countries.

The prevalence of SDs was 4% in first-episode schizophrenia; 12% in patients aged younger than 30 years; 25% in patients aged 30 to 50 years; and 40% in patients aged older than 60 years. The precision of these estimates is limited by the absence of large untreated samples. Therefore, the risk of TD associated with antipsychotic treatment must be considered against the expected prevalence of SDs in the study population.

2. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naïve patients with first-episode psychoses: a systematic review. *Psychol Med*. 2009;39:1065-1076.

A median 9% prevalence of SDs in antipsychotic-naïve patients seen with FEP

Pappa and Dazzan reviewed 13 studies for the prevalence of SDs in antipsychotic-naïve patients (N = 741). The median prevalence of SDs was 9%. The results also showed that SDs may be associated with negative symptoms and cognitive impairment. These findings support the idea that spontaneous abnormal movements are part of the pathophysiology of schizophrenia in some patients.

3. Lee J, Poon LY, Chong SA. Spontaneous dyskinesia in first-episode psychosis in a Southeast Asian population. *J Clin Psychopharmacol*. 2008;28:536-539.

No cases of SDs seen in a large sample of Southeast Asian patients with FEP

This study rated 908 patients with FEP on the AIMS. Three patients had minimal to mild dyskinetic movements, but none satisfied the Schooler and Kane criteria for SDs. Furthermore, the dyskinetic movements resolved within 3 to 6 months of antipsychotic treatment. The researchers hypothesized that ethnically based differences in the prevalence of SDs are attributable to underlying genetic factors.

4. Chakos MH, Alvir JM, Woerner MG, et al. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Arch Gen Psychiatry*. 1996;53:313-319.

A 15.6% incidence of persistent TD found in patients at 4-year follow-up after FEP

TABLE 1. Replicated risk factors for tardive dyskinesia

- Genetics: *COMT*, *DRD2*, *MnSOD*, *CYP1A2*, *CYP2D6* polymorphisms
- Increasing age
- Use of FGAs more than SGAs
- Non-white race/ethnicity
- Early extrapyramidal symptoms

Chakos and colleagues prospectively followed 118 patients with FEP. After 4 years, the cumulative incidence of persistent TD was 15.6%. Importantly, poor response to treatment after FEP was a significant predictor of time to TD. Treatment responders had a significantly lower risk of presumptive TD than nonresponders (hazard ratio [HR] = 0.29). Furthermore, each increase of 100-mg chlorpromazine-equivalent units of antipsychotic dose was associated with a 5% increase in the risk of presumptive TD. There may be a disease-related vulnerability to TD that manifests with antipsychotic exposure.

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6. Kane JM, Smith JM. Tardive dyskinesia prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry*. 1982;39:473-481.

7. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of SGA use: a meta-analysis. *J Clin Psychiatry*. 2017;78:e264-e278.

A 25% mean prevalence of TD found in patients treated with SGAs

A meta-analysis of 41 studies (N = 11493) on the prevalence of TD in the era of SGA use found a 25% prevalence of TD, with significant variation in individual studies. Rates of TD were lower with current SGA treatment than with FGA treatment (21% versus 30%).

This association was moderated by older age, geography (lower in Asia), longer illness duration, and higher frequency of parkinsonism. The researchers concluded that TD remains highly prevalent, with higher incidence during treatment with FGAs. However, there was insufficient information on the severity of TD to permit interpretation of its clinical impact.

8. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161:414-425.

Annual incidence of TD lower in patients treated with SGAs compared with FGAs

This meta-analysis compared the incidence of TD resulting from SGA use (n = 2769). Haloperidol (n = 408) was used as a comparator in 3 trials. Correll and colleagues found a mean annual 2.1% incidence of TD in patients treated with SGAs versus 5.4% in patients treated with haloperidol. However, the relatively high mean dose of haloperidol (13 mg/d) may have influenced findings.

9. O'Brien A. Comparing the risk of tardive dyskinesia in older adults with first-generation and second-generation antipsychotics: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2016;31:683-693.

The risk of probable TD found to be more than 3-fold lower in older adults taking SGAs compared with FGAs

O'Brien performed a quantitative review of 23 studies of the risk of TD in adults aged 55 or older who had been treated with antipsy-

chotics. Patients (n = 1108) who had received FGAs had a 38% prevalence of probable TD. For FGAs, the incidence of probable TD at 1 year was 23% (n = 181) with an increase to 57% at 3 years. By contrast, for SGAs the incidence of probable TD at 1 year was 7% (n = 44), and the risk of persistent TD at 1 year was 3%. O'Brien notes that although rates of TD with prolonged use of FGAs are high, evidence regarding long-term risk of TD in older adults with SGAs is lacking.

10. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2, and MnSOD genes: a meta-analysis of pharmacogenetic interactions. *Mol Psychiatry*. 2008;13:544-556.

Associations found between polymorphisms in COMT, DRD2, and MnSOD genes and risk of antipsychotic-induced TD

Bakker and colleagues 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 (odds ratio (OR) = 0.63-0.66). For the Taq1A polymorphism in *DRD2*, a risk increasing effect for the A2 variant (OR=1.3) and 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 polygenic component for the pharmacogenetic interactions underlying TD.

11. Patsopoulos NA, Ntzani EE, Zintzaras E, Ioannidis JP. CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. *Pharmacogenet Genomics*. 2005;15:151-158.

Loss-of-function alleles for CYP2D6 are associated with increased risk of TD

This meta-analysis of *CYP2D6* (cytochrome P450 2D6) gene polymorphisms comprised schizophrenia patients with and without TD. Three *CYP2D6* "loss of function" alleles (*3, *4, and *5) are associated with the "poor metabolizer" phenotype. Patsopoulos and colleagues identified 8 studies (n = 569) of loss of function alleles (grouped together), 3 studies (325 patients) of the *2 allele, and 4 studies (n = 556) of the *10 allele. *CYP2D6* loss of function alleles were associated with a significant 1.4-fold increased odds of TD. By contrast, the *2 and *10 alleles were not associated with TD.

12. Lanning RK, Zai CC, Müller DJ. Pharmacogenetics of tardive dyskinesia: an updated review of the literature. *Pharmacogenom*. 2016;17:1339-1351.

Mixed results seen in study of promising candidate genes associated with TD

Promising candidate genes associated with TD include *HSPG2* (heparin sulfate proteoglycan 2, perlecan), *DPP6* (dipeptidyl peptidase-like protein-6), *MTNR1A* (melatonin receptor 1A), *SLC18A2* (vesicular monoamine transporter 2 [VMAT]), *PIP5K2A* (involved in oxidative stress responses), and *CNR1* (cannabinoid receptor 1). Lanning and colleagues note that findings are still encumbered by mixed results in heterogeneous samples, and that bioinformatics tools, gene-gene interaction, and epigenetic analyses are needed to further clarify these associations.

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Non-white ethnic group, early extrapyramidal symptoms, and increasing age found to be predictors of TD

Tenback and colleagues undertook a meta-analysis of risk factors for the onset of TD in patients with schizophrenia. They found that non-white ethnicity (relative risk [RR] = 1.8), early extrapyramidal

symptoms (RR = 1.6), and increasing age (RR = 1.02) were significant predictors of TD. Gender, antipsychotic dose, and akathisia were not predictors of TD. The researchers note that the association between early extrapyramidal symptoms and the risk of TD has important clinical implications for identifying high-risk patients for early intervention.

14. Miller DD, McEvoy JP, Davis SM, et al. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. *Schizophr Res*. 2005;80:33-43.

Older patients with longer exposure to antipsychotics most likely to meet Schooler-Kane criteria for TD

Using baseline data from the CATIE schizophrenia trial, this study compared 212 subjects who met the Schooler-Kane criteria for probable TD with 1098 subjects without TD. Miller and colleagues found that patients with TD were older, had greater lifetime exposure to antipsychotic medication, were more likely to have received FGAs and anticholinergics, had more substance use comorbidity, and had greater severity of psychopathology and extrapyramidal symptoms. By contrast, neither diabetes nor hypertension was associated with increased risk of TD, nor was TD associated with greater cognitive impairment.

15. Ballesteros J, Gonzalez-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of 7 independent studies. *J Clin Psychopharm*. 2000;20:188-194.

TD found to be associated with increased all-cause mortality in patients with psychiatric disorders

A meta-analysis of patients with primarily schizophrenia or affective disorders (N = 868) was undertaken to evaluate the association between TD and all-cause mortality. The median study follow-up period was approximately 4 years. TD was associated with a significant, 1.4-fold increased risk in mortality, and the association was stronger in prospective studies. The potential mechanisms underlying this association remain unknown.

Mechanisms

The causes of TD remain unknown, but they are likely complex and multifactorial. As detailed above, there is evidence for a polygenic contribution to TD risk, which may interact with other non-genetic 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 non-human primates. Another key model is antipsychotic-induced vacuous chewing movements (VCM) in rodents.

Three leading hypotheses for the etiopathophysiology of TD involve dopamine receptor hypersensitivity, gamma-aminobutyric acid (GABA) insufficiency, and oxidative stress; however, there is conflicting evidence regarding each theory.¹⁻³ Other neurotransmitter systems that may be implicated in the pathophysiology of TD include glutamate and opioids.

A prevailing theory of TD pathogenesis is the "dopamine receptor hypersensitivity" hypothesis. According to this theory, chronic dopamine D2 receptor blockade by antipsychotics results in a compensatory increase (ie, upregulation) in D2 receptor synthesis, and subsequent increased sensitivity to dopamine in nigrostriatal pathways. Findings broadly consistent with this hypothesis 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.

Another theory is that GABA insufficiency in the neurocircuitry-

controlling motor function underlies TD. There is some evidence in rodent and non-human primate models, as well as human data to suggest decreased glutamic acid decarboxylase activity—the enzyme that synthesizes GABA—and decreased GABA levels in TD. However, there are also studies that negate this theory, and clinical trial evidence does not support the efficacy of several GABA agonists in the treatment of TD.

By contrast, the “oxidative stress” hypothesis posits that antipsychotic treatment is associated with increased production of reactive oxygen species/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 (albeit modest) evidence for efficacy of agents with antioxidant properties, including vitamin B₆, vitamin E, and Ginkgo biloba.

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3. Lister J, Nobrega JN, Fletcher PJ, Remington G. Oxidative stress and the antipsychotic-induced vacuous chewing movement model of tardive dyskinesia: evidence for antioxidant-based prevention strategies. *Psychopharmacology (Berl)*. 2014;231:2237-2249.

Treatment

Early screening for and recognition of TD based on risk factors and regular AIMS exams is paramount, as 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 the presumed causative antipsychotic. A slow taper of the offending agent may prevent antipsychotic withdrawal-emergent dyskinesias. Given that a majority of patients with schizophrenia require chronic antipsychotic treatment, switching to a different agent with lower risk of TD is recommended. When clinically indicated, treatment with clozapine may also be beneficial for patients with TD.¹

For patients with chronic, established TD, treatment with a myriad of different adjunctive agents has been investigated (Table 2). Only one agent to date—valbenazine, a VMAT2 inhibitor, which modulates presynaptic dopamine release—is FDA-approved for adults with TD. Two recent trials of valbenazine support its efficacy and safety.^{2,3} In addition, branched chain amino acids (BCAAs) are FDA-approved as dietary supplements for managing TD in men, but not in women. BCAAs decrease the availability of phenylalanine to the brain, thereby decreasing synthesis of biogenic amine neurotransmitters.⁴

There is evidence for other VMAT2 inhibitors in the treatment of TD, including tetrabenazine and deutetabenazine.^{5,6} Systematic reviews have also found (limited) evidence for the efficacy of vitamin B₆ and Ginkgo biloba extract in the treatment of TD.^{7,8} A meta-analysis found evidence for modest benefits of adjunctive vitamin E, but a more recent systematic review found that although vitamin E does not improve symptoms, it may protect against deterioration of TD.^{9,10} By contrast, another systematic review found inconclusive and unconvincing evidence for GABA agonists, such as baclofen and valproic acid, in the treatment of TD.¹¹

KEY LITERATURE

1. Hazari N, Kate N, Grover S. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr*. 2013;6:439-451.
[Beneficial effects of clozapine found in patients with TD](#)

Hazari and colleagues identified 15 clinical trials and 28 case series/reports of clozapine use in patients with TD. In most studies, 200- to 300-mg clozapine daily was useful, and benefits were typically seen within 4 to 12 weeks. Clozapine withdrawal emergent dyskinesias were also infrequent. There is some evidence for new-onset or worsening TD with clozapine treatment, although participants had previous antipsychotic exposure and a prior history of TD.

2. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174:476-484.

3. O'Brien CF, Jimenez R, Hauser RA, et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Mov Disord*. 2015;30:1681-1687.

[Valbenazine found to significantly improve TD in adults with schizophrenia, schizoaffective disorder, or mood disorders](#)

Researchers 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: 234 subjects were randomized and 205 (88%) completed the study. At endpoint, both valbenazine 40 mg and 80 mg were associated with significant reductions versus placebo on the AIMS dyskinesia score: 24% of participants in the 40-mg daily group and 40% of those in the 80-mg daily 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. A 52-week study is ongoing.

4. Richardson MA, Bevans ML, Read LL, et al. Efficacy of the branched-chain amino acids in the treatment of tardive dyskinesia in men. *Am J Psychiatry*. 2003;160:1117-1124.

[BCAAs may be safe, effective treatment for men with TD](#)

Richardson and colleagues undertook a 3-week randomized controlled trial (RCT) of high-dose BCAAs (222 mg/kg) 3 times daily; 36 men completed the trial. BCAAs were associated with a mean 37% decrease in the frequency of TD movements compared with 3.4% decrease in the placebo group. A significant difference was seen with BCAAs in the number of responders with a reduction of 30% or more in TD movements and in the number of responders with a reduction of 60% or more.

5. Kaur N, Kumar P, Jamwal S, et al. Tetrabenazine: spotlight on drug review. *Ann Neurosci*. 2016;23:176-185.

[Off-label use of tetrabenazine may be effective for treatment of TD](#)

Tetrabenazine is a VMAT2 inhibitor that is FDA-approved for the treatment of chorea in Huntington disease and other hyperkinetic disorders. Evidence for efficacy of tetrabenazine for TD stems from 2 very small RCTs (10 patients), 4 open-label studies (77 patients), and 2 retrospective studies (163 patients). In these studies, 40% to 100% of patients treated with tetrabenazine showed improvement in TD symptoms.

Potential limitations of tetrabenazine, however, are active hepatic metabolites with short half-lives (requiring frequent dosing), and potential neuropsychiatric adverse effects, including depression, somnolence, and parkinsonism, which may be dose-limiting.

6. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetabenazine for tardive dyskinesia: the ARM-TD study. *Neurology*. 2017;88:2003-2010.

TABLE 2. Potential treatment options for tardive dyskinesia

Agent	Mechanism of action	Dose	Comments
Valbenazine	VMAT2 inhibitor	40-80 mg/d	FDA approved for TD
Tetrabenazine	VMAT2 inhibitor	50-200 mg/d	FDA approved for chorea
Deutetrabenazine	VMAT2 inhibitor	12-48 mg/d	
Vitamin B ₆	Effects on biogenic amines; antioxidant	400-1200 mg/d	
BCAA	Decrease availability of phenylalanine	222 mg/kg/d	Men only
Vitamin E	Antioxidant	400-1600 IU/d	
Ginkgo biloba extract	Antioxidant	240 mg/d	

BCAA, branched chain amino acids.

Note: Discontinue the offending antipsychotic via slow taper, and switch to a different antipsychotic with less risk of EPS/TD. Consider a trial of clozapine if clinically indicated.

Deutetrabenazine significantly improved TD in adults with schizophrenia, schizoaffective disorder, or mood disorders

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

The results showed a significant reduction (−3 points) in AIMS scores versus placebo. Moreover, the rates of psychiatric adverse effects were low—deutetrabenazine significantly reduced TD and was well tolerated.

7. Adelufosi AO, Abayomi O, Ojo TM. Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev.* 2015;4:CD010501.

Limited evidence for use of vitamin B₆ for reducing the severity of TD

The authors identified 3 trials (80 inpatients) of adjunctive vitamin B₆ in schizophrenia. In 2 RCTs (mean duration, 18 weeks; dose range, 400-1200 mg/d), vitamin B₆ was associated with significant improvement in TD (> 40% improvement in the ESRS score) and lower end-point ESRS score versus placebo. However, overall, the evidence for vitamin B₆ is insufficient and limited by an inadequate number of studies, small sample sizes, and short follow-up periods.

8. Zheng W, Xiang YQ, Ng CH, et al. Extract of Ginkgo biloba for tardive dyskinesia: meta-analysis of randomized controlled trials. *Pharmacopsychiatry.* 2016;49:107-111.

Findings suggest that Ginkgo biloba extract is safe and effective for TD

Zheng and colleagues undertook a meta-analysis of 3 12-week RCTs of Ginkgo biloba extract in 299 Chinese patients with schizophrenia. The patients' mean age was 56, and the dose of Ginkgo biloba extract was 240 mg. Ginkgo biloba extract was well tolerated and associated with a significant reduction in AIMS scores (−2.3 points)

compared with placebo. Although Ginkgo biloba extract appeared to be safe and effective, more studies are needed in non-Chinese populations and to explore its effects on cognition.

9. Barak Y, Swartz M, Shamir E, et al. Vitamin E (alpha-tocopherol) in the treatment of tardive dyskinesia: a statistical meta-analysis. *Ann Clin Psychiatry.* 1998;10:101-105.

Vitamin E found to be a safe, well-tolerated adjunctive treatment with modest benefits for patients with TD

Barak and colleagues undertook a meta-analysis of 12 studies (223 patients), including 10 RCTs, of 4 to 36 weeks of treatment with adjunctive vitamin E (400-1600 IU/d) for TD. Vitamin E was associated with significant improvement: 29% of patients receiving vitamin E had lower AIMS scores compared with 5% of those who received placebo. Vitamin E was generally well tolerated and without clinically significant adverse effects.

10. Soares-Weiser K, Maayan N, McGrath J. Vitamin E for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev.* 2011;2:CD000209.

11. Alabed S, Latifeh Y, Mohammad HA, Rifai A. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev.* 2011;4:CD000203.

Vitamin E did not improve symptoms, but it may protect against deterioration of TD

The researchers identified 11 RCTs (427 inpatients) of adjunctive vitamin E in schizophrenia. Vitamin E was not associated with any improvement in TD (RR = 0.86-0.95); however, it was associated with significantly less deterioration of symptoms compared with placebo (RR = 0.38), based on 5 trials (98 subjects) deemed of limited quality. Compared with other adjunctive treatments for TD, the results of this meta-analysis suggest that vitamin E may be a good choice for further evaluation.

Conclusion

TD is a serious, and potentially disabling, movement disorder that affects approximately one-quarter of patients with schizophrenia. In antipsychotic-treated patients, regular screening for TD by clinical assessment, such as the AIMS, is critical. A number of different genetic variants are associated with increased risk of TD, and other replicated risk factors for TD include increasing age, non-white ethnic group, and early extrapyramidal symptoms.

The etiopathophysiology of TD remains unknown, although leading theories involve abnormalities in dopaminergic, GABAergic, and antioxidant defense systems, and are being investigated in rodent and non-human primate models. If TD occurs, discontinuing the offending antipsychotic via slow taper, and switching to a different, lower-risk antipsychotic, is recommended.

A number of treatment options exist for persistent TD, including the recently FDA-approved VMAT2 inhibitor valbenazine. Other VMAT2 inhibitors and antioxidants are being vigorously investigated. Future research in this area is clearly warranted to elucidate mechanisms and novel treatment strategies. □

INGREZZA™ (valbenazine) capsules

for oral use

Brief Summary: for full Prescribing Information and Patient Information, refer to package insert.

INDICATIONS AND USAGE

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

WARNINGS AND PRECAUTIONS

Somnolence

INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Somnolence
- QT Prolongation

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Variable and Fixed Dose Placebo-Controlled Trial Experience

The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 28% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

Adverse Reactions Leading to Discontinuation of Treatment

A total of 3% of INGREZZA treated patients and 2% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions

Adverse reactions that occurred in the 3 placebo-controlled studies at an incidence of $\geq 2\%$ and greater than placebo are presented in Table 1.

Table 1: Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at $\geq 2\%$ and >Placebo

Adverse Reaction ¹	INGREZZA (n=262) (%)	Placebo (n=183) (%)
General Disorders		
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Nervous System Disorders		
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4%	4.9%
Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia (akathisia, restlessness)	2.7%	0.5%
Gastrointestinal Disorders		
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Musculoskeletal Disorders		
Arthralgia	2.3%	0.5%

¹ Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

Other adverse reactions of $\geq 1\%$ incidence and greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Endocrine Disorders: blood glucose increased

General Disorders: weight increased

Infectious Disorders: respiratory infections

Neurologic Disorders: drooling, dyskinesia, extrapyramidal symptoms (non-akathisia)

Psychiatric Disorders: anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with INGREZZA

Table 2: Clinically Significant Drug Interactions with INGREZZA

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Implication:	Concomitant use of INGREZZA with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.
Prevention or Management:	Avoid concomitant use of INGREZZA with MAOIs.
Examples:	isocarboxazid, phenelzine, selegiline
Strong CYP3A4 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (C_{max} and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.
Examples:	itraconazole, ketoconazole, clarithromycin
Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors may increase the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or Management:	Consider reducing INGREZZA dose based on tolerability when INGREZZA is coadministered with a strong CYP2D6 inhibitor.
Examples:	paroxetine, fluoxetine, quinidine
Strong CYP3A4 Inducers	
Clinical Implication:	Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.
Prevention or Management:	Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort ¹
Digoxin	
Clinical Implication:	Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).
Prevention or Management:	Digoxin concentrations should be monitored when co-administering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure related adverse reactions. Dosage adjustment of digoxin may be necessary.

¹ The induction potency of St. John's wort may vary widely based on preparation.

Drugs Having No Clinically Important Interactions with INGREZZA

Dosage adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 based on *in vitro* study results.

OVERDOSAGE

Human Experience

The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

Management of Overdosage

No specific antidotes for INGREZZA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poisson.org).

For further information on INGREZZA, call 844-INGREZZA (844-647-3992).



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CP-VBZ-US-0203 04/17

FOR ADULTS WITH **TARDIVE DYSKINESIA (TD)**,
THE FIRST AND ONLY INDICATED TREATMENT

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Important Information

INDICATION & USAGE

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IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS

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ADVERSE REACTIONS

The most common adverse reaction ($\geq 5\%$ and twice the rate of placebo) is somnolence. Other adverse reactions ($\geq 2\%$ and $>$ placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the inside back cover for brief summary of Prescribing Information and visit www.INGREZZA.com for full Prescribing Information.

REFERENCE: INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; April 2017.



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