Valbenazine for Tardive Dyskinesia

Oliver Freudenreich [1], Gary Remington [2]

Abstract

Tardive dyskinesia (TD) remains a clinical concern for any patient who receives an antipsychotic. While the overall risk of developing TD is lower with newer antipsychotics compared to older agents, a significant number of patients who require long-term treatment will develop TD. Recently, valbenazine (brand name Ingrezza) became the first drug to be approved by the FDA specifically for the treatment of TD. In this New Drug Review, we summarize the basic pharmacology and clinical trial results for valbenazine. Valbenazine is a modified metabolite of the vesicular monoamine transporter 2 (VMAT-2) inhibitor tetrabenazine, which is approved for the treatment of the hyperkinetic movement disorder, Huntington's disease. In short-term clinical trials, valbenazine at a dose of 80 mg/day improved TD, with an effect size that is clinically significant (d=0.90). The effect size for the 40-mg/day dose was lower (d=0.52). Compared to tetrabenazine, valbenazine has better clinical characteristics (i.e., once-a-day dosing, better short-term side effect profile). However, only long-term experience in routine clinical populations can delineate valbenazine's full benefits, optimal dosing, and risks not identified during short-term registration trials.

Key Words: Tardive Dyskinesia, VMAT-2 Inhibitor, Valbenazine, Schizophrenia

Introduction

Antipsychotic drugs can result in a variety of motor side effects. Of particular concern during chronic antipsychotic use is tardive dyskinesia (TD), which in its classic form is characterized by involuntary, choreiform movements affecting the oro-bucco-lingual region (1) but can also involve the extremities and the trunk. If severe, TD is functionally disabling. However, even mild cases can be socially stigmatizing as abnormal movements are obvious to laypeople. Once established, TD tends to persist in the majority of patients even if antipsychotics are stopped, with remission rates being variously estimated to be as high as 33% (2) or as low as 2–13% (3, 4). Many patients with schizophrenia require ongoing treatment with an antipsychotic to prevent psychotic relapse, and stopping treatment is clinically not possible.

It is worth noting that abnormal movements in individuals treated with antipsychotics may not reflect only TD or related tardive movements. For example, drug-naive individuals with schizophrenia manifest dyskinetic movements, with a review of this topic reporting a median rate of 9% (5). Along similar lines, spontaneous dyskinesias are seen with increased frequency in older individuals, and can as well be incorrectly diagnosed as tardive in nature (6). This said, antipsychotic-related extrapyramidal symptoms, including TD, came to define the side effect profile of conventional first-generation antipsychotics, in particular the high-potency agents such as haloperidol (7). The reader is referred to two recent reviews that address the topic of risk

[1]*Schizophrenia Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts*
[2]*Schizophrenia Program, Centre for Addiction and Mental Health, Toronto, Ontario*

Address for correspondence: Oliver Freudenreich, MD, FAPM, Erich Lindemann Mental Health Center, 25 Staniford Street, Boston, MA 02114
E-mail: Freudenreich.Oliver@mgh.harvard.edu

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factors for TD that have been highlighted over the years (8, 9).

The advent of newer, second- and third-generation antipsychotics (SGA, TGA) was initially greeted with great hopes for a reduced liability for TD. Unfortunately, this has not completely been borne out: while lower, the estimated annual incidence rates for SGAs (3.9%) approach those for first-generation antipsychotics (FGAs) (5.5%) (10). A more recent meta-analysis examining TD prevalence has similarly suggested that the difference between those of FGAs and SGA/TGAs, while significant, is not as great as initially imagined. More specifically, prevalence rates for those currently receiving an SGA/TGA was 20.7% (95% CI=16.6%–25.4%, N=5,103) vs. 30.0% for FGAs (95% CI=26.4%–33.8%, N=5,062; Q=9.17, p=0.002) (11).

Thus, TD continues to be a clinical issue of great relevance for all patients who are treated with an antipsychotic or metoclopramide. For the latter alone, 7 million prescriptions are written annually (12). The broadening indications for antipsychotics beyond schizophrenia and an increase in off-label use have also resulted in a larger pool of psychiatric patients exposed to antipsychotics (13), creating a large cohort at risk for TD, perhaps as many as 5 million people exposed, with 700,000 developing TD (12). The implications of increasing off-label use are not well understood vis-à-vis TD, but such a trend calls into play earlier work suggesting that TD liability may actually be higher in individuals with a non-schizophrenia diagnosis (14, 15).

The treatment of TD has been disappointing. No medication is FDA approved specifically for TD as none is clearly effective, with some possible exceptions. A recent evidence-based guideline by the American Academy of Neurology found merely probable efficacy for clonazepam and ginko biloba, followed by amantadine and tetrabenazine (TBZ) (16). In the United States, tetrabenazine (TBZ, brand name Xenazine) is FDA approved for the prototypical hyperkinetic movement disorder, Huntington's disease, and many clinicians use TBZ off-label to manage their patients with TD (17). However, the use of TBZ is hampered by poor tolerability (sedation, insomnia, akathisia, Parkinsonism) and the need for frequent dosing (up to three times daily) due to unfavorable pharmacokinetic characteristics as well as the need for titration due to orthostatic hypotension (18). In addition, TBZ carries a black box warning about an increased risk for depression and suicidality (see package insert for Xenazine [19]).

TBZ is the prototype of a class of drugs labeled vesicular monoamine transporter 2 (VMAT-2) inhibitors (20). VMAT-2 are presynaptic transport proteins that play a key role in the monoamine neurotransmitter life cycle in the central nervous system (21). Located in the membrane of intracellular synaptic vesicles, VMAT-2 transporter proteins regulate the uptake and packaging of monoamine neurotransmitters from the cytosol (where they are susceptible to monoamine oxidase catabolism) into synaptic vesicles. Inhibiting the VMAT-2 transporter prevents the uptake of neurotransmitters into presynaptic vesicles, effectively amounting to dopamine (and serotonin) depletion. Reduced neurotransmitter availability might ameliorate biological and chemical changes that result from chronic dopamine blockade, particularly dopaminergic supersensitivity as a result of up-regulated dopamine receptors and neuronal degeneration, both of which are believed to be in part responsible for the clinical expression of TD (22). VMAT-2 is, therefore, an interesting pharmacological target for drugs to treat hyperkinetic movement disorders including Huntington's disease, TD, and Tourette syndrome.

Due to its chiral molecular nature, TBZ has a complicated metabolism that leads to metabolites with undesired off-target action (23). TBZ is itself a 1:1 mixture of (+)- and (-)-enantiomers that are hydrogenated to four different dihydrotetrabenazine (HTBZ) metabolites (two per enantiomer) via a carbonyl reductase: (+)-α-HTBZ, (+)-β-HTBZ, (-)-α-HTBZ, and (-)-β-HTBZ. For all practical purposes, (+)-α-HTBZ can be considered the desired metabolite: it is a potent inhibitor of VMAT-2 and is also highly selective (i.e., displays little off-target binding). By contrast, the (-) metabolites in particular are inhibitors of serotonergic and dopaminergic neurons, believed to contribute to certain side effects associated with the use of TBZ (e.g., dopamine antagonism causing Parkinsonism, serotonergic antagonism causing depression). A simplified scheme for the metabolism of TBZ and its relationship to valbenazine (see below) is provided in Figure 1.

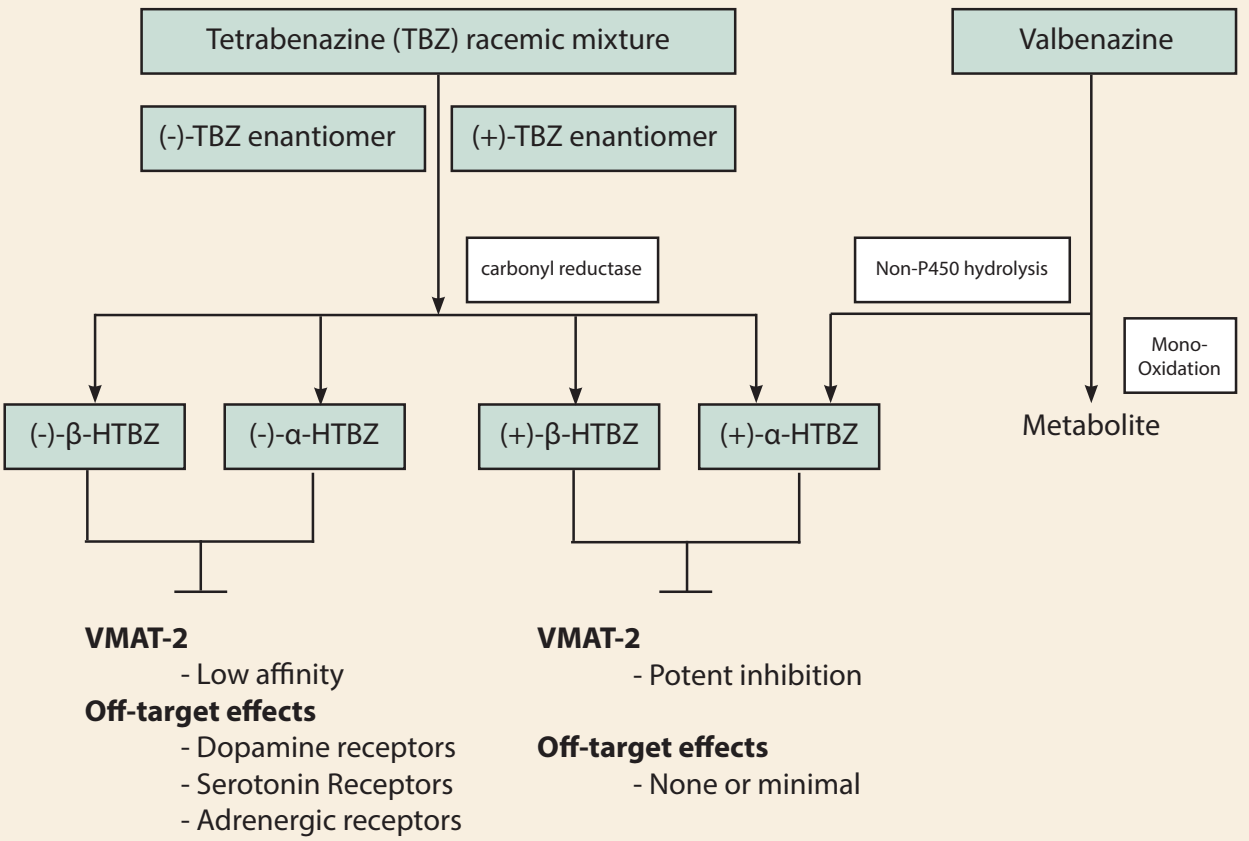
Attempts to develop VMAT-2 inhibitors that are better tolerated and easier to administer than TBZ have resulted in clinical trial programs to improve on the clinical profile of TBZ. The first success of these efforts, valbenazine (VBZ), was approved by the FDA on April 11, 2017 for the treatment of adults with TD. Other efforts to improve on TBZ are also underway (e.g., increasing TBZ's half-life via deuteration for deutetrabenazine [24]).

Valbenazine

Pharmacodynamics

Valbenazine (NBI-98854) was developed to improve the safety and tolerability of TBZ by minimizing off-target interactions and prolonging its half-life to allow for once-a-day dosing. The parent drug, valbenazine, is metabolized to two major metabolites: (+)-α-dihydrotetrabenazine (HTBZ) and a mono-oxy metabolite (NBI-136110). All three compounds are active and show highly selective VMAT-2 binding without significant off-target binding at

Figure 1 Tetrabenazine and Valbenazine Metabolism



serotonergic or dopaminergic sites (presented as a poster [25]). Consistent with its lack of dopamine blockade, valbenazine administration shows little increase in prolactin levels. However, valbenazine itself binds less potently to VMAT-2 compared to HTBZ and can be considered a pro-drug that needs to be converted to the active drug (23).

Pharmacokinetics

Valbenazine, administered orally, reaches maximum plasma concentrations (t_{max}) within 0.5–1 hour. Steady state plasma concentrations are attained within a week. Its absolute oral availability approximates 50%, while the C_{max} of its major metabolite, (+)-α-HTBZ, is reached 4–8 hours after drug administration.

Plasma protein binding of valbenazine and (+)-α-HTBZ exceeds 99%. Valbenazine is extensively metabolized by hydrolysis of the valine ester to form the active metabolite, (+)-α-HTBZ. Oxidative metabolism, primarily via CYP3A4/5, forms mono-oxidized valbenazine and other minor metabolites, and (+)-α-HTBZ is further metabolized via CYP2D6. The half-lives of valbenazine and (+)-α-HTBZ are in the range of 15–22 hours, allowing for once daily dosing (26).

Efficacy

A clinical trials program (KINECT 1, KINECT 2, KINECT 3, KINECT 4) led to the development of valbenazine (see Table 1).

In addition to pivotal short-term registration studies (i.e., KINECT 2 and KINECT 3), longer-term studies were also conducted (i.e., KINECT 3 extension and KINECT 4). All trials used the Abnormal Involuntary Movement Scale (AIMS) as the gold standard rating scale to assess the severity of TD (27). A strong methodological feature in the clinical trials program was the assessment of clinical efficacy of valbenazine using centralized video ratings of the AIMS exams by experts who were blinded to the treatment assignment and also to visit type (i.e., baseline or end-of-study visit). KINECT 2 and KINECT 3 have been published; results from other trials have been presented as posters at scientific meetings.

KINECT 2 (ClinicalTrials.gov Identifier: NCT01733121)

Table 1 Completed Placebo-Controlled Phase 2/3 Clinical Trials of Valbenazine for Tardive Dyskinesia

Study Name	Clinical Trial Phase	Study Duration	Sample Size (randomized)	Valbenazine Dosing	Main Findings (primary outcome variable)
KINECT 1	2	6 weeks	109	50 mg/day 100 mg x 2 week, then 50	Not significant
KINECT 2	2	6 weeks	100	25 to 75 mg/day	Significant AIMS score improvement:* 2.6 points (valbenazine) 0.2 points (placebo)
KINECT 3	3	6 weeks	234	40 and 80 mg/d	Significant AIMS score improvement:* 3.2 points (80-mg valbenazine) 1.9 points (40-mg valbenazine)† 0.1 placebo

*least square means. †not significant for 40 mg; primary outcome variable was placebo versus 80 mg.

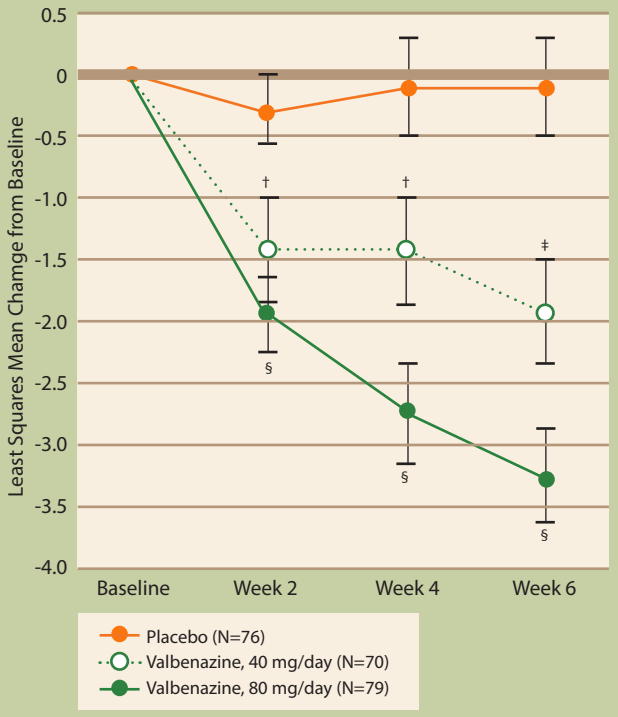
was a pivotal short-term (6-week), double-blind, placebo-controlled Phase 2 trial that established efficacy of valbenazine for tardive dyskinesia (28) and led to an FDA breakthrough-therapy designation for valbenazine. 102 subjects diagnosed with antipsychotic- or metoclopramide-induced TD were randomized. Almost all patients had a schizophrenia spectrum disorder or a mood disorder. Subjects were randomized to receive either placebo or up to 75 mg of valbenazine administered once daily. Valbenazine was started at 25 mg/day and increased by 25 mg every two weeks, up to a maximum dose of 75 mg/day, based on tolerability and efficacy. 76% of subjects received the 75-mg dose. The baseline AIMS score for subjects was 8.0. The primary end-point (AIMS change between baseline and week 6) was statistically significant (p=0.0005) in the modified intent-to-treat analysis (45 valbenazine subjects versus 44 placebo subjects) using least squares means with AIMS severity as covariate: treatment with valbenazine reduced the AIMS score by an average of 2.6 points (standard error of the mean 1.2) compared to 0.2 for placebo (standard error of the mean 1.1). This improvement was not different for patients with schizophrenia or mood disorders. A secondary end-point (Clinical Global Impression of Change-Tardive Dyskinesia [CGI-TD]) was also significant (p<0.0001). Treatment-emergent side effects occurred in 49% of valbenazine patients compared to 33% of placebo patients. Fatigue and headaches were most common (9.8% each).

KINECT 3 (ClinicalTrials.gov Identifier: NCT02274558) was a second short-term, 6-week, double-blind, placebo-controlled Phase 3 trial examining the efficacy of 40 mg and 80 mg/day of valbenazine for tardive dyskinesia in patients with schizophrenia, schizoaffective disorder, or a mood disorder. Results of this trial (and its extension, see below) have been published (29) or presented as a poster (30), respectively. The 234 patients with moderate-to-severe TD were randomized, and 225 were included in the intent-to-treat population. A significant reduction on the primary outcome variable (AIMS score change from baseline to week 6 for 80-mg valbenazine) by 3.2 points (least squares mean) compared to 0.1 points for placebo was found (p<0.001). This corresponds to an effect size of d=0.90, which is considered clinically meaningful. There was no significant difference for the 40-mg dose (-1.9 least squares mean change, p=0.002), although AIMS scores were reduced with an effect size of d=0.52. For the 40-mg dose, most of the response was noted within the first 2 weeks of the 6-week study (evaluations were carried out at 2-week intervals). A significant treatment response, defined as a >50% reduction in AIMS score was evident by 6 weeks (p<0.05), whereas the 80-mg dose indicated response from week 2 and was greater at each assessment (p<0.001 at week 6).The key short-term efficacy findings, including the time course of response from KINECT 3, are depicted in Figure 2.

In this trial, and in contrast to KINECT 2, there was no statistically significant difference seen on the CGI-TD. Adverse effects were rare. Rates at least twice as high as placebo were noted for akathisia (placebo 1%, VBZ 40 mg 4%, VBZ 80 mg 3%), arthralgia (placebo 1%, VBZ 40 mg 1%, VBZ 80 mg 4%), dry mouth (placebo 1%, VBZ 40 mg 7%, VBZ 80 mg 0%), vomiting (placebo 0%, VBZ 40 mg 0%, VBZ 80 mg 4%), and dyskinesia (placebo 0%, VBZ 40 mg 0%, VBZ 80 mg 4%) but not for somnolence. Ratings of psychopathology—including PANSS, YMRS, MADRS, CDSS, C-SSRS (see below for full scale names)—remained stable.

The 42-week extension of the KINECT 3 trial (with blinded dosing but no placebo group) showed sustained improvement over the treatment period (30). Once treatment was stopped, TD reverted back toward baseline AIMS level. KINECT 4 (ClinicalTrials.gov Identifier: NCT02405091)

Figure 2 **Change from Baseline in AIMS Dyskinesia Score Among Paricipants Receiving Valbenazine or Placebo, by Study Visit (Intent-to-Treat Population)***



*Mixed-effects model for repeated measures. AIMS=Abnormal Involuntary Movement Scale; the dyskinesia score is the sum of AIMS Items 1–7. The indicated significance levels refer to comparison with placebo. Error bars indicate standard error of the mean.
†p<0.05 ‡p<0.01 § p≤0.001

is a one-year, open-label, Phase 3 safety and tolerability study where enrolled subjects receive either 40 or 80 mg of valbenazine daily for 48 weeks.

Side Effects and Safety

A major clinical concern using neurotransmitter depleting agents is worsening of psychopathology as well as the induction of depression and suicidality. In the short-term trials of valbenazine, no worsening of psychopathology was seen using established rating scales of psychopathology (Positive and Negative Syndrome Scale [PANSS], Calgary Depression Scale for Schizophrenia [CDSS], Montgomery-Asberg Depression Rating Scale [MADRS], Young Mania Rating Scale [YMRS]). There was also no signal for an increased risk in suicidality or suicidal behavior as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) (31).

A safety analysis for a pooled long-term exposure population of 430 subjects from three studies (KINECT, KINECT 3, KINECT 4) was presented as a poster (32). The mean duration of valbenazine exposure in this cohort was 204 days (±119 days); the median duration 225 days (range 1 to 356 days). Treatment due to adverse effects was discontinued in 14.7%. Valbenazine did not increase suicidality based on spontaneous reporting and C-SSRS responses. Of note, almost 40% reported a history of lifetime suicidal ideation or behavior. Valbenazine did not have notable effects on cardiac conduction (QTc interval) or hepatic function. The package insert nevertheless notes the possibility of QTc interval prolongation and the need for caution in certain clinical situations (e.g., concomitant treatment with CYP3A4 and 2D6 inhibitors). Subjects remained psychiatrically stable as assessed by disorder-specific rating scales (i.e., PANSS and CDSS for schizophrenia, YMRS and MADRS for mood disorders). Parkinsonism or akathisia, as assessed by the Simpson-Angus Scale (SAS) and the Brief Adherence Rating Scale (BARS), respectively, were not observed. In clinical trials comprised of study subjects with TD, valbenazine was thus well-tolerated, and no concerning safety signal was detected.

Other Indications

Valbenazine is also being studied for another hyperkinetic movement disorder, Tourette syndrome. Two Phase 2 clinical trials, T-FORWARD (ClinicalTrials.gov Identifier: NCT02581865) and T-Force GREEN (ClinicalTrials.gov Identifier: NCT02679079) are currently underway for adults as well as children and adolescents (ages 6 to 17) with Tourette syndrome, respectively.

Summary

The approval of valbenazine is welcome news for patients with TD who have few, if any, good treatment options once TD is established. Table 2 summarizes basic pharmacology to aid clinicians in prescribing. While the package insert recommends an increase to 80 mg/day after one week of treatment with the starting dose of 40 mg/day, some patients may show sufficient benefit from the 40-mg dose. However, since there were no notable tolerability issues (e.g., sedation) between the 40- and 80-mg dose in clinical trials one can argue against using a lower dose routinely, particularly since the 80-mg dose was more effective. Patients who experience early side effects from the 40-mg starting dose or where there are concerns about drug-drug interactions should remain on the 40-mg dose.

The clinical trials mimicked real-world conditions by including patients on clozapine who often have legacy TD from antipsychotic treatment prior to a clozapine trial (clozapine itself, while associated with a lower TD liability, can still cause TD). Treating clozapine patients with valbenazine is thus not contraindicated, but overlapping side

Table 2 Clinical Summary of Valbenazine

Valbenazine (brand name INGREZZA)		
Approval date		April 11, 2017
Indication		Adults with tardive dyskinesia
Drug class		VMAT-2 inhibitor
Metabolism		Active metabolite: [+]-α-HTBZ
Half-life		15–22 hours
Dosing	Starting dose	40 mg/day; after one week, increase dose to 80 mg/day
	Target dose	80 mg/day Patient with moderate-to-severe hepatic impairment: 40 mg/day Patients receiving strong CYP3A4 inhibitors: 40 mg/day Patients receiving strong CYP2D6 inhibitors: consider 40 mg/day if tolerability issue
	Maximum dose	80 mg/day
Food/Drug interactions		A high-fat meal decreases valbenazine's C_{max} and AUC by 47% and 13%, respectively. [+]-α-HTBZ C_{max} and AUC are not affected. Valbenazine can, therefore, be taken with or without food. Increased C_{max} and AUC, in the range of 1.5- to 2-fold, may be observed with co-administration of a strong CYP3A4 inhibitor (e.g., ketoconazole).
Side effects		Warnings/precautions include: somnolence (may impair driving/operating hazardous machinery); QT prolongation (avoid use in individuals with congenital long QT syndrome and arrhythmias associated with a prolonged QT interval); pregnancy/breastfeeding (can cause fetal harm). Based on 3 placebo-controlled studies of 6-weeks duration, side effects in valbenazine-treated patients that exceeded 2% and the placebo controls included: somnolence (10.9%), anticholinergic effects (e.g., constipation, dry mouth) (5.4%), balance disorders (e.g., fall) (4.1%), headache (3.4%), akathisia (2.7%), vomiting (2.6%), nausea (2.3%), arthralgia (2.3%).

Based on: package insert for valbenazine (brand name Ingrezza). Available from: http://www.ingrezza.com/PI. San Diego, California, Neurocrine Biosciences, Inc.; 2017.

effect profiles need to be taken into account (e.g., sedation, constipation).

The extent of use of valbenazine in routine clinical practice remains to be seen. While the prevalence of TD remains a concern, even with the newer antipsychotics, in many cases severity may not warrant intervention. Moreover, TD has also been associated with "la belle indifference," where individuals appear unaware of the movements, hence rejecting treatment; indeed, in one study no or low awareness characterized over 50% of patients with TD (33). Further, both clinicians and patients can be hesitant to add medications to treat side effects when, in fact, these medications carry their own risk of side effects.

Going forward, only long-term studies in real-world settings and outside carefully selected research subjects can clarify valbenazine's full potential and also its risks. Responses to medications in clinical trials are average responses, reflecting a range of individual responses. It remains to be seen who benefits the most from valbenazine, when to best use it and how to best use it. For example, are there patients whose TD essentially disappears with treatment? Can it be used concomitantly with antipsychotics to reduce the antipsychotic dose? Should it be used prophylactically in high-risk patients like geriatric patients? Is efficacy dose-related? Can it be used to gradually reverse dopamine hypersensitivity? So far, the extension studies conducted in chronic patients with TD suggest that long-term treatment with valbenazine might be necessary as its dyskinetic benefit is lost once treatment is stopped. However, all clinical trials have enrolled antipsychotic-treated patients, and the short- and long-term efficacy of valbenazine in antipsychotic-free patients (for those patients where this is an option) requires further study. VMAT-2 inhibitors, while selective for the central nervous system, do not differentiate between dopamine and serotonin reuptake into vesicles. Reducing available neurotransmitters in the synaptic cleft poses risks (Parkinsonism, anxiety, depression and suicidality) that will need to be carefully studied and understood to devise management strategies. It is reassuring that the extension studies of valbenazine did not detect concerning safety signals.

VMAT-2 inhibitors as a class are promising drugs that might target disease relevant pathophysiology in TD (34). However, it is unclear if treatment with a VMAT-2

inhibitor merely masks symptoms of tardive dyskinesia or if its administration reverses biological changes from chronic dopamine blockade. A better understanding of VMAT-2 neurobiology might lead to new treatment options for disorders related to dopamine, including hyperkinetic movement disorders (20).

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