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Clinical experience and treatment considerations with vesicular monoamine transport 2 inhibitors

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Abstract

Vesicular monoamine transporter 2 inhibitors (VMAT2i) are currently Food and Drug Administration–approved for the treatment of Huntington disease chorea and tardive dyskinesia. Additionally, they are often used for other hyperkinetic movement disorders in clinical practice. Due to a lack of head-to-head clinical trials, management of VMAT2i in the clinical setting may be unclear and rely on the clinical experience of the practitioner. Due to the limited distribution model, which typically requires VMAT2i to be dispensed by specialty pharmacies, access and initiation of treatment may present as barriers. Patient cases allow for the exploration of switching between VMAT2i, alternative routes of administration, utilization in pediatric and off-label conditions, and how to successfully initiate and monitor a patient on VMAT2i therapy.

Keywords: vesicular monoamine transporter 2 inhibitor, hyperkinetic movement disorder, specialty pharmacy, pediatric

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Introduction

Hyperkinetic movement disorders are characterized by a variety of repetitive involuntary movements. Approved by the FDA in 2008, vesicular monoamine transporter 2 inhibitors (VMAT2i) for conditions including tardive dyskinesia (TD) and Huntington disease (HD) chorea are available for use by neurologists and psychiatrists.[1] As of 2019, the VMAT2i approved for use in the United States include tetrabenazine (TBZ) for HD chorea, deutetrabenazine (DBZ) for TD and HD chorea, and valbenazine (VBZ) for TD and HD chorea.[2–4] These medications inhibit synaptic vesicular monoamine transporter 2, resulting in reversible depletion of neuroactive monoamines, such as dopamine, histamine, norepinephrine, and serotonin, to reduce involuntary, spontaneous movements. DBZ is structurally related to TBZ but contains deuterium, allowing for a prolonged plasma half-life and reduced plasma fluctuations due to decreased susceptibility to cytochrome P450 (CYP) 2D6 metabolism.[5] VBZ is a prodrug metabolized by CYP3A4 to the active metabolite alpha-dihydrotetrabenazine, which is subsequently metabolized by CYP2D6.[6]

Based on a lack of head-to-head clinical trials, selection of the most appropriate VMAT2i is routinely related to insurance approval and affordability plus nuanced differences in adverse event (AE) and drug interaction profiles (Table 1).[2–4] TBZ tablets must be given in divided doses up to 4 times daily, whereas DBZ is available as an immediate

Take Home Points:

1. Selection of vesicular monoamine transporter 2 inhibitor (VMAT2i) therapy is based on patient- and medication-specific factors. Patients should be closely monitored throughout therapy for efficacy, tolerability, and changes in other factors that may affect adherence and/or access to continued treatment.
2. Current data assessing the use of VMAT2i in non–FDA-approved conditions and patient populations is limited. Therefore, patient management may be based on clinical experience, and close safety monitoring should occur when patients fall outside of established guidance.
3. Patient education regarding adverse events, expected therapeutic outcomes, and ways to overcome common barriers to access and adherence should be completed at the time of VMAT2i initiation and routinely assessed during treatment to assist in therapeutic success.

release (IR) tablet administered twice daily and an extended release (XR) tablet administered once daily. Both medications should be avoided at any level of hepatic impairment and are metabolized by CYP2D6. Major drug interactions for both include strong CYP2D6 inhibitors (examples are bupropion, fluoxetine, paroxetine), QT-prolonging agents (examples are antipsychotics, citalopram, escitalopram, tricyclic antidepressants), and central nervous system depressants. An electrocardiogram (EKG) and liver function tests (LFTs) should be monitored at baseline and as clinically indicated during treatment with both medications.[3,4] VBZ capsules and VBZ sprinkle capsules are administered once daily at bedtime and may be used cautiously in hepatic impairment. VBZ is metabolized by CYP3A4/5 and CYP2D6, and major drug interactions include strong CYP3A4 inducers/inhibitors, strong CYP2D6 inhibitors, and digoxin. VBZ causes no clinically significant QT prolongation, but LFTs should be monitored at baseline and as clinically indicated during treatment.[2]

VMAT2i may only be dispensed through limited distribution networks, requiring patients to utilize specialty mail-order pharmacies; additionally, limited evidence exists for use in off-label conditions. Outside of treatment initiation, monitoring for therapy response and AE may require more frequent communication with patients than traditional office visit intervals allow.

Case 1: Switching VMAT2i Therapies

A 38-year-old with HD receiving TBZ 37.5 mg 3 times daily reports significant improvement in chorea and no AE during an HD clinic visit; however, the patient endorses midday dose nonadherence (4 days per week) due to recent employment changes with no standard lunch time. The patient asks about other treatment options requiring less frequent dosing.

Medication adherence is influenced by various factors, including those related to the condition, intervention, socioeconomics, the health care system, and the individual patient. In general, evidence suggests that individuals with high adherence rates have 3 times higher likelihood of a good treatment outcome; those with adherence rates of less than 80% have a twofold to threefold increased mortality risk compared with those with higher adherence rates.[7] Whereas interventions to improve adherence may be implemented at any level, patient-specific factors are often most effective to target. Interventions with supporting data include focusing on habit formation (eg, linking medication administration with environmental cues, such as brushing teeth, and tailored behavioral strategies).[7] Additional interventions to improve adherence include patient education, regimen simplification, blister packing, automated pill dispensers, and utilizing technology (eg, mobile apps, alarms) for reminders.

An indirect treatment comparison (ITC) of the landmark HD chorea trials for DBZ and TBZ was completed in 2017. The risk of selected outcomes related to AE and discontinuation were estimated by subtracting the applicable placebo-adjusted risks for DBZ from TBZ. Sensitivity analyses were performed to address differences between trials, and *p*-values were obtained from *z*-tests. Overall results favored DBZ with a lower risk of moderate-to-severe AE ($p < .05$), neuropsychiatric AE ($p < .05$), and dose reduction or dose reduction/suspension ($p < .001$) in both adjusted and unadjusted analyses.[8] As a limitation, the gold standard would be a randomized clinical trial to corroborate these results. Additionally, authors noted that included DBZ patients had less advanced HD with a potentially different disease course than those on TBZ.[8] Conversely, results of the ITC align in terms of clinical practice experience.

In 2023, an ITC of the landmark HD chorea trials for VBZ and DBZ was completed with a focus on efficacy. Compared with DBZ, VBZ resulted in significantly greater improvement during early treatment (weeks 2 and 4, $p < .05$) and similar improvement at later time points (week 6 and endpoint). These findings indicate that patients may find an effective dose of VBZ within 2 to 4 weeks of initiation, whereas DBZ patients may take longer. The full publication of results is not available.[9] Aggarwal et al conducted an ITC of the landmark TD trials in 2019 to compare the efficacy and safety of VBZ and DBZ. The only statistically significant finding was greater improvement with VBZ 80 mg daily at 8 and 12 weeks compared with DBZ ($p < .05$).[10] As before, the gold standard would be a randomized clinical trial to corroborate the results of the ITC given the disparate results.

TABLE 1: Comparison of vesicular monoamine transporter 2 inhibitors based on Food and Drug Administration approval[2-4]

	Deutetrabenazine (DBZ) IR and XR	Tetrabenazine (TBZ)	Valbenazine (VBZ) and VBZ Sprinkles
Black Box Warnings	Depression and suicidality in patients with Huntington disease		
Hallmark Clinical Trials	AIM-TD[28] ARM-TD[30] FIRST-HD[31]	TETRA-HD[32]	KINECT 3[33] KINECT-HD[34]
Maximum Daily Dose[a]	48 mg given in 1 (XR) dose with or without food or 2 (IR) divided doses with food	150 mg given in up to 4 divided doses with or without food	80 mg given in 1 dose with or without food
Renal/Hepatic Adjustments	Avoid in hepatic impairment	Avoid in hepatic impairment	Reduce in moderate or severe hepatic impairment to 40 mg daily
Metabolism	CYP2D6 to active metabolites alpha-HTBZ and beta-HTBZ	CYP2D6 to active metabolites alpha-HTBZ and beta-HTBZ	CYP3A4/5 to active metabolite alpha-HTBZ
CYP Interactions	Strong CYP2D6 inhibitors (maximum 36 mg per day)	Strong CYP2D6 inhibitors (maximum 50 mg per day)	Strong CYP3A4 inhibitors (maximum 40 mg per day); strong CYP3A4 inducers (use not recommended); strong CYP2D6 inhibitors (maximum 40 mg per day)
Other interactions	MAOIs, QT prolonging agents, reserpine, alcohol and other sedating agents	MAOIs, QT prolonging agents, reserpine, alcohol and other sedating agents	MAOIs, digoxin
Monitoring Parameters	EKG, LFTs, AE (pseudoparkinsonism, psychiatric, sedation), disease state–specific scale(s)	EKG, LFTs, AE (pseudoparkinsonism, psychiatric, sedation), disease state–specific scale(s)	LFTs, AE (anticholinergic effects, psychiatric, sedation), disease state–specific scale(s)
Common AE (All FDA Indications)	Somnolence, diarrhea, dry mouth, fatigue, insomnia, and nasopharyngitis	Sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, nausea	Somnolence/lethargy/sedation, urticaria, rash, insomnia

AE = adverse events; CYP = cytochrome; EKG = electrocardiogram; HTBZ = dihydrotetrabenazine; IR = immediate release; LFTs = liver function testing; MAOIs = monoamine oxidase inhibitors; XR = extended release.
[a]Based on Food and Drug Administration–approved prescribing information.

Based on TBZ's and DBZ's chemical structure relationship, direct conversion between medications is possible at a dosing ratio of approximately 2:1.[3] Frank et al evaluated the safety and efficacy of converting using an open-label overnight switch from TBZ to equivalent doses of DBZ. Participants stayed at equivalent doses for week 1 and then were titrated weekly through week 4 for dose optimization. No worsening of symptoms was noted after conversion with a similar AE profile.[11] No direct comparison exists between DBZ IR and XR; however, clinical experience indicates that patients may maintain chorea control with fewer breakthrough symptoms and lower AE rates when receiving DBZ XR due to steadier serum concentrations and/or improved medication adherence. DBZ IR to XR conversion should occur with the same total daily dose.[3]

No direct conversion exists for VBZ. Based on clinical experience, patients taper off other VMAT2i if experiencing an AE to DBZ or TBZ and then initiate VBZ after a 3 to 5 day washout to prevent misattribution of AE. If converting due to lack of efficacy, patients are switched to VBZ 40 mg nightly overnight with a rapid titration based on tolerability and efficacy.

Given significant improvement with TBZ and lack of significant AE, conversion to DBZ 48 mg per day (maximum FDA-approved dose) could be considered. Converting to VBZ would not be preferred as this could expose the patient to a separate AE profile that may be less tolerable for this patient. Additionally, the patient would need to titrate VBZ due to a lack of data supporting equivocal doses to a regimen balancing efficacy and AE, whereas DBZ has been shown to have a lower AE risk and similar efficacy as TBZ with direct conversion.[8,11] After discussing options with the patient using a shared decision-making process, transitioning to DBZ XR once daily may be preferred rather than twice daily IR due to concerns for adherence with multiple daily doses. If adherence remains a concern with once daily dosing, education should be provided regarding adherence interventions described earlier.

Case 2: Alternative Routes of Administration

A 46-year-old with TD receiving VBZ 80 mg nightly reports significant improvement in oral lingual movements as indicated by Abnormal Involuntary Movement Scale (AIMS) evaluation during a psychiatry appointment. The patient does endorse beneficial mild drowsiness from VBZ, which is assisting in the management of comorbid sleep onset insomnia. A new diagnosis of squamous cell carcinoma of the neck requires a percutaneous endoscopic gastrostomy (PEG) tube for nutritional support and medication administration. The oncologist inquires if VBZ can be administered via PEG tube.

In clinical practice, TBZ tablets are often chosen for patients utilizing a PEG or nasogastric (NG) tube because the prescribing information does not advise against this route of administration.[4] Based on clinical experience, if utilized, the PEG/NG tube should be flushed thoroughly before and after each administration to prevent inactive ingredients of lactose and starch causing tube occlusion. Unfortunately, crushing TBZ tablets multiple times per day may lead to nonadherence for patients on complex medication regimens.

Prescribing information for DBZ IR and XR recommends against the crushing of tablets for PEG/NG tube administration; however, this is sometimes done in clinical practice.[3] Wietholter et al describe a 38-year-old with TD secondary to atypical antipsychotic exposure who developed worsening athetosis, hyperkinesia, and severe orofacial dyskinesia after ziprasidone initiation. Crushed DBZ IR treatment was initiated via PEG tube. No noticeable AE were reported, and TD symptoms improved after 1 week of DBZ IR 24 mg twice daily with reduction in AIMS score from a mean of 4 to 2 after 3 weeks of therapy.[12] Knebel et al did submit a clarification indicating caution should be used when interpreting the report of the communication with DBZ's manufacturer as safety and efficacy data are not available from clinical trials for crushing the tablet. Additionally, they note that DBZ IR contains excipients and has physical characteristics (eg, dissolution profile) not characteristic of IR products.[13] DBZ XR should not be crushed as it utilizes an osmotic delivery system containing an outer IR coating with an inner XR core. Upon consumption, DBZ XR's outer IR coating releases about 25% of the medication; then, water diffuses into the inner XR core for a consistent rate of release of the remaining 75%. The DBZ XR shell is excreted in the feces. In clinical practice, patients stabilized on DBZ IR who require PEG/NG tubes and are not candidates for TBZ conversion are educated on the potential risks of crushing DBZ IR tablets and monitored closely (Tables 1 and 2).

Last, the prescribing information for VBZ sprinkle capsules does offer recommendations for alternate routes of administration by allowing the capsules to be opened and sprinkled over soft food, only avoiding the use of milk or drinking water. The prescribing information for VBZ sprinkles specifically states not to administer via enteral tubes due to risk of obstruction.[2] However, Sajatovic et al conducted studies to evaluate the in vitro dissolution of regular VBZ whole capsules versus crushed contents (ie, a powder plug), stability of crushed contents mixed into various soft foods, and suitability/stability of adding crushed contents to water via gastronomy (G) tube. They found VBZ crushed contents did not affect dissolution performance, crushed contents may be administered via soft foods or liquids if consumed within 2 hours, and crushed contents are compatible with G-tube administration using hot or cold water and a cup rinse.[14]

Based on the new requirement for this patient to receive nutritional support and medications via PEG tube, the team could consider crushing VBZ capsules and administering with water each night with subsequent PEG tube rinse. Whereas TBZ is used more often when crushed tablets are needed, this patient reports significant improvement in oral lingual movements with VBZ and beneficial mild drowsiness and prefers to remain on the medication rather than switching. Whereas VBZ does have a sprinkles formulation, the prescribing information specifically states not to administer via enteral tubes due to risk of obstruction, and there are no studies demonstrating safety.[2] Regardless of the formulation chosen, based on a lack of robust clinical data or manufacturer-endorsed recommendations, close monitoring for efficacy and safety should occur after changing routes of administration.

Case 3: Off-Label Utilization

A 16-year-old with Tourette syndrome (TS) began exhibiting motor tics around age 6 years followed by vocal tic development. Past treatment trials include comprehensive behavioral intervention for tics with moderate benefit, aripiprazole resulting in weight gain, clonidine being ineffective, pimozide resulting in sedation, risperidone with mild benefit, and topiramate being ineffective. Active tics currently include jaw rolling, head rolling, shoulder jerking, hand stretching and tensing, arm stretching, rubbing hands, coughing, humming, and throat clearing. The patient is experiencing significant neck pain and seeing effects on writing ability and is becoming concerned regarding social activities. A Yale Global Tic Severity Scale (YGTSS) assessment shows a motor tic severity score of 18, phonic tic severity score of 12, total tic severity score of 30, and impairment score of 30 (ie, a moderate score, indicating tics are associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning). The patient and guardians are interested in a VMAT2i trial during the neurology visit today.

TABLE 2: Initial education and follow-up items based on clinical practice

	Deutetrabenazine (DBZ) IR and XR	Tetrabenazine (TBZ)	Valbenazine (VBZ) and VBZ Sprinkles
Indication and Goal of Therapy	Decrease in or resolution of uncontrollable movements		
Dosing and Administration	IR: twice daily with food XR: once daily with or without food	Up to 4 times daily with or without food	VBZ: nightly at bedtime with or without food VBZ sprinkles: sprinkle the contents of capsule over a bowl containing 1 tablespoon of soft food only (no milk or drinking water). Swallow the drug/food mixture immediately. If necessary, the mixture can be stored for up to 2 hours at room temperature. Discard of any unused portion after 2 hours. Drink a glass (eg, 240 mL) of water right after administration.
Adherence and Missed Doses	IR: take a missed dose if >6 hours before next dose XR: take a missed dose if >12 hours before next dose Both: must re-itrate if >7 days are missed in a row	Take a missed dose if >6 hours before next dose Must retitrate if >5 days are missed in a row	Take a missed dose if >12 hours before next dose
Drug Interaction Monitoring	Medication reconciliation and targeted review Alcohol and other CNS depressants/sedating agents Notify office and/or pharmacy of any medication changes, including short term (ie, antibiotic) and over-the-counter items		
Reproductive Considerations	Reproductive: DBZ may increase serum prolactin concentrations, which may lead to amenorrhea or impotence Pregnancy: No AE observed in animal reproduction studies Lactation: decision to breastfeed should conside risks to the infant versus benefits to the infant/parent	Pregnancy: AE were observed in some animal models, limited experience in humans Lactation: decision to breastfeed should consider risks to the infant versus benefits to the infant/parent	Pregnancy: AE were observed in some animal models Lactation: not recommended during VBZ therapy or until 5 days after the last dose
Warnings and Safety Precautions	Depression and suicidality in patients with Huntington disease Extrapyramidal symptoms (akathisia and/or pseudoparkinsonism) Hypersensitivity to active or inactive ingredients Neuroleptic malignant syndrome QT prolongation Somnolence or sedation		
Common AE	GI upset Nasopharyngitis Sleep disturbances Xerostomia	Balance/coordination difficulties GI upset Sleep disturbances Upper respiratory tract infection	Anticholinergic effects Balance or coordination difficulties GI upset Headache Sedation
Laboratory Monitoring	EKG, LFTs	EKG, LFTs	EKG, LFTs
When to Call Provider or Seek Medical Attention	New or worsening mood changes or thoughts of self-harm New or worsening movement symptoms Allergic reaction Signs or symptoms of neuroleptic malignant syndrome New or worsening cardiac symptoms (palpitations, abnormal heart rate, etc) Fatigue or sedation that is worsening or significantly impacting quality of life		

TABLE 2: Initial education and follow-up items based on clinical practice (continued)

	Deutetrabenazine (DBZ) IR and XR	Tetrabenazine (TBZ)	Valbenazine (VBZ) and VBZ Sprinkles
Storage	Store at room temperature in a cool, dark place		
Financial Assistance Options[a]	Commercial insurance: copay card Medicare: grant fund or patient assistance program if qualified	Commercial insurance: copay card for brand name Medicare: grant fund if qualified	Commercial insurance: copay card Medicare: grant fund or patient assistance program if qualified

AE = adverse events; CNS = central nervous system; EKG = electrocardiogram; GI = gastrointestinal; IR = immediate release; LFTs = liver function testing; XR = extended release.
[a]Foundational assistance may be available for patients with Medicare and specific diagnoses.

No VMAT2i is currently FDA approved for TS, other tic disorders, or in patients younger than 18 years of age. As the oldest VMAT2i, TBZ has the most published literature regarding off-label use with small studies confirming benefit in the treatment of dystonia, TD, and TS.[15] However, no large-scale randomized controlled trials are likely to be conducted due to generic availability. Use of DBZ or VBZ in off-label conditions is largely based on clinical practice experience. Clinical experience does indicate a role for VMAT2i in conditions including other chorea, cerebral palsy, and Meige syndrome. According to clinicaltrials.gov, trials are actively recruiting for DBZ in patients with dystonia (18+ years) and VBZ as adjunctive treatment for schizophrenia (13+ years), trichotillomania (18 to 65 years), and dyskinesia due to cerebral palsy (6 to 70 years).[16–20]

The European Clinical Guidelines for Tourette syndrome and other tic disorders were published in 2021 and recommend behavioral interventions first line and aripiprazole, risperidone, and tiapride as second-line treatment options. TBZ is mentioned as a potential alternative to antipsychotics with a note that further studies are needed to solidify it as a treatment option.[21] Niemann et al published a retrospective real-world experience study in 2019 focusing on the treatment of VMAT2i for a variety of hyperkinetic movement disorders in 135 patients (HD n = 25, TD n = 28, TS n = 67, other n = 15) with age range varying significantly based on diagnosis of interest (eg, 28 to 77 years for HD symptoms and 9 to 79 years for TS/tic symptoms). The mean treatment duration was 5.1 months for TBZ (n = 31) with a mean daily dose of 48.8 mg, 8 months for DBZ (n = 51) with a mean daily dose of 34.4 mg and 6 months for VBZ (n = 20) with a mean daily dose of 64 mg. Using a Likert scale measuring illness severity, 69.9% to 71.9% of patients during treatment scored 1 (normal or mildly ill) compared with 13% to 26.7% of patients before treatment with VMAT2i. Therapy continuation rates for VMAT2i at the end of the study period were 64.5% TBZ, 78.8% DBZ, and 47.6% VBZ. The authors concluded that VMAT2i effectively controlled hyperkinetic movement disorders, and AE were mild and able to be improved or resolved following dose reduction, medication discontinuation, or adjunctive medications.[22] Makhoul et al published a retrospective real-world experience study in 2023 that highlighted a chart review supplemented with a telephone survey, including patients treated with any VMAT2i from January 2017 to January 2021. The focus was the long-term experience of VMAT2i in patients specifically with TS and did include some of the same patients as the article published by Niemann et al. In the longer term study, the breakdown of VMAT2i use was TBZ (n = 135) with a mean treatment duration of 43 months and daily dose of 56.8 mg, DBZ (n = 71) with a mean treatment duration of 18.5 months and daily dose of 29.4 mg, and VBZ (n = 19) with a mean treatment duration of 8.8 months and daily dose of 62.7 mg. No patients with a documented clinical response reported feeling worse in terms of tic control, and responses based on chart review were slightly better (4.5%), better (43.8%), much better (26.8%), or very much better (3.6%) with VMAT2i therapy. The most common AE seen was drowsiness in 26.7% of TBZ patients only.[23] In both studies, a significant barrier to access was noted to be lengthy and cumbersome insurance approval processes.[22,23]

The higher frequency of TBZ use in the studies by Niemann et al and Makhoul et al reflect clinical practice.[22,23] In addition to previously stated reasons, TBZ is available as a generic and may be preferred by insurance plans. Whereas studies support the use of VMAT2i for TS, the improvement in open-label studies for DBZ were unable to be replicated in 2 randomized, double-blind, placebo-controlled trials. There are many possible reasons for this, including the difficulty in studying patients with a highly variable condition and/or subtherapeutic dosing.[24,25] Another consideration for off-label use is doses above the FDA-approved maximum for any condition. TBZ does not have a maximum recommended dose outside of the CYP2D6 variants; however, DBZ and VBZ have maximum recommended doses of 48 and 80 mg daily, respectively.[2–4] In clinical practice, doses up to DBZ 96 and VBZ 160 mg daily have been used for patients with a partial response and no significant or troublesome AE on lower regimens.

Before initiation of a VMAT2i, LFTs and an EKG should be assessed because of the recommendation to avoid use or reduce the dose in patients with organ dysfunction or QT prolongation (Table 1). Additionally, disease-specific assessments should be completed to allow for pretherapy versus posttherapy comparison (eg, AIMS for TD, Unified Huntington's Disease Rating Scale for HD, YGTSS for TS, etc).[26–28] If titrating TBZ above 50 mg daily, a CYP2D6 metabolizer status assessment is recommended with a maximum dose of 50 mg for poor metabolizers compared with 100 mg for intermediate or extensive metabolizers; however, this is often not completed in clinical practice until TBZ doses exceed 100 mg daily.[4]

Given the lack of complete response or AE to multiple pharmacological options, a VMAT2i is a reasonable treatment option for this patient. Assessing baseline organ function with LFTs and EKG in addition to discussing the pros and cons of each VMAT2i with the patient and guardian(s) using a shared decision-making approach would be appropriate. Given the availability of a generic and the amount of published literature, TBZ would likely be the initial treatment. If the patient responds favorably but has an intolerable AE, direct conversion to DBZ would be the next preferred option given the lower AE rates seen clinically. If the patient has no response to TBZ, a trial with VBZ would be the next preferred option.

Case 4: Initiation of Treatment

A 57-year-old presents to the neurology movement disorders clinic with schizoaffective disorder complaining of worsening orobuccal movements. Prior medication trials include haloperidol, olanzapine, perphenazine, and ziprasidone. The patient's AIMS score is mild for facial muscle movement, moderate for lips or perioral area, moderate movement severity, mild movement incapacitation, and moderate distress for patient awareness. Preappointment LFTs are normal, and an EKG shows QTcF 454 ms. The patient is taking bupropion extended release (XL) 150 mg daily and risperidone 1 mg twice daily. The clinic decides to initiate DBZ XR via titration kit to 30 mg daily for TD.

Accurate medication reconciliation is essential to ensure safe therapy initiation and proper AE education. When choosing a VMAT2i, patient-specific factors must be considered due to the lack of head-to-head clinical trials, and a shared decision-making approach should be utilized to discuss the risks versus benefits of each VMAT2i.

A black box warning for increased risks of depression and suicidality in patients with HD exists for VMAT2i. Therefore, VMAT2i should not be initiated in patients with untreated or inadequately treated depression or suicidal ideation. Additional warnings that apply to all VMAT2i include extrapyramidal symptoms, such as akathisia and/or pseudoparkinsonism, hypersensitivity, neuroleptic malignant syndrome, QT prolongation, and somnolence/sedation.[2–4] The most common AEs for DBZ are insomnia and nasopharyngitis compared with somnolence for VBZ in patients with TD.[2,3] TBZ is not FDA approved for TD; however, the most common AE in HD chorea are akathisia, anxiety, depression, fatigue, insomnia, nausea, and sedation or somnolence.[4] For DBZ with HD, diarrhea, dry mouth, fatigue, and somnolence compared with insomnia, rash, somnolence, and urticaria for VBZ are the most common AE.[2,3] Because each VMAT2i requires individualized titration, it may be 4 or more weeks before therapeutic benefit is observed; additionally, clinical experience supports increasing benefit as time on treatment increases. Patients may require more frequent interactions than are able to be met using traditional office visit intervals when starting or changing doses; therefore, phone calls and other reliable methods should be utilized at standard intervals to allow for therapy modifications sooner than the 3- to 6-month office visit schedule. A full list of initial patient education and follow-up items that are routinely covered in clinical practice may be found in Table 2.

Initiating treatment with VMAT2i may have additional barriers, including insurance approval and utilization of specialty pharmacies. With the availability of 3 VMAT2i, many insurance plans may have a preferred or step therapy process that requires patients to start with a VMAT2i that may not be preferred clinically. Due to this, lengthy and cumbersome prior authorizations and/or appeals may be needed. Generic TBZ is available to all pharmacies; however, access to DBZ, brand TBZ, and VBZ may be restricted to specialty mail-order pharmacies that may not be familiar to patients or providers. Specialty pharmacies focus on medications that are considered high cost or high touch (ie, requiring extensive patient assessment, education, and monitoring) and may be able to assist patients in obtaining insurance access and/or overcoming other common barriers to adherence. However, if patients are not expecting the outreach by these pharmacies or providers do not know which the insurance requires, patients may never be able to start therapy.

Another significant barrier to VMAT2i therapy is affordability. As VMAT2i may be the only FDA-approved medication for some of the hyperkinetic movement disorders and 2 of them are available as brand name only, DBZ and VBZ, many insurance companies may place these in higher formulary tiers, resulting in higher copayments or coinsurances. For patients with commercial insurance, copay cards are available for on-label indications of brand TBZ and all indications for DBZ and VBZ; however, these may be difficult for patients to access on their own. Specifically, DBZ currently requires the patient to register for a traditional copay card and a credit card. The patient must then

provide both sets of billing information to the pharmacy to obtain the promised $0 copay. If the pharmacy is unfamiliar with this type of 2-step billing system, the patient may be charged an unexpected out-of-pocket cost. As copay cards are not an option for government-funded insurance patients (ie, Medicare), other options are needed. For patients with TD, a grant is currently available through the HealthWell Foundation if they qualify, and the fund is open. In addition, when available, the HealthWell Foundation has a grant for HD and a grant for movement disorders. Brand and generic TBZ have no patient assistance program (PAP). The manufacturers of DBZ and VBZ currently offer a PAP for qualified patients.

After using a shared decision-making approach, the patient consents to treatment with DBZ XR. A baseline AIMS assessment has been documented, and a review of LFTs and EKG shows no concerns. Based on concurrent medications, the patient is educated about the drug CYP 2D6 interaction between DBZ XR (maximum recommended dose 36 mg daily) and bupropion XL along with monitoring for AE, such as GI upset and new or worsening movements. Additionally, the patient should alert the clinic to any new or unusual changes in mood or thoughts of suicidality immediately. Insurance approval is obtained, and the prescription for DBZ XR is triaged to the appropriate specialty pharmacy. As the patient has commercial insurance, the office assists the patient with registering for the copay savings card, and the patient is educated that the manufacturer-provided credit card should be utilized to pay for each prescription. A follow-up phone call to assess tolerability is scheduled for 3 weeks, and an office visit is scheduled for 6 weeks to assess an AIMS, LFTs, EKG, and tolerability.

Conclusion

Use of VMAT2i therapies outside FDA-approved indications and parameters is less clear with limited evidence available in the medical literature. No head-to-head clinical trials exist to guide treatment selection, leading to a requirement for patient-specific characteristics and medication AE profiles to be examined when initiating VMAT2i therapy. Patient education regarding AE, expected therapeutic outcomes, and ways to overcome common barriers to access and adherence should be completed at time of initiation and routinely assessed during treatment to assist in therapeutic success.

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