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A systematic review on treatment of tardive dyskinesia with valbenazine and deutetrabenazine

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Abstract: Recent reports state that the prevalence of tardive dyskinesia (TD) is 32% with typical antipsychotics, and 13% with atypical antipsychotics. Current evidence-based recommendations determine an unmet need for efficacious treatment of TD. This systematic review was planned to update the evidence for TD treatment, comparing two vesicular monoamine transporter 2 (VMAT2) inhibitors, deutetrabenazine (DBZ), and valbenazine (VBZ). Of 75 PubMed search results, 11 studies met the review criteria. Efficacy and tolerability were demonstrated in a series of randomized, placebo-controlled clinical trials in our review study, and the Abnormal Involuntary Movement Scale response of ⩾50% reduction in score was robust for VBZ 80 mg/day in short-term and long-term studies. On the contrary, DBZ was equally efficacious at 12 mg twice daily, but additional information about long-term efficacy and persistence of effect is needed.

Keywords: clinical trial, deutetrabenazine, psychopharmacology review, tardive dyskinesia, valbenazine, VMAT2 inhibitor

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Introduction

Tardive dyskinesia (TD) is an involuntary movement disorder of the nervous system associated with paresthesia, pain, an inner urge to move, and other sensory abnormalities due to prolonged exposure to dopamine-receptor antagonists such as antipsychotics.[1] TD is most commonly observed in individuals treated with antipsychotics for psychotic disorders like schizophrenia, schizoaffective, and bipolar disorders.[2] Second-generation antipsychotics were associated with a lower annual incidence of TD, that is, 0.8% of those under 50 years of age compared with 5.3% of patients over age 50 years.[1] It can present as repetitive and jerking movements of the face, neck, and tongue that are not under control of the patient.[3] TD is used to define any hyperkinetic movement disorder like tremor, dystonia, akathisia, tics, chorea, and myoclonus.[1] TD typically occurs after at least 1 year of continuous exposure to dopamine-receptor-blocking agents (DRBA), especially first-generation antipsychotics; but it can be seen in patients after as little as 3 months of therapy. It can also be seen with drugs like metoclopramide, promethazine, prochlorperazine, and tricyclic antidepressants.[4]

Some published reports state that the prevalence of TD is 32% with typical antipsychotics, and 13% with atypical antipsychotics.[5] Almost one out of four patients receiving antipsychotics develop TD, especially in those taking a higher dose of antipsychotics for a long duration.[3] Interestingly, there are few cases of TD caused by tetrabenazine.[6] The risk of developing TD can be decreased by prescribing the lowest efficacious dose of antipsychotic.[4] Use of potent DRBA, long-term exposure, and a past history of movement disorders secondary to DRBA are also associated with a higher rate of extrapyramidal side effects like TD.[2]

Chronic antipsychotic-induced dopamine-receptor blockade causes an upregulation and increased sensitivity of dopamine receptors, resulting in an increase in dopamine neurotransmission in the

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basal ganglia.[4] Some studies suggest that TD could be due to the antipsychotic-induced damage to the group of striatal gamma aminobutyric acid (GABA)-containing neurons.[7] Even after completely stopping DRBA, TD may persist for years in a patient. In some patients, TD reverses completely while they are on DRBAs, and in a few patients, after stopping the offending agent.[1]

As TD has become a commonly studied topic in recent years, a systematic review was performed to merge accessible data on clinical conclusions from studies regarding deutetrabenazine (DBZ) and valbenazine (VBZ) in managing symptoms of TD. In order to assist psychiatrists and other mental-health professionals in treating TD, the primary objective of this systematic review was to provide evidence to enable a comparison between DBZ and VBZ for treating TD.

Mechanism of action

VBZ acts by decreasing the cytosolic uptake and storage of dopamine into the synaptic vesicles by selectively inhibiting vesicular monoamine transporter 2 (VMAT2) receptor, thereby making it available for cytosolic enzymes.[8] Due to the lack of neurotransmitter in the vesicles, the presynaptic release of monoamine neurotransmitters is reduced.[8]A detailed analysis *via* Cerep screen for dopamine, serotonin, and adrenergic receptor/transporter subtypes revealed a high specificity of VBZ and its metabolites for the VMAT2 transporter.[8] Alternatively, DBZ is a highly selective and inhibitor of VMAT2. DBZ depletes dopamine stores in the synaptic nerve vesicles by inhibition of the VMAT2.[9] This increases the availability of dopamine peripherally that cannot be transported to synaptic vesicles, and it eventually undergoes degradation in the body. Therefore, the dopamine levels available for use are diminished, thereby decreasing the abnormal movements of TD.[9]

Methods

Search strategy

The MEDLINE database was used to identify papers published in English from 1 January 1980 to 31 March 2018. The search strings were 'valbenazine OR deutetrabenazine AND tardive dyskinesia'. Results appearing in more than one search were removed (Figure 1). Tetrabenazine was excluded from systematic review, as studies comparing the efficacy and safety of tetrabenazine and VBZ has been done previously.[10]

Criteria for study selection

All searches and screening were conducted independently by two authors (RSP, HS) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement recommendations (Figure 1). Randomized controlled trials, single-arm studies, cohort studies, and case series involving at least five cases of TD were included in our review analysis to evaluate and compare the efficacy and safety of VBZ and DBZ for TD. Case reports of fewer than five TD cases, meta-analyses, literature reviews, and studies on subjects other than humans, pharmacokinetic analyses, guidelines for use, mini-articles, and letters to editors were excluded. Screening of irrelevant studies, such as titles and abstracts, was completed to remove results based on the specific exclusion criteria. The remaining eligible studies were evaluated further through full-text analysis.

Data extraction

Using the full text of selected papers, an evaluation was performed to document the type of study and design, the representative sample size, whether the study was completed at a single site and comparators, as well as the efficacy and safety outcomes of the VBZ and DBZ study. If the study looked at other movement disorders in addition to TD then only TD results were recorded. This information was later analyzed for the TD population in order to formulate an illustrative review.

The initial MEDLINE database searches generated 75 results. The titles and abstracts were screened, based on our objective, and resulted in the exclusion of 64 studies from our systematic review. A total of 11 studies met the criteria for our systematic review and full-text articles were further evaluated for eligibility as shown in Figure 1. Nine studies were identified for VBZ and two studies were identified for DBZ. Sample size, dose of VBZ and DBZ, duration of treatment and assessment tools varied greatly across the studies. No one-on-one studies were obtainable that compared DBZ and VBZ for TD management.

Results and discussion

Eleven studies emerged from the in-depth screening process and eligibility assessment and were

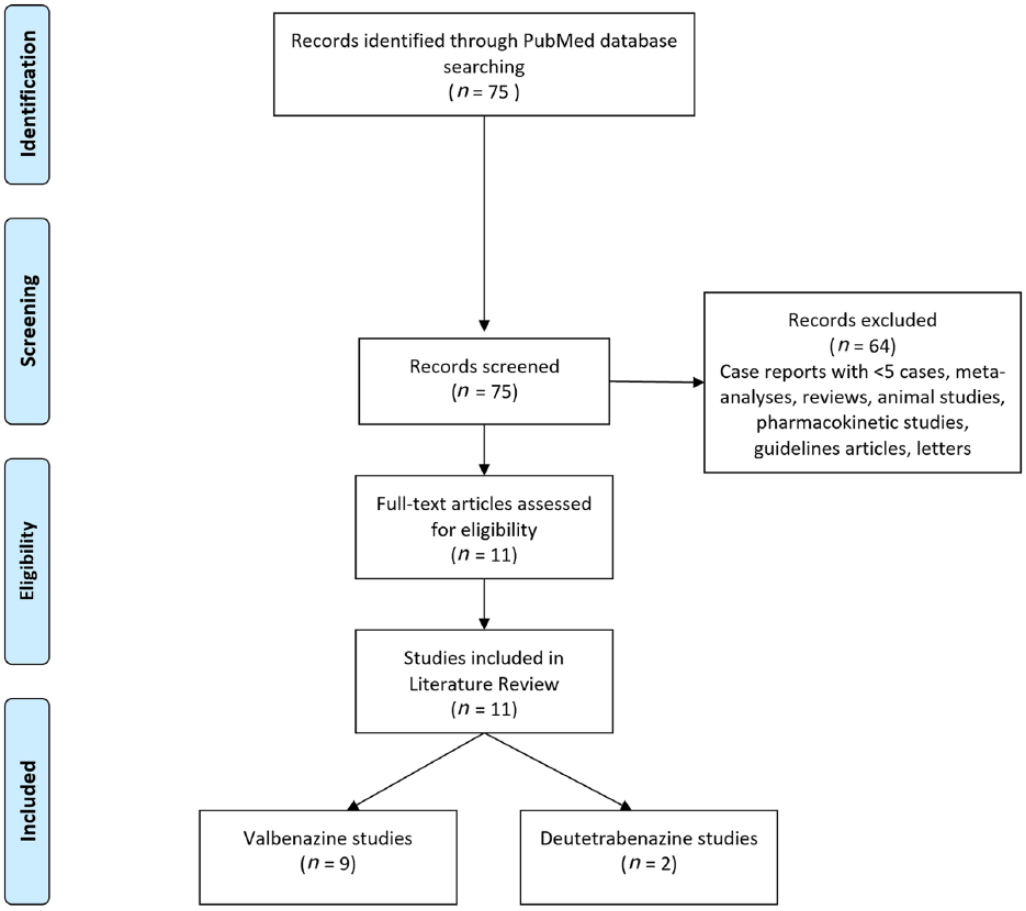

Figure 1. Results of systematic review.
Search terms: 'valbenazine AND tardive dyskinesia', 'deutetrabenazine AND tardive dyskinesia'. Search criteria: English language, date range 1 January 1980–31 March 2018.

reviewed. A descriptive summary of all studies that met our inclusion criteria is presented in Table 1. The majority of the VBZ[9–15] and DBZ[18,19] studies were randomized, double-blind, placebo-controlled (DBPC) trials, except two studies, as Thai-Cuarto and colleagues[18] conducted a pooled study of three DBPC trials to assess safety of VBZ, and Grigoriadis and colleagues[19] conducted the KINECT 3 extension study to evaluate the pharmacology of VBZ. Efficacy of VBZ and DBZ were assessed by the Abnormal Involuntary Movement Scale (AIMS) and Clinical Global Impression of Change (CGIC)–Tardive Dyskinesia (CGI-TD) score.

Review of valbenazine studies

To evaluate the role of VBZ in TD, we analyzed eight randomized, double-blind studies with a total of 1821 study subjects. In general, VBZ was found to be an efficacious intervention with a safe and well-tolerated profile. Three of the double-blinded, placebo-controlled trials were carried out for 6 and 12 weeks,[11–13] while five of the studies were conducted for an extended period with a maximum of 52 weeks[14–18] to analyze long-term effects of VBZ.

All the studies included subjects diagnosed with schizophrenia, schizoaffective, or mood disorders with concomitant presence of TD. Presence of DSM-IV-diagnosed TD for at least 3 months prior to screening was a prerequisite for inclusion in these studies. Qualitative assessment of TD was also conducted in patients using AIMS. Blinded individuals' rating videos used standardized AIMS assessments at the initial visit to obtain a baseline and repeated this assessment at each subsequent encounter. Further evaluation of treatment response and efficacy of VBZ was evaluated by the CGI-TD score. CGI-TD was used by the investigators to rate the overall change in

Table 1. Study design summary.

Study	Design	Duration	Population	Intervention	Comparator	Ref.
VBZ studies						
O'Brien *et al.*	Randomized, DBPC	6 weeks	TD ($n = 100$)	VBZ q.i.d. 25–75 mg/day ($n = 51$)	PBO o.d. ($n = 49$)	13
Hauser RA *et al.*	Randomized, DBPC, phase III	6 weeks	TD ($n = 234$) for ⩾3 months	VBZ 40 mg o.d. ($n = 76$); 80 mg o.d. ($n = 80$)	PBO o.d. ($n = 78$)	12
Luo R *et al.*	Study 1 Randomized, DBPC, single dose, fixed-sequence study Study 2 Randomized, DBPC, single- and multiple-dose study	12 weeks	TD Study 1 ($n = 16$) Study 2 ($n = 40$)	Study 1 Cohort 1: VBZ ($n = 6$) 1 mg, 2 mg, 5 mg, or 12.5 mg; Cohort 2: VBZ ($n = 6$) 12.5 mg, 25 mg, 50 mg or 75 mg, sequential dose escalation Study 2 Initial phase: VBZ ($n = 6$) 75 mg, 100 mg, 125 mg or 125 mg sequential dose escalation Second phase: 50 mg ($n = 8$) and 100 mg ($n = 8$)	Study 1 Cohort 1: PBO ($n = 2$) Cohort 2: PBO ($n = 2$) Study 2 Initial phase: PBO ($n = 2$) Second phase: PBO ($n = 4$)	11
Factor SA *et al.*	Randomized, double-blind, KINECT 3	52 weeks	Completed KINECT 3 ($n = 198$)	VBZ 40 mg o.d. ($n = 97$); 80 mg o.d. ($n = 101$)	None	14
Josiassen *et al.*	Randomized, double-blind, pooled three trials, phase II/III	KINECT: 12 weeks KINECT 3: 52 weeks KINECT 4: open label	TD ($n = 430$) for ⩾3 months, AIMS Scale	VBZ 40 mg o.d. ($n = 197$); VBZ 80 mg o.d. ($n = 230$)	None	17
Correll *et al.*	Randomized, DBPC, fixed dose, phase II/III	DBPC 6 weeks; VE 46 weeks	TD ($n = 205$) for ⩾3 months, AIMS	VBZ 40 mg o.d. ($n = 24$); 80 mg o.d. ($n = 27$)	PBO ($n = 26$)	15
Kane *et al.*	Randomized, DBPC, fixed dose, phase II/III	DBPC 6 weeks; VE 46 weeks	TD ($n = 205$) for ⩾3 months, AIMS	VBZ 40 mg o.d. ($n = 48$); 80 mg o.d. ($n = 52$)	PBO ($n = 50$)	16
Thai-Cuarto *et al.*	Randomized, DBPC, pooled three trials, phase II/III	6 weeks followed by 42 weeks' extension	TD ($n = 400$) for ⩾3 months, AIMS	VBZ 40 mg o.d. ($n = 110$); 80 mg o.d. ($n = 112$)	PBO ($n = 178$)	18
Grigoriadis *et al.*	Double-blind extension, KINECT 3	48 weeks plus 4-week washout	TD ($n = 198$)	VBZ q.i.d. 80 mg/day ($n = 101$); 40 mg/day ($n = 97$)	None	19
DBZ studies						
Fernandez *et al.*	Randomized, DBPC, flexible-dose study, phase II/III	12 weeks	TD ($n = 117$) for ⩾3 months and AIMS score ⩾ 6	DBZ 6 mg b.i.d. ($n = 58$) and titrated weekly by 6 mg/day, if required, for up to 6 weeks	PBO b.i.d. ($n = 59$)	20
Anderson *et al.*	Randomized, DBPC, fixed-dose study, phase III	12 weeks	TD ($n = 298$)	DBZ 6 mg b.i.d. ($n = 75$); 12 mg b.i.d. ($n = 74$); 18 mg b.i.d. ($n = 75$)	PBO b.i.d. ($n = 74$)	21

DBPC, double-blind, placebo-controlled; TD, tardive dyskinesia; VBZ, valbenazine; DBZ, deutetrabenazine; PBO, placebo; o.d., once daily; b.i.d., twice daily; q.i.d., four times a day; NNT, number needed to treat; Ref., reference number; AIMS, Abnormal Involuntary Movement Scale; VE, VBZ extension study.

TD. More than 50% of the total score improvement in the AIMS score from baseline was considered as response threshold. In most of the studies, the proportion of participants on VBZ reached a rigorous AIMS response level *versus* the placebo. Furthermore, persistence of improved AIMS and CGI-TD scores were observed in VBZ extended trials.

The randomized, placebo-controlled trials by Hauser and colleagues[12] and O'Brien and coworkers[13] were conducted over a period of 6 weeks to assess the efficacy of VBZ as compared with placebo in TD. Both of these studies yielded significant improvement in TD with VBZ compared with placebo, indicated by a change in the AIMS and CGI-TD scores. In the study by Hauser and colleagues,[12] least-squares (LS) mean change in the AIMS score from baseline to −0.1 for placebo, 1.9 for VBZ 40 mg/day and −3.2 for VBZ 80 mg/day, while the AIMS response in the study by O'Brien and colleagues[13]was 19% placebo and 49% VBZ ($p = 0.002$). Finally, CGI-TD scores in O'Brien and colleagues' study[13] showed significant improvement in the study population with VBZ (Table 2).

Subjects who completed 6 weeks' DBPC KINECT 3 were eligible to enter the VBZ extension (VE) for either 42 weeks[14–16]or 48 weeks[17,19] with a subsequent 4-week washout period. VE trials conducted to assess long-term effects of VBZ yielded persistently improved results on the total AIMS score through the end of VBZ treatment. It is important to note that deterioration of score was observed through the 4-week washout period. In all VE studies through the end of extension weeks, LS mean changes of AIMS scores were from baseline to −3.0 with VBZ 40 mg/day and to −4.8 with VBZ 80 mg/day ($p < 0.001$).

In trials by Correll and colleagues[15] and Kane and coworkers,[16] CGI-TD LS mean scores at week 6 before entering into the VE were 2.9 for VBZ 40 mg/day, 2.9 for VBZ 80 mg/day and 3.2 for placebo (no statistically significant difference). Through the end of VE period CGI-TD, LS mean scores were 2.4 for VBZ 40 mg/day and 2.1 for VBZ 80 mg/day, though no statistical testing between dosing was done. In the trial by Grigoriadis and colleagues,[19] CGI-TD response after 48 weeks of treatment ('much improved' or 'very much improved') was 76% with VBZ 80 mg/day and 59% VBZ 40 mg/day. After the 4-week treatment washout, increase in the AIMS and CGI-TD response demonstrated that TD symptoms were reverting to baseline assessment level.

In the study by Factor and colleagues,[14] subjects who were switched from placebo (in DBPC) to VBZ (in VE) showed significant improvement in AIMS, with 39.4% improvement for VBZ 80 mg/day and 27.3% for VBZ 40 mg/day. In the study by Grigoriadis *et al.*,[19] AIMS response after 48 weeks (⩾50% reduction in symptoms from baseline) was 52% and 28% for VBZ 80 mg and 40 mg, respectively.

Although the improvements on CGI-TD scores were not statistically significant, the results for CGI-TD response were significantly higher for VBZ as compared with placebo ($p < 0.0001$) in the study by O'Brien *et al.*[13] Moreover, a higher percentage of patients showed a response to VBZ as compared with placebo (67 *versus* 16%, $p < 0.0001$). CGI-TD LS mean scores at week 6 before entering into the VE were 2.9 for VBZ 40 mg/day, 2.9 for VBZ 80 mg/day and 3.2 for placebo (no statistically significant difference). Through the end of VE period, CGI-TD LS mean scores were found to be 2.4 for VBZ 40 mg/day and 2.1 for VBZ 80 mg/day, though no statistical testing between dosing was seen. In the study conducted by Grigoriadis *et al.*,[19] CGI-TD response ('much improved' or 'very much improved') at week 48 was 76% with VBZ 80 mg/day and 59% VBZ 40 mg/day. After 4-week treatment washout, there was an increase in the AIMS and CGI-TD response rates, demonstrating that TD symptoms were decreasing toward baseline. The efficacy summary based on VBZ studies is shown in Table 2.

Overall, VBZ was well tolerated by most of the patients and was found to have an acceptable safety profile (Table 3). The most common adverse effects (AEs) experienced with VBZ in 6-week[12,13] and 12-week[11] trials were insomnia, nervousness, fatigue, headache, and decreased appetite. Headache, urinary tract infection, diarrhea, dizziness, and somnolence were most frequently encountered AEs in extended VBZ trials.[12,17–19] During the trials, the psychiatric condition of the subjects remained stable, with no concerning effects reported.

Review of deutetrabenazine studies

DBZ studies included two randomized, DBPC trials, each using a single daily dose of DBZ over a period of 12 weeks.[20,21] In the flexible-dose study

Table 2. Efficacy summary.

Study	Efficacy summary	Ref.
VBZ studies		
O'Brien *et al.*	(1) AIMS score, LS mean change from baseline to week 6 (primary end point): −0.2 PBO, −2.6 VBZ ($p = 0.001$) (2) AIMS response at week 6 (⩾50% improvement from baseline): 19% PBO, 49% VBZ ($p = 0.002$) (3) CGI-TD score, LS mean at week 6: 3.1 PBO, 2.2 VBZ ($p < 0.001$) (4) CGI-TD response at week 6 ('much improved' or 'very much improved'): 16% PBO, 67% VBZ ($p < 0.001$)	13
Hauser RA, *et al.*	(1) AIMS score, LS mean change from baseline to week 6 (primary end point): −0.1 PBO, 1.9 VBZ 40 mg/day, −3.2 VBZ 80 mg/day (2) AIMS response at week 6 (⩾50% improvement from baseline): 9% PBO, 40% VBZ 80 mg ($p < 0.001$), 24% VBZ 40 mg ($p = 0.02$) (3) CGI-TD at week 6 (secondary end point) No significant difference between either dosage of VBZ and PBO (4) CGI-TD score: PBO 3.2, 2.9 VBZ 40 mg/day ($p = 0.074$), 2.9 VBZ 80 mg/day ($p = 0.056$)	12
Factor SA, *et al.*	(1) AIMS score, LS mean change from baseline to week 48: −3.0 VBZ 40 mg, −4.8 VBZ 80 mg/day ($p < 0.001$) (2) CGI-TD: 2.4 VBZ 40 mg/day, 2.1 VBZ 80 mg/day (3) PGIC: 2.2 VBZ 40 mg/day, 2.0 VBZ 80 mg/day	14
Correll CU, *et al.*	(1) AIMS score, LS mean change from baseline to week 6: −1.9 VBZ 40 mg, −3.2 VBZ 80 mg/day ($p < 0.001$) (2) AIMS score, LS mean change from baseline to week 48: −3.0 VBZ 40 mg, −4.8 VBZ 80 mg/day (no statistical testing between dosing) (3) AIMS score, LS mean change from week 48 to week 52: 8.4 VBZ 40 mg/days, 9.8 VBZ 80 mg/day (4) CGI-TD LS mean score week 6: 2.9 VBZ 40 mg/day, 2.9 VBZ 80 mg/day, PBO 3.2 (no statistically significant difference) (5) CGI-TD LS mean score week 48: 2.4 VBZ 40 mg/day, 2.1 VBZ 80 mg/day (no statistical testing between dosing) (6) CGI-TD LS mean score from week 48 to week 52: 3.1 VBZ 40 mg/day, 3.5 VBZ 80 mg/day	15
Kane JM, *et al.*	(1) AIMS score, LS mean change from baseline to week 6: −1.9 VBZ 40 mg, −3.2 VBZ 80 mg/day ($p < 0.001$) (2) AIMS score, LS mean change from baseline to week 48: −3.0 VBZ 40 mg, −4.8 VBZ 80 mg/day (no statistical testing between dosing) (3) AIMS score, LS mean change from week 48 to week 52: 8.4 VBZ 40 mg/days, 9.8 VBZ 80 mg/day (4) CGI-TD LS mean score week 6: 2.9 VBZ 40 mg/day, 2.9 VBZ 80 mg/day, PBO 3.2 (no statistically significant difference) (5) CGI-TD LS mean score week 48: 2.4 VBZ 40 mg/day, 2.1 VBZ 80 mg/day (no statistical testing between dosing) (6) CGI-TD LS mean score from week 48 to week 52: 3.1 VBZ 40 mg/day, 3.5 VBZ 80 mg/day	16
Grigoriadis *et al.*	(1) AIMS score, LS mean change from baseline to week 48: −4.8 VBZ 80 mg, −3.0 VBZ 40 mg (2) CGI-TD score mean at week 48, 2.1 VBZ 80 mg, 2.4 VBZ 40 mg (3) AIMS response at week 48 (⩾50% improvement from baseline): 52% VBZ 80 mg, 28% VBZ 40 mg (4) CGI-TD response at week 48 ('much improved' or 'very much improved'): 76% VBZ 80 mg, 59% VBZ 40 mg (5) After treatment washout (week 52), increases in AIMS and CGI-TD response rates indicated that TD severity was reverting to baseline levels	19
DBZ studies		
Fernandez HH, *et al.*	(1) AIMS score, LS mean change from baseline to week 12 (primary end point): −1.6 PBO, −3.0 DBZ ($p = 0.019$) (2) AIMS response at week 12 (⩾50% improvement from baseline): 17.5% PBO, 23.2% DBZ (NNT = 18) (3) There was no statistically significant difference between DBZ and placebo on the CGIC and PGIC scales (4) CGIC response at week 12 (score 1 or 2): 40.4% PBO, 48.2% DBZ (NNT = 13) (5) PGIC response at week 12 (score 1 or 2): 29.8% PBO, 42.9% DBZ (NNT = 8)	20
Anderson KE, *et al.*	(1) AIMS score, LS mean change from baseline to week 12 (primary end point): −1.4 PBO, −2.1 DBZ 6 mg b.i.d., −3.2 DBZ 12 mg b.i.d., −3.3 DBZ 18 mg b.i.d. ($p = 0.019$) (2) AIMS response at week 12 (⩾50% improvement from baseline): 12.1% PBO, 13.3% DBZ 6 mg b.i.d. (NNT = 80), 34.7% DBZ 12 mg b.i.d. and 32.7% DBZ 18 mg b.i.d. (NNT = 5) (3) There was no statistically significant difference between DBZ and PBO on the CGIC and PGIC scales (4) CGIC response at week 12 (score 1 or 2): 25.9% PBO, 28.3% DBZ 6 mg b.i.d. (NNT = 41), 49% DBZ 6 mg b.i.d. (NNT = 5), 43.6% DBZ 6 mg b.i.d. (NNT = 6) (5) PGIC response at week 12 (score 1 or 2): 31% PBO, 23.3% DBZ 6 mg b.i.d. (NNT = 13), 44.9% DBZ 6 mg b.i.d. (NNT = 8), 40% DBZ 6 mg b.i.d. (NNT = 12)	21

VBZ, valbenazine; DBZ, deutetrabenazine; PBO: placebo; o.d., once daily; b.i.d., twice daily; q.i.d., four times a day; NNT, number needed to treat; AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia Scale; LS, least square; PGIC, Patient Global Impression of Change; Ref., reference number.

Table 3. Safety summary.

Study	Safety summary	Ref.
VBZ studies		
Luo R, *et al.*	(1) Most common TEAEs for VBZ *versus* PBO in study 1 were headache (12.5%) (2) Most common TEAEs for VBZ *versus* PBO in study 2 were insomnia (37.5% *versus* 0%), nervousness (25% *versus* 0%), fatigue (7.1% with VBZ 50 mg, 25% with VBZ 100 mg); disturbance in attention and nervousness were dose dependent (3) Two discontinuations because of TEAE were 16.6% in PBO, 12.5% in the VBZ 50 mg q.i.d. dose groups, and 37.5% in the VBZ 100 mg q.i.d. dose group	11
Hauser RA, *et al.*	(1) Most common TEAEs for VBZ (both dosage-groups combined) *versus* PBO were somnolence (5.3% *versus* 3.9%), akathisia (3.3% *versus* 1.3%), and dry mouth (3.3% *versus* 1.3%) (2) Suicidal ideation was most common in the PBO group (5.3% *versus* 2.6% in the VBZ groups combined) (3) Discontinuation due to serious TEAE was 2.6% in the PBO group (altered mental status due to exacerbation of COPD; exacerbation of schizoaffective disorder) and 3.3% for VBZ (hostility/altered mental status; worsening of schizoaffective disorder; suicide attempt; suicidal ideation; and reactivation of viral hepatitis)	12
Factor SA, *et al.*	(1) Most common TEAEs for VBZ were headache 7.2% (40 mg) and 6.9%(80 mg); UTI 6.2% (40 mg) and 6.9% (80 mg); diarrhea 3.1% (40 mg) and 7.9% (80 mg); dizziness 4.1%(40 mg) and 6.9% (80 mg); suicidal ideation 5.2% (40 mg) and 5% (80 mg); and depression 6.2% (40 mg) and 2% (80 mg) (2) Any TEAEs leading to discontinuation were 13.4% for VBZ 40 mg and 17.8% for VBZ 80 mg	14
Jossiassen RC, *et al.*	(1) The most common TEAEs in the schizophrenia/schizoaffective disorder subgroup were UTI (6.1%), headache (5.8%) and somnolence (5.2%) (2) The most common TEAEs in the mood disorder subgroup were headache (12.4%), UTI (10.7%) and somnolence (9.1%); discontinuation due to AEs was 14.7%	17
Thai-Cuarto D, *et al.*	(1) Most common TEAEs were dizziness (1.8% with VBZ 40 mg, 0% with VBZ 80 mg, 2.2% with PBO) and fall (0.9% with VBZ 80 mg, 1.8% with VBZ 40 mg, 0% with PBO) (2) Most common TEAEs in VBZ extension period were dizziness (4.1% with VBZ 40 mg, 6.9% with VBZ 80 mg), fall (3.1% with VBZ 40 mg, 2.0% with VBZ 80 mg) syncope (3.1% with VBZ 40 mg, 1.0% VBZ 80 mg) and chest pain (2.1% with VBZ 40 mg, 2.0% with VBZ 80 mg)	18
O'Brien *et al.*	(1) Discontinuation due to TEAEs: 10% PBO, 10% VBZ (2) Serious TEAEs: 4% PBO, 0% VBZ (3) Any TEAE: 33% PBO, 49% VBZ (4) Three most common TEAEs (VBZ *versus* PBO): fatigue (10% *versus* 4%), headache (10% *versus* 4%), decreased appetite (8% *versus* 0%)	13
Grigoriadis *et al.*	(1) Discontinuation due to TEAEs: 13% VBZ 40 mg, 18% VBZ 80 mg (2) Serious TEAEs: 13% VBZ 40 mg, 16% VBZ 80 mg (3) Any TEAE incidence: 62% VBZ 40 mg, 76% VBZ 80 mg (4) Four most common TEAEs (combined VBZ 40 and 80 mg): headache (7%), UTI (7%), diarrhea (6%), dizziness (6%)	19
DBZ studies		
Fernandez HH, *et al.*	(1) Most common AEs for DBZ *versus* PBO were somnolence (13.8% *versus* 10.2%), insomnia (6.9% *versus* 1.7%) and akathisia (5.2% *versus* 0) (2) Only 1.7% of DBZ-treated patients had discontinuation of DBZ due to AEs compared with 3.4% patients receiving PBO	20
Anderson KE, *et al.*	(1) Most common AEs for DBZ (pooled all doses) *versus* PBO were nasopharyngitis (4.1% *versus* 1.4%), diarrhea (4.1% *versus* 2.8%), anxiety (3.6% *versus* 2.8%) and fatigue (2.7% *versus* 1.4%) (2) 5.4% patients on DBZ 6 mg b.i.d., 2.7% on 12 mg b.i.d. and 4.1% on 18 mg b.i.d. had discontinuation of DBZ due to adverse events compared with 2.8% patients receiving PBO.	21

AE, adverse event; COPD, chronic obstructive airway disease; VBZ, valbenazine; DBZ, deutetrabenazine; PBO, placebo; TD, tardive dyskinesia; TEAE, treatment-emergent adverse event; b.i.d., twice daily; q.i.d., four times a day; Ref., reference number; UTI, urinary tract infection.

(n = 117),[20] DBZ was started at 6 mg twice daily (b.i.d.) and titrated weekly by 6 mg/day, if required, for up to 6 weeks, followed by a maintenance phase of 6 weeks at the same dose. In the fixed-dose study (n = 298),[21] DBZ 6 mg b.i.d. (n = 75), 12 mg b.i.d. (n = 74) or 18 mg b.i.d. (n = 75) was administered; dose escalation of 6 mg/day through week 4 until the randomized dose was achieved, followed by a maintenance period for the subsequent 8 weeks. In both studies, the completion rate was ~90%.

These studies[20,21] included adults with a diagnosis of TD and DRBA for ⩾3 months, AIMS ⩾ 6 and stable underlying psychiatric illness. Stable regimens of psychoactive and other concomitant medications (except tetrabenazine, reserpine, α-methyl-p-tyrosine, strong anticholinergic medications, metoclopramide, dopamine agonists and levodopa) for medical or psychiatric comorbidities were permitted. The change in the AIMS score after 12 weeks of treatment was assessed by individuals with extensive experience in movement disorders through a blinded video rating system.

Change in the total AIMS score for items 1–7, from baseline to week 12 was used in both studies as the primary endpoint to test the efficacy and safety of DBZ. In the study by Fernandez and colleagues,[20] there was a significant decrease in TD severity ratings with DBZ *versus* placebo (p = 0.019; Table 2). LS differences between DBZ and placebo was −1.4 [95% confidence interval (CI) −2.6 to −0.2]. The proportion of patients who met a rigorous AIMS response threshold, defined as ⩾50% improvement in the total AIMS score from baseline, were significantly higher with DBZ *versus* placebo (23.2% *versus*. 17.5%). No statistically significant difference was found between DBZ *versus* placebo on the CGIC or Patient Global Impression of Change score.[18] Treatment with DBZ led to a twofold-higher odds of decreasing abnormal involuntary movements to 'minimal/extreme normal' in the lips/perioral area [50.0% *versus* 32.3%; odds ratio (OR) = 2.1], jaw (40.6% *versus* 21.7%; OR = 2.5), tongue (41.9% *versus* 29.4%; OR = 1.7), upper extremities (50.0% *versus* 33.3%; OR = 2.0), and neck, shoulders and hips (50.0% *versus* 41.7%; OR = 1.4) compared with the placebo.[20]

Similarly, in the study by Anderson and colleagues,[21] symptom improvement assessed by comparing baseline scores with scores after 12 treatment weeks was maintained in the AIMS total (Table 2). There was a significant improvement in TD symptom severity ratings with DBZ *versus* placebo (Table 2). LS differences between DBZ and placebo was −1.9 (95% CI −3.09 to −0.79; p = 0.001), −1.8 (95% CI −3.00 to −0.63; p = 0.003) and −0.7 (95% CI −1.84 to 0.42; p = 0.217) for DBZ 18 mg, 12 mg and 6 mg b.i.d., respectively. The proportion of patients who met a required AIMS response level, defined as ⩾50% improvement in the total AIMS score, were significantly higher with DBZ 12 mg (34.7%) and 18 mg (32.7%) *versus* placebo (12.1%). DBZ 12 mg b.i.d. and 18 mg b.i.d. showed clinical improvement from baseline in AIMS scores for patients with mood disorders like bipolar disorder and depression (LS mean change −3.1 and −3.6, respectively *versus* placebo −0.5) and schizophrenia/schizoaffective disorder (LS mean change −3.2 and −3.0, respectively *versus* placebo −1.9).

The most frequently reported side effects with DBZ in the study by Fernandez and colleagues[20] were somnolence, insomnia, and akathisia (Table 3). In the study by Anderson and colleagues,[21] nasopharyngitis and diarrhea (4.1% each) were the most common AEs. The efficacy summary based on VBZ studies is presented in Table 2 and its safety profile is in Table 3.

Limitations

A few limitations to this review were identified. As the studies compared were of different types, there was no way to perform a meta-analysis of their results. After thorough analysis, VBZ and DBZ were compared in a descriptive manner to assess and compare the safety and efficacy of each drug. Therefore, this is a qualitative review rather than a quantitative analysis. For this systematic review, MEDLINE was used due to its widespread use, but it is possible that the review was not entirely comprehensive if a paper was not published in this database. Despite these limitations, it is reasonable to conclude that the studies used in this systematic review are representative of published studies on VBZ and DBZ.

Conclusion

Studies on the use of DBZ and VBZ for treatment of TD specify that each of these VMAT2 inhibitors led to improvement in patients suffering from TD. Extended VBZ trials (up to 52 weeks) yielded persistently improved results on the AIMS total score for the duration of the study. Nevertheless,

the overarching evidence for long-term success of DBZ is limited, as there were only two available controlled studies of 12 weeks' duration. The clinical trials showing the ability to treat TD included both short-term and long-term studies and they were better designed and controlled than the studies with DBZ. Efficacy and tolerability were demonstrated in a series of randomized, placebo-controlled clinical trials in this review study and the AIMS response of ⩾50% reduction in score was strong for VBZ 80 mg/day.

On the contrary, DBZ was equally efficacious at the 12 mg b.i.d., but further assessment of longitudinal efficacy and continued symptom reduction is necessary. The recent approval of VBZ and DBZ as the first and second US-Food-and-Drug-Administration-approved psychopharmacologic medications to manage TD is likely to transform current psychiatric practice. Future research is needed to study the impact of VMAT2 inhibitors like VBZ and DBZ on TD and related movement disorders.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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