Tetrabenazine: Spotlight on Drug Review

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Key Words

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Abstract

Background: Tetrabenazine (TBZ) is the only US Food and Drug Administration-approved drug for the treatment of chorea related to Huntington's disease and other hyperkinetic disorders. TBZ was first synthesized in 1950, and was then used for the treatment of psychosis. But later its potential in treating hyperkinetic disorders was proved by its ability to block vesicular monoamine transporters 2 and deplete monoamine stores. There is still lack of awareness about the therapeutic potential of this drug. **Summary:** TBZ had been approved only for the treatment of chorea, but several clinical studies have been conducted by different research groups and it was concluded that TBZ is effective in various other conditions such as tardive dyskinesia, dystonia, tics, and Tourette's syndrome, thus, highlighting the need for further clinical trials in these conditions. **Key Message:** The intention of this review is to sum up the information regarding chemistry, mechanism of action, pharmacokinetics, interactions, contraindications, adverse effects, and clinical efficacy of TBZ in diseases other than Huntington's chorea.

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Introduction

Tetrabenazine (TBZ) is a dopamine-depleting agent. It is the only US Food and Drug Administration (FDA)-approved drug for the treatment of chorea coupled with Huntington's disease (HD) and other hyperkinetic disorders [1]. In August 2008, TBZ was approved by US FDA for the treatment of chorea under the brand name xenazine. TBZ is also available in Europe and Australia under the name xenazine, and in Canada under the name nitoman. Other countries where TBZ is marketed are Denmark, France, Germany, Ireland, Israel, Italy, New Zealand, Portugal, Spain, Switzerland, and United Kingdom (UK) [2].

History

O. Schneider and A. Brossi initially synthesized TBZ in 1950s at the research laboratory of Hoffmann-La Roche in Basel. TBZ was approved for the treatment of psychoses/schizophrenia in Finland, Netherlands, UK, and Switzerland, but it was soon outmoded by phenothiazines because physicians declared phenothiazines more efficacious [3, 4]. The effects of TBZ were similar to reserpine, which led to a clinical trial of TBZ in various involuntary movement disorders – such as Huntington's chorea,

Fig. 1. Structure of TBZ

hemiballismus, Torsion dystonia, and facial dyskinesias [5–7]. Finally in August 2008, TBZ was approved by US FDA for the treatment of chorea.

Chemistry

The chemical structure of TBZ is shown in figure 1. The chemical name of TBZ is 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo(a)quinolizin-2-one. TBZ has the molecular formula $C_{19}H_{27}NO_3$ and its molecular weight is 317.43.

Chemical and Physical Properties

TBZ is a white to light yellow crystalline powder with a bitter taste. It does not mix well with water, but is soluble in hot water, alcohol, and chloroform. Its melting range is 259–262°F, and it has pKa 6.51. Xenazine (TBZ) is supplied as a yellowish-buff scored tablet containing 25 mg of TBZ, or as a white non-scored tablet containing 12.5 mg of TBZ [8].

Mechanism of Action

Neurons consist of vesicles that store neurotransmitters, which are situated close to the end of each axon. Some neurotransmitters are synthesized directly in the vesicles whereas some others are synthesized in the cell body of neuron and subsequently shipped down into the vesicles for later release [9]. Due to storage inside vesicles, neurotransmitters have high levels in neurons and low levels in the synaptic cleft. This ensures a gradual and regulated release of neurotransmitters in the synaptic cleft from vesicles by the process of exocytosis [8]. Vesicular monoamine transporters (VMATs) are responsible for the translocation of cytosolic monoamines (serotonin, dopamine, norepinephrine, and histamine) into synaptic

vesicles in monoaminergic neurons [10]. There are 2 distinct subtypes of VMATs, namely VMAT1 and VMAT2. These subtypes have distinct pharmacological properties and tissue distribution. VMAT1 is mainly expressed in neuroendocrine cells and VMAT2 is chiefly expressed in the central nervous system (CNS) [11, 12]. Both reserpine and TBZ are considered as VMAT inhibitors.

TBZ is a potent VMAT2 blocker as shown in figure 2. TBZ binds reversibly to VMAT2, thereby interrupting its function. This interruption in turn inhibits the uptake of monoamines and prevents dopamine release from vesicles. Its action lasts for 16–24 h. The greatest binding density for TBZ is in the caudate nucleus, nucleus accumbens, and putamen areas [4]. Another mechanism by which TBZ acts is by blocking the presynaptic and postsynaptic dopamine receptors as shown in in vitro studies [13, 14]. On the contrary, another monoamine depletor—reserpine—binds irreversibly to both VMAT1 and VMAT2. This makes reserpine's duration of action considerably longer. Due to its VMAT1 binding, reserpine shows peripheral adverse effects such as orthostatic hypotension and diarrhea [2, 15].

Pharmacokinetics

TBZ can be administered without any concern about food since trials have shown that the mean peak plasma concentration (C_{max}) or area under the curve concentration is not affected by the administration of food following a single dose of TBZ [8]. TBZ undergoes rapid first-pass metabolism by hepatic carbonyl reductase to 2 compounds: alpha-dihydrotetrabenazine (α -HTBZ) and beta-dihydrotetrabenazine (β -HTBZ), which in turn are metabolized by cytochrome 2D6 (CYP2D6)-mediated O-demethylation. The α -HTBZ metabolite is active, while the β -HTBZ metabolite is chemically inert [16].

Oral bioavailability of TBZ was found to be in the range of 0.049 ± 0.032 and the mean absorption time was 481 ± 50 min [17]. After administration of single doses from 12.5 to 50 mg of TBZ, the maximum plasma concentration and the area under the curve for the metabolites α - and β -HTBZ increased approximately in proportion to the dose, which indicated linear kinetics [18].

A single oral dose of TBZ has been shown in clinical testing to undergo extensive (>75%) absorption from the gastro-intestinal tract. After oral administration, however, due to a high first-pass metabolism, the systemic bioavailability of TBZ is low but absorption is rapid within 1 h [8]. Both forms of HTBZ are less protein bound and have a high bioavailability than TBZ. Protein binding of

Fig. 2. Mechanism of action of TBZ.

HTBZ forms is 44–59% and TBZ is 83–88% [17]. TBZ has a half-life ($t_{1/2}$) of 10 h whereas its metabolites α -HTBZ and β -HTBZ have a half-life ($t_{1/2}$) of 2–8 and 2–5 h, respectively [16]. At clinically appropriate concentrations in vivo, TBZ and its α -HTBZ or β -HTBZ metabolites are not likely to be a substrate or inhibitor of P-glycoprotein and do not inhibit or induce CYP enzymes [8].

TBZ gets metabolized after oral administration, and the metabolites eliminate primarily via the renal route. A mass balance study was conducted in 6 healthy volunteers. According to the data obtained, the excretion of 75% (approximately) of the dose was through urine and approximately 7–16% was by fecal recovery. No TBZ in the unchanged form has been found in human urine [8]. In urinary excretion, less than 10% of the administered dose has been reported from α -HTBZ or β -HTBZ. Rest of the metabolites consists of circulating metabolites, including sulfate and glucuronide conjugates of HTBZ metabolites and oxidative metabolism products [19].

Dosage Administration

Individualized Dosing in Adults

The dose for an individual patient should be titrated carefully to select the most suitable dose. The individualized dose can be selected by titrating the dose weekly until that dose is observed which seems beneficial for controlling chorea and is well tolerated [20]. Initial recommended dose of TBZ is 12.5 mg once daily in the morning. Then a dose of 12.5 mg twice a day in the morning and evening is used in the subsequent week. The dose should be increased by 12.5 mg every week till the best effective and tolerated dose is selected [16]. If any patient needs more than 37.5–50 mg TBZ dose per day, then the dosing should be divided in regimen of 3 times a day [21]. Maximum limit for each dose is 25 mg. Patients who require more than 50 mg/day should be tested for CYP2D6 genotype. More than 100 mg/day of TBZ is not advised for any patient [22].

Tapering of dose is not required for the discontinuation of TBZ therapy. Chorea can recur within 12–18 h after taking the last dose of TBZ. Re-titration of TBZ dose is required if the treatment is suspended for more than 5 days. But if the treatment is resumed within 5 days, then there is no need for re-titration, and the previous maintenance dose can be selected [21].

Dosing Recommendations Above 50 mg/day in Extensive/Intermediate Metabolizers

Similar method of titration will be followed by increasing the dose weekly by 12.5 mg till the effective and tolerated dose is selected. Doses should be divided into 3 times a day regimen. One hundred milligrams is considered as the maximum recommended daily dose and 37.5 mg is considered as the maximum single dose for this group [19].

Dosing Recommendations Above 50 mg/day in Poor Metabolizers

The method of titration is the same as that of extensive or intermediate metabolizers. The only difference is in the maximum recommended daily dose and maximum single dose. Fifty milligrams is considered as the maximum recommended daily dose and 25 mg is considered as the maximum single dose for this group [19].

Adverse Effects of TBZ

The common side effects of TBZ are somnolence, acute akathisia, insomnia, fatigue, agitation, depression, anxiety, nausea, diarrhea, and parkinsonism [16, 23]. These side effects can be controlled by titrating or reducing the dose of TBZ. Because of this reason, these side effects are termed as dose limiting side effects [3].

Other types of side effects are rare and include panic attacks, orthostatic hypotension, mental problems, balance and gait difficulties, hallucinations, confusion, 'trance-like/zombie', blurred vision, dizziness, headaches, paresthesias, paranoia, pharyngeal spasm, and pain [24].

TBZ leads to serious risks such as suicidal ideation, depression, and neuroleptic malignant syndrome (NMS). TBZ is available with black box warning because TBZ can result in depression or can deteriorate an already present depression [20]. A controlled trial conducted in HD included 54 patients, out of which 19% were receiving TBZ; 19% of the total 54 patients showed occurrence of depression whereas in placebo group none of the patients experienced depression. Moreover, suicide was

committed by one patient and suicidal ideation was experienced by one patient. However, in the placebo group no prevalence of these effects was found [25].

Special Populations Pregnancy

In humans, no specific well controlled studies have been conducted during pregnancy, so evidences for safety are not present. TBZ crosses placenta, therefore it should not be prescribed during pregnancy. TBZ is classified as pregnancy category C drug [21].

Lactating Mothers

TBZ is also secreted in breast milk, but it is not clearly identified that it is TBZ or its metabolite that is secreted in human milk. The choice about discontinuing the TBZ therapy should be made according to the condition of patient [20, 21].

Pediatrics

Limited published reports are available regarding the effects of TBZ on the pediatric population. In a study, 5 children of age between 22 months and 10 years, suffering from severe chorea; were administered with TBZ. It was reported that chorea was efficiently controlled and TBZ was well tolerated by 4 patients, but comparatively high doses were required [26].

Geriatrics

No specific controlled studies have been conducted in the geriatric population [20].

Renal Insufficiency

No controlled pharmacokinetic studies have been performed in patients with renal impairment [27].

Hepatic Insufficiency

A study compared 12 patients having liver disease (mild to moderate) with Child–Pugh scores of 5–9 and 12 normal healthy subjects of same age and gender; and a dose of 25 mg of TBZ was administered [19]. Metabolism of TBZ to its metabolite was decreased in hepatically impaired patients. The plasma concentration of TBZ was either the same or more in the group of hepatic disease patients as compared to normal subjects. The elimination half-life of TBZ was extended to 17.5 h and of α -HTBZ and β -HTBZ was extended up to 10 and 8 h, respectively in hepatically impaired group. The main TBZ peak concentration (C_{max}) was found to be 7–190 folds greater in the group with hepatic disease than that of normal subjects. On the whole, the exposure of metabolites of TBZ (α -HTBZ and β -HTBZ)

was more (30–39% approximately) in patients with hepatic impairment as compared to the healthy group [19].

TBZ is contraindicated in patients with liver disease as it is not feasible to adjust the dosage of TBZ to ensure safe use.

Drug Interactions

- The metabolites of TBZ, α -HTBZ and β -HTBZ, are metabolized by isoenzyme CYP2D6. The concomitant use of TBZ with CYP2D6 inhibitors and inducers can affect the metabolism of these metabolites. Dose reduction of TBZ is necessary when CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) are administered to a patient who is already on TBZ therapy. The maximum single dose of TBZ should not exceed 25 mg and the daily dose should not exceed 50 mg per day in patients taking strong inhibitors of CYP2D6 isoenzyme [16, 21, 27].
- Both reserpine and TBZ are VMAT2 inhibitors; thus, their concomitant use should be avoided. Caution should be taken when changing the therapy from reserpine to TBZ for any patient because of longer action duration and irreversible binding of reserpine to VMAT2. A period of 20 days is recommended between stopping of reserpine therapy and before starting of TBZ therapy [8, 23].
- The use of TBZ in combination with neuroleptics, antibiotics, Class IA and III antiarrhythmics increases the risk of QTc prolongation. Additionally, extrapyramidal effects and NMS are also observed in cases of concomitant use of TBZ with neuroleptics [23].
- Several drug interactions of TBZ have been reported with antidepressant drugs. Concomitant use of TBZ and monoamine oxidase inhibitors (MAOIs) can lead to CNS toxicity including confusion, restlessness, and behavioral alterations [27]. Use of TBZ along with tricyclic antidepressants can antagonize TBZ-induced locomotor activity in animals [20, 28].
- Co-administration with alcohol may worsen the sedation caused by TBZ [21].
- TBZ should be cautiously administered along with antihypertensives and β -blockers, because it may enhance the danger of orthostatic hypotension [20].

Indications

TBZ has been approved by US FDA for the treatment of HD-related chorea.

Contraindications

TBZ is contraindicated in patients who are vigorously suicidal, or patients without treatment or with insufficiently treated depression [23]. TBZ is also contraindicated in patients having weakened hepatic function. TBZ administration along with reserpine and MAOIs is contraindicated because it may worsen the condition [19]. TBZ should not be administered before 14 days of discontinuing MAOI therapy and not before 20 days of discontinuing reserpine therapy. The combination of TBZ and alcohol is contraindicated due to additive sedation [21].

Warnings and Precautions

Dosage of TBZ in patients should be considered cautiously. The need for TBZ therapy should be re-examined once in a while in patients by checking the advantageous effects on chorea and the symptoms due to worsening of disease [23]. The dose should be quantified carefully up to the dose that is beneficial in patient because some of the observed side effects are dependent on dose [21]. To increase the daily dose of patient above 50 mg, CYP2D6 gene should be tested for the metabolic nature of the patient. If the patient is a poor metabolizer, then the exposure will be considerably higher after taking TBZ (α -HTBZ by 3-fold and β -HTBZ by 9-fold) as compared to extensive or intermediate metabolizers [19].

TBZ has the potential to cause NMS because of its dopamine transmission reducing ability. The clinical manifestations of this syndrome include mental changes, muscle rigidity, hyperpyrexia, autonomic dysfunction (irregular blood pressure and sweating), and raised creatinine phosphokinase levels [20]. TBZ can worsen depression and suicidal thoughts, due to which it comes with a black box warning.

Clinical Studies in Movement Disorders

Huntington's Chorea

Evidence of therapeutic potential of TBZ in HD chorea was initially published in 1960s [5, 29, 30]. Since then, several long- and short-term studies have been conducted and published that proves the beneficial role of TBZ in chorea patients [3].

Short-Term Studies

A study in 2006 was conducted by the Huntington's study group, which was a multicenter double-blind, randomized, placebo-controlled trial of 12 weeks to check

the safety, tolerability, and efficacy of TBZ for the treatment of chorea. A total of 84 patients aged 27–77 years having a score of >5 on Total Functional Capacity Scale and a score of ≥ 10 on Unified Huntington's Disease Rating Scale (UHDRS) were enrolled in the trial. Fifty four patients were randomly included in the TBZ group and the remaining 30 patients were included in the placebo group. The starting dose was 12.5 mg/day, which was then increased every week by 12.5 mg till the 7th week until the chorea was efficiently controlled, intolerable side effects came up or a dose of 100 mg/day was reached. This was considered as the titration period. Then the dose was left unaltered for the remaining 5 weeks until the patient became intolerable to the adverse effects, and this period was considered as the maintenance period. On UHDRS, alteration from baseline in the total maximal chorea score was measured as the chief efficacy outcome. TBZ group showed a decrease of 5.0 units in chorea and placebo group showed a reduction of 1.5 units as compared to the baseline. On Clinical Global Impressions Improvement Scale, 24% of subjects of placebo group attained a score of ≤ 3 as compared to 69% of subjects of TBZ group. This finding also suggested superiority of the TBZ group over the placebo group. At the end of the washout period, no distinction between TBZ and placebo groups was observed when compared in terms of baseline for cognitive, motor, and behavioral severity. In the treatment group, stopping the TBZ therapy worsened the existing chorea. TBZ was well tolerated by all the subjects. However, insomnia and drowsiness were common adverse effects. Moreover, dose was decreased in some cases as 2 patients reported depressed mood, 2 patients reported parkinsonism, and 4 patients reported akathisia. One subject of TBZ group committed suicide during the study, but his rating on the Hamilton Depression Scale was normal from previous assessments [31].

Another short-term study was conducted in 2007 by Kenney et al. [32]. Ten patients were included in this study (range between 35 and 71 years of age). The included patients had enough disability due to chorea for it to be measured. Inclusion in the study required stable TBZ dosing in subjects. Last dose of TBZ was given in the evening to the subjects and they were included in the study the subsequent day. Baseline assessment was done after 12 h of last evening dose. UHDRS motor assessment and Beck Depression Inventory was used for baseline assessment. Then the morning dose was administered to the subjects and assessment was done after every 2 h with UHDRS until the baseline chorea re-emerged. After the TBZ administration, UHDRS chorea score diminished

on an average by $42.4 \pm 17.8\%$. The mean duration of effect was found to be 5.4 ± 1.3 h [32].

In 2008, another short-term, randomized, double blind study was performed and published by Frank et al. [33]. This study proved that chorea re-emerges after the withdrawal of TBZ due to short half-life. Thirty patients (ages between 39 and 75 years) who were taking TBZ for the previous 2 months were enrolled in the study. The study lasted for 5 days. Participants were randomly divided into 3 different groups. The first group was the withdrawal group with 12 patients, in which TBZ was withdrawn on the 1st day of study. The second group was a partial withdrawal group with 12 patients, where TBZ was withdrawn on the 3rd day. In the last group that consisted of 6 patients, there was no withdrawal. This group remained on TBZ all 5 days. The UHDRS chorea scores were increased by 5.3 units from 1st to 3rd day in subjects from the withdrawal group. On the contrary, the UHDRS scores of partial or no withdrawal group were increased by 3.0 units ($p = 0.0773$). A post-hoc analysis illustrated a linear trend for the re-emergence of chorea ($p = 0.0486$) [33].

Long-Term Studies

A long-term retrospective study was conducted by Fasano et al. [34] in 2008. Sixty eight HD patients having mean disease duration of 55.8 ± 34.7 months and mean age at onset of HD of 43.3 ± 11.8 years were included in the study. TBZ dose was increased weekly up to a maximum dose of 150 mg/day. Patients treated with TBZ had 35.3 ± 14.7 mg as mean dose at first follow-up and had 57.5 ± 14.7 mg as mean dose at last follow-up. The baseline for UHDRS motor scale was noted as 39.4 out of 120 and the mean UHDRS chorea score was noted as 10.4 out of 28. The mean UHDRS chorea score was 8.2 ± 4.1 during the first follow-up and was 9.5 ± 5.0 during the last follow-up. This showed a significant reduction as compared to the baseline score. TBZ dose was increased by 63%, and the mean UHDRS motor scores showed an increase by 32% as compared to the baseline. Thirty four patients stated at least one side effect from the most common ones and 2 patients withdrew from the study due to side effects (psychiatric disturbance and asthenia). TBZ was discontinued in 5 patients due to lack of any beneficial effect [34].

Tardive Dyskinesia

The American Psychiatric Association Task Force defined tardive dyskinesia (TD) as an abnormal involuntary hyperkinetic movement, which occurs in a patient taking neuroleptic treatment (minimum of 3 months) with no additional particular basis for movement disorders [35].

Table 1. Clinical trials of TBZ in TD

Study design	Numbers	Mean TBZ dosage, mg/day	Outcome	Study
Randomized, double-blind, crossover versus placebo	6	100	50% patients from TBZ group had improved movements as compared to 0% from placebo group	[50]
Open-label, single-blind, crossover versus placebo	24	122.5	Abnormal movements were vanished in 33% patients and were attenuated in 25% patients	[51]
Open-label, single-blind, placebo controlled, crossover	10	175	Clear or moderate improvement in abnormal movements in 60% patients	[52]
Randomized, double-blind, placebo-controlled, crossover	4	200	100% patients showed improvement	[53]
Open-label	23	91.3	100% patients showed improvement in movement	[54]
Open-label, single-blinded	20	57.9	The mean score on the Abnormal Involuntary Movement Scale (AIMS) motor subset improved 54.2%, and the subjective scores improved 60.4%. 855 patients showed marked improvement	[55]
Retrospective	17	Not reported	41% patients showed improvement in movement	[56]
Retrospective	149	Not reported	84% patients showed improvement	[57]

There was continuous exposure to dopamine receptor blocking agents such as neuroleptic drugs (typical and atypical), antiemetics and agents used for disorders of gastrointestinal tract (e.g., promethazine and metoclopramide), calcium channel blockers (flunarizine, cinnarizine), and tricyclic antidepressants (e.g., amoxapine) [36]. The term includes various phenotypes such as stereotypy, dystonia, akathisia, orofacial lingual movements, myoclonus, and tremors [28].

Several small, blinded, randomized trials were carried out to check the efficacy of different drugs in TD and TBZ is one of them. Since 2008, after the FDA approval for the use of TBZ in Huntington's chorea, TBZ became the drug of choice for the treatment of moderate to severe condition of TD [37]. Several studies were conducted to check the effectiveness of TBZ in TD and are discussed in table 1.

TBZ is well tolerated in terms of safety. It has a short half-life and moreover, most of the adverse effects such as parkinsonism, depression, drowsiness related to TBZ are dose limiting. So TBZ may emerge as a safe drug for different phenotypes of TD in future [38].

Tic and Tourette's Syndrome

'Tic disorder' is a term coined for a medical state which embodies a particular form of repetitive, non-rhythmically recurrent, stereotyped, chiefly involuntary

movement [39]. The American Psychiatric Association published The Diagnostic and Statistical Manual of Mental Disorders (5th ed) in 2013 and enlisted Gilles de la Tourette syndrome (TS) as one of the key tic disorder [40]. The indications of TS are wide-ranging including motor and non-motor (emotional and cognitive abnormalities) disturbances. Motor and vocal tics for more than 1 year with tic-free phase of less than 3 successive months are prominent diagnostic attributes of TS, which start up sooner than the age of 18 [39, 41]. Reports from the start of TS research suggest its connection with dopamine system dysfunctioning [42]. Agents such as α -adrenergic agonists (e.g., clonidine), antipsychotics (typical and atypical), dopamine agonists (e.g., pergolide), anticonvulsants (e.g., topiramate) have been used to decrease the severity of TS, and TBZ is also one of them [43, 44]. Various open-label, non-randomized, retrospective studies have been carried out to check the efficacy of TBZ in the treatment of TS but the limitation is that no randomized, controlled study has been conducted. Studies conducted thus far are listed in table 2.

Dystonia

Dystonia is a neurological disorder identified by unnecessary, involuntary, repetitive sustained contraction of muscles, leading to twisting movements and unnatural

Table 2. Clinical trials of TBZ in Tic and Tourette's syndrome

Study design	Numbers	Mean TBZ dosage, mg/day	Outcome	Study
Non randomized, open-label, crossover	7	270	Only 40% patients showed improvement	[58]
Open-label, retrospective	9	82	78% patients showed improvement, out of which 44% patients had an improvement duration for >6 months and 33% had for <6 months	[59]
Retrospective	15	Not reported	80% patients showed improvement	[60]
Retrospective	17	81.6	94% showed improvement	[61]
Retrospective	47	83.5	57.4% patients showed improvement	[24]
Retrospective	9	Not reported	Improvement was only seen in 33% patients	[56]
Retrospective	77	50.4	83% patients showed improvement	[57]
Open-label, prospective	120	70.5	76% patients showed improvement	[62]

Table 3. Clinical trials of TBZ in dystonia

Study design	Numbers	Mean TBZ dosage, mg/day	Outcome	Study
Prospective, single-blind	9	128	Only 38% patients were improved	[7]
Single-blind, placebo controlled, crossover	8	175	37.5% patients showed improvement	[52]
Double-blind, randomized, placebo controlled, crossover	12	162.5	Improvement was seen in about 92% patients	[53]
Retrospective	14	Adult: 90 Pediatric: 75	71% patients improved	[63]
Retrospective	15 19 57 25 5 3	Tardive dystonia: 155.4 Generalized dystonia: 114.5 Cranial dystonia: 109 Focal dystonia: 119 Essential blepharospasm: 85 Hemidystonia: 150	Marked or moderate improvement was noticed in 76% patients	[61]
Retrospective	41	Not reported	Improvement was seen in 49% patients	[56]
Retrospective	132	50.4	68% patients showed improvement	[57]

postures [45, 46]. Dystonia can be classified on the basis of the age of onset (early and late), distribution (focal, segmental, multifocal, hemi, generalized), and cause (primary, secondary, as a mark of another neurologic disorder, pseudo dystonia) [47]. Treatment options available for dystonia include dopaminergic agents (e.g.,

levodopa), antidopaminergic agents (e.g., clozapine, TBZ), anticholinergics (e.g., trihexyphenidyl), muscle relaxants (e.g., clonazepam, baclofen), botulinum toxin, and deep brain stimulation of globus pallidus interna [48, 49]. Some of the conducted studies are discussed in table 3.

Other Disorders

TBZ has been tested in various other disorders such as myoclonus and hemiballismus. Only a few studies have been performed in myoclonus, hemiballismus, and other movement disorders [24, 57]. More trials need to be conducted to check the effect of TBZ in these disorders.

Conclusion

TBZ, a VMAT2 blocker, diminishes monoamine stores. It has proven its potential through clinical trials in several hyperkinetic disorders including TD, tic and Tourette's syndrome, dystonia, and myoclonus. Currently, TBZ is only approved for the treatment of chorea in the US. Common side effects include insomnia, depression, parkinsonism, akathisia, and NMS.

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Authors Contributions

N.K.: literature review, data collection, and article writing; S.J.: literature review, data collection, and article writing; R.D.: data interpretation and critical revision of article; P.K.: data interpretation and critical revision of article.

Disclosure Statement

The authors have no conflict of interest.

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