New Drug Review

Tetrabenazine for the Treatment of Hyperkinetic Movement Disorders: A Review of the Literature

Jack J. Chen, PharmD, FCCP, BCPS, CGP[1]; William G. Ondo, MD[2]; Khashayar Dashtipour, MD, PhD[3]; and David M. Swope, MD[3]

[1]Movement Disorders Clinic, Loma Linda University, Schools of Medicine and Pharmacy, Loma Linda, California; [2]Department of Neurology, University of Texas Health Science Center–Houston, Houston, Texas; and [3]Department of Neurology, Loma Linda University, Loma Linda, California

ABSTRACT

Background: Tetrabenazine (TBZ) is a monoamine storage inhibitor that was first introduced in the 1970s for the management of hyperkinetic movement disorders. Despite acceptance and usage worldwide, TBZ was only recently approved in the United States for the treatment of Huntington chorea. This review focuses on the use of TBZ in various hyperkinetic movement disorders, which are considered "rare" or "orphan" diseases, to help practitioners better understand its clinical role and use.

Objective: This review describes the clinical efficacy and tolerability of TBZ in the management of dystonia, Huntington chorea, tardive dyskinesia (TDk), and tic disorders.

Methods: A Cochrane Library, EMBASE, MedlinePlus, PubMed, and clinical trials database search (up to May 2012) was conducted to identify articles and studies using the subject terms *tetrabenazine, Huntington disease, dystonia, tardive dyskinesia, Tourette, tics*, and *hyperkinetic movement*. Only English-language articles were reviewed.

Results: TBZ variably undergoes extensive first-pass metabolism to active metabolites, some of which are metabolized by the cytochrome P450 2D6 isozyme. Pharmacology studies demonstrate that TBZ reversibly inhibits the activity of vesicular monoamine transporter 2, resulting in depletion of central dopamine. For management of dystonias, 1 of 3 small prospective blinded studies and 4 of 5 retrospective studies reported clinical benefit with TBZ use in pediatrics and adults. For Huntington chorea, 2 randomized, double-blind, placebo-controlled studies along with open-label studies demonstrate the effectiveness of TBZ in adults. For TDk, 9 of 11 studies (prospective controlled and retrospective) reported positive benefit. For Gilles de la Tourette syndrome, 9 of 11 studies (prospective controlled and retrospective) reported positive benefit on motor and phonic tics in pediatric and adult patients. Overall, adverse effects are dose and age related and include depression, fatigue, parkinsonism, and somnolence.

Conclusions: TBZ is an effective oral therapy for chorea of Huntington disease and may be considered as an alternative agent for the management of dystonia, TDk, and tic disorders (these latter 3 conditions are off-label uses in the United States). The drug possesses an acceptable tolerability profile and has been used in pediatric and adult populations. (*Clin Ther*. 2012; 34:1487–1504)

Key words: dystonia, Huntington disease, tardive dyskinesia, tetrabenazine, tics.

INTRODUCTION

Hyperkinetic movement disorders is a general term used to describe a wide array of movement disorders characterized by excessive repetitive or sporadic involuntary movements.[1] Examples include chorea (eg, Huntington disease [HD]), dystonia, stereotypies (eg, tardive dyskinesia [TDk]), and tic disorders (eg, Gilles de la Tourette syndrome [TS]). These disorders are considered "rare" or "orphan" diseases.[2] The specific pathophysiology of these disorders is diverse and

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poorly understood; however, the basal ganglia and dysregulation of neurotransmitters, including dopamine, seem to be involved.[3]

In the United States, only tetrabenazine (TBZ) is indicated by the US Food and Drug Administration (FDA) for chorea of HD, haloperidol and pimozide for TS, and botulinum toxin injectable for idiopathic focal dystonias.[4–7] No drug is FDA approved for TDk. Traditionally, the oral pharmacologic therapies for the various hyperkinetic movement disorders have provided mixed or modest benefits and are limited by adverse effects.[4–7]

TBZ is a benzoquinolizine pharmacophore that selectively depletes monoamines and improves hyperkinetic movement symptoms.[8] Although initially tested as a potential antiparasitic agent as well as a potential antihypertensive, TBZ was first marketed in Switzerland in 1959 as a tranquilizer. Clinicians soon observed that TBZ improved hyperkinetic movements and, in 1971, the United Kingdom and Ireland were the first countries to market TBZ for hyperkinetic movement disorders. Subsequently, TBZ become available in several countries for official use in various hyperkinetic movement disorders (**Table I**). In 2008, the United States approved TBZ for the management of chorea associated with HD. A literature search revealed that recent TBZ review articles primarily highlight its role in the management of HD chorea,[9–13] and 1 review focused on the off-label use of TBZ for TDk.[14] Two recent reviews of TBZ summarized efficacy and tolerability for a broader range of hyperkinetic movement disorders.[8,15]

The current review summarizes the efficacy and tolerability of TBZ across 4 hyperkinetic movement disorders (dystonia, Huntington chorea, TDk, and tic disorders) and includes analysis of recently published clinical data not provided in previous reviews. An increased awareness of the role of TBZ in hyperkinetic movement disorders will enable clinicians to better understand the available treatment options for these orphan diseases.

Table I. Tetrabenazine: indications for movement disorders.

Country	Indications
Australia	Chorea, dystonia, hemiballismus, TDk
Canada	Hemiballismus, HD chorea, senile chorea, TDk, tics, Gilles de la Tourette syndrome
Denmark	Hyperkinesias
France	Hemiballismus, HD chorea
Germany	HD chorea, TDk
Ireland	Hemiballismus, HD chorea, senile chorea
Israel	Movements disorders disabling or socially embarrassing
Italy	HD chorea, TDk
New Zealand	Hemiballismus, HD chorea, senile chorea, TDk
Portugal	Hemiballismus, HD chorea, senile chorea, TDk
United Kingdom	Hemiballismus, HD chorea, senile chorea, TDk
United States	HD chorea

TDk = tardive dyskinesia; HD = Huntington disease.

METHODS

A Cochrane Library, EMBASE, MedlinePlus, and PubMed search (up to May 2012) was conducted to identify articles using the subject terms *tetrabenazine, Huntington disease, dystonia, tardive dyskinesia, Tourette, tics*, and *hyperkinetic movement*. References within articles and drug information from the manufacturer were also used to identify relevant literature. Only data in English and from published or "in press" literature were included for the discussions on TBZ efficacy and tolerability. A clinical trials database (http://clinicaltrials.gov) was used to identify ongoing relevant studies. Case reports, case series, and open-label studies (involving <5 TBZ-treated patients) were included for discussion about tolerability and safety but excluded from efficacy analysis. Supplemental clinical information was also identified by the authors, who were movement disorder specialists with clinical experience using TBZ for hyperkinetic indications.

CLINICAL PHARMACOLOGY

TBZ (chemical name: 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo(a)quinolizin-2-one) has chiral centers at the 3 and 11b carbon atoms and can theoretically exist in 4 isomeric forms (*RR*, *SS*, *RS*, and *SR*).[10] Commercially available TBZ is a racemic mixture of the *RR* and *SS* isomers. After oral administration, TBZ is rapidly absorbed within 1 hour;

however, the systemic bioavailability of the parent drug is low (5%) due to a high first-pass metabolism.[16] TBZ undergoes first-pass metabolism, by hepatic carbonyl reductase, to at least 2 isomers of dihydrotetrabenazine (DHTBZ): α-DHTBZ and β-DHTBZ.[17] Both metabolites are pharmacologically active, with α-DHTBZ demonstrating activity similar to the parent drug.[9] Both metabolites reach C_{max} within 1 to 2 hours and are primarily metabolized by cytochrome P450 (CYP) 2D6 (CYP2D6). The $t_{½}$ of α- and β-DHTBZ ranges from 2 to 8 hours and 2 to 5 hours, respectively.[9,10]

In humans, the steady-state AUC values of the DHTBZ metabolites are 82.6- to 199-fold higher than that of TBZ.[18] In rats, the mean (SD) V_d of DHTBZ is 7.8 (4.08) L/kg. Protein binding of TBZ, α-DHTZ, and β-DHTBZ range from 82% to 85%, 60% to 68%, and 59% to 63%, respectively.[9]

Neither TBZ nor its metabolites induce or inhibit major CYP450 isozymes. Therefore, TBZ will not interfere with metabolism of other drugs that are CYP450 substrates. However, because some of the DHTBZ metabolites are substrates for CYP2D6, other drugs that induce or inhibit this isozyme may alter DHTBZ concentrations.[9,10]

The primary pharmacologic action of TBZ and its active metabolites is to inhibit the human vesicular monoamine transporter 2 (VMAT2). The function of VMAT is to transport monoamines (eg. dopamine, serotonin, norepinephrine) from the cellular cytoplasm into synaptic vesicles.[19,20] There are 2 human isoforms of this transporter: VMAT1 and VMAT2. VMAT1 is primarily in peripheral endocrine and paracrine cells. The VMAT2 transporter is predominantly expressed in the brain.[21] Inhibition of VMAT2 prevents translocation of neurotransmitter monoamines from the cytoplasm into synaptic vesicles; therefore, the monoamines are exposed to premature degradation. The binding of TBZ and DHTBZ stereoisomers to VMAT2 is stereospecific, and each isomer may have different pharmacologic and/or toxicologic profiles, which remain to be determined.

Preclinical as well as positron emission tomography studies in humans demonstrate that α-DHTBZ retention and binding is greater in monoaminergic regions of the basal ganglia (eg, locus coeruleus, raphe nuclei, striatum, substantia nigra) than in extrastriatal sites (eg, cerebellum, cortex, thalamus), in which binding is ~70% lower.[22–25] In vivo imaging in humans also shows that α-DHTBZ, but not β-DHTBZ, binds to the striatum.[24]

In a comparative postmortem brain tissue analysis, TBZ-treated patients with HD had 67% lower concentrations of striatal (caudate) dopamine than the HD patients not treated with TBZ (1113 vs 3281 ng/g tissue, respectively; $P < 0.01$).[26] Although TBZ is often referred to as a monoamine depletor, it more accurately is a monoamine storage inhibitor. After a single dose, the onset of action occurs within 60 minutes, and the duration of inhibition ranges from 16 to 24 hours.[10] In addition to VMAT2 transporter inhibition, TBZ also alters serotonin 5-HT2 and β-adrenoceptor density and is a weak postsynaptic dopamine-2 receptor antagonist.[27] We suspect that because TBZ has only a weak affinity for dopamine-2 receptors, this may not play a significant role in its mechanism of action for management of hyperkinetic movements.

Pharmacologic reduction of central monoamines has demonstrated behavior affects such as decreased locomotor activity and aggression in animals.[28] TBZ also has been shown to inhibit conditioned avoidance reactions, decrease nondiscriminated avoidance procedures, and slow spontaneous electroencephalography activity in animals.

Reserpine is another drug that inhibits VMAT.[28] However, reserpine is an irreversible inhibitor of VMAT2 as opposed to TBZ, which is a reversible inhibitor. TBZ and its active metabolites demonstrate a 10,000-fold higher binding affinity for VMAT2 than for VMAT1, unlike reserpine, which exhibits comparable binding affinities for VMAT1 and VMAT2.[10] In addition, TBZ and its metabolites do not seem to exert significant monoamine-depleting effects in peripheral tissues.[10,29]

These differences are important because the nonselectivity and site of activity of reserpine (including inhibition of VMAT1 expressed in neuroendocrine cells and α-receptors) is hypothesized to contribute to adverse effects such as diarrhea, erectile dysfunction, orthostatic hypotension, and nasal congestion.[29]

CLINICAL EXPERIENCE

Chorea of HD

Chorea is a syndrome characterized by brief, unpatterned involuntary movements resulting from a continuous flow of random muscle contractions. The pattern of movement may sometimes seem playful, conveying a feeling of restlessness to the observer. When choreic movements are more severe—assuming a flinging, sometimes violent, character—they are called ballism. Chorea caused by different conditions is phenomeno-

logically similar.[30] There are hundreds of causes of chorea, including both genetic (eg, HD) and secondary (eg, drug-induced) etiologies. HD is the most frequent cause of genetic chorea, with reported prevalence rates in North America and Europe ranging from 3 to 7 per 100,000 persons.[30]

Clinical Features of HD

HD is characterized by a triad of movement disorder, cognitive decline, and behavioral changes. The presence of concomitant motor and behavioral features of HD is important to consider against TBZ efficacy and adverse effects. Although chorea is the prototypical movement disorder in HD and is usually present with middle-age or elderly onset, the full spectrum of motor impairment in HD includes eye movement abnormalities, parkinsonian features and dystonia (particularly in juvenile HD), myoclonus, tics, ataxia, dysarthria and dysphagia, and spasticity with hyperreflexia and extensor plantar responses.[31–34]

In very advanced disease, chorea is often superseded by dystonia and akinesia.[35] One study demonstrated that dystonia is found in >90% of patients with HD, although only rarely does it become as prominent as in idiopathic dystonias.[35] Falls occur in 60% of patients and are correlated with motor deficits, cognitive decline, and behavioral changes.[36] Behavioral impairment is almost universal in HD and may occasionally antedate motor manifestations. Major depression is common, diagnosed in >40% of subjects, and along with marked impulsivity, may be responsible for increased suicide rates in HD. Suicide is actually more common in earlier stages of the disease and does not correlate with motor impairment. The spectrum of behavioral abnormalities in HD is broad and includes impulsivity, anxiety or panic attacks, obsessive-compulsive symptoms, manic features, psychosis, irritability and aggressive behavior, sexual disinhibition, and apathy.[37–41]

Patients with HD almost universally go through cognitive decline, mental slowing, impaired problem-solving abilities, and other signs of a frontal dysexecutive syndrome, and they eventually become demented. These patients present with the prototype of so-called subcortical dementia.[42–44] HD is relentlessly progressive, with death occurring 5 to 30 years after symptom onset. Patients with end-stage HD are typically rigid and akinetic, demented, and mute. Immobility and dysphagia often lead to aspiration pneumonia, the most common cause of death in these patients.[45,46]

Etiology and Pathogenesis of HD

HD is caused by a trinucleotide (CAG) repeat expansion in the gene encoding for huntington on chromosome 4p16.3. It is widely expressed within the brain, but the exact function of normal huntingtin is still unknown.[47] Repeat CAG expansions of 40 or more cause HD with complete penetrance. Individuals with 36 to 39 repeats may also develop HD, but penetrance is incomplete.[48] Rarely, HD is associated with repeat expansions of less than 35.[49–51]

Neurodegeneration in HD most prominently affects the striatum with loss of medium spiny neurons and layers III, IV, and V of the cortex with loss of large neurons, and is characterized by the presence of intranuclear inclusion bodies consisting of amyloid-like fibrils that contain mutant huntingtin, ubiquitin, synuclein, and other proteins.[52–54] The mutant protein has been shown to form nuclear aggregates but how this leads to neurodegeneration remains unclear. Current evidence suggests that formation of aggregates of huntingtin is not primarily responsible for neuronal loss in HD. Alternative hypotheses suggested include transcriptional dysregulation, excitotoxicity, altered energy metabolism, impaired axonal transport, and altered synaptic transmission.[55]

Management of HD-Associated Chorea

Symptomatic treatment of chorea is needed if it causes functional disability or social embarrassment. With the exception of TBZ, a variety of available agents (eg, amantadine, neuroleptics, atypical antipsychotics) have been used, with inconsistent or little benefit.[4,56,57] Surgery, such as pallidotomy or pallidal stimulation, has been used for medically refractory cases of HD chorea.

Amantadine and Neuroleptic Agents

Despite a lack of robust clinical trial data, amantadine and neuroleptic agents are commonly used for symptomatic management of chorea in HD.[4,56] Based on the hypothesis that chorea of HD may be due to excess excitatory neurotransmission (eg, glutamate), amantadine has been used. Although amantadine is well tolerated, effectiveness is mixed.[56] Based on the dopaminergic hypothesis of chorea, the typical neuroleptic agents (eg, haloperidol, pimozide) and atypical agents (eg, aripiprazole, clozapine, olanzapine, quetiapine) have been used with success.[56,58] Other agents such as fluphenazine, molindone, risperidone, thioridazine, thiothixene, and

trifluoperazine provide inconsistent effect. The adverse-effect profile of neuroleptic agents are often concerning to clinicians (and patients) and include dystonic reactions, endocrine-metabolic abnormalities, parkinsonism, sedation, TDk, and weight gain.

Tetrabenazine

In 2006, Bonelli and Wenning published an evidence-based review of agents used to manage HD.[56] The authors' literature review found that the antichorea effect of TBZ was supported in 7 of 8 small double-blind studies and 6 of 10 uncontrolled studies or case series. In addition, in a review of the best available clinical data (up to December 2007), as per the Cochrane Collaboration handbook, Mestre et al[4] evaluated 22 trials (N = 1254) and concluded that only TBZ showed a clear efficacy for the control of HD chorea. The conclusion was driven primarily by results of the Tetrabenazine as anti-chorea therapy in Huntington Disease (TETRA-HD) study.[59] Since that time, additional randomized controlled trial data and nonrandomized data have confirmed that TBZ is efficacious in controlling chorea in HD.[60–65] A summary of these more recent studies are discussed in the following text, and highlights of the pivotal data from the 3 registration trials supporting the New Drug Application filing of TBZ to the FDA are provided in **Table II**.

The TETRA-HD study was a randomized, double-blind, placebo-controlled, parallel-arm clinical study that evaluated TBZ for the management of chorea in patients with HD.[59] This study was pivotal for the FDA approval of TBZ. The Huntington Study Group evaluated the efficacy of TBZ in 84 patients with HD and chorea in a randomized, double-blind, placebo-controlled fashion over 12 weeks. Overall, patients were similar with regard to age, CAG repeat length, sex, duration of HD, and history of depression. A total of 54 patients received TBZ (up to 100 mg per day), and 30 patients received placebo. Oral TBZ was titrated up to a maximum of 100 mg/d or until therapeutic effect was reached. The primary efficacy end point was to evaluate the effect of TBZ on chorea as measure by using the Unified Huntington's Disease Rating Scale (UHDRS). Compared with placebo, TBZ reduced chorea severity with an adjusted effect size of −3.5 UHDRS units (95% CI, −5.2 to −1.9; P = 0.0001). This finding represented an average improvement of 23.5% in chorea severity. A total of 69% of TBZ-treated patients had a reduction of at least 3 UHDRS units, compared with 20% of the patients receiving placebo (adjusted odds ratio, 9.9 [95% CI, 3.2 to 29.9]; $P < 0.0001$). A secondary efficacy outcome evaluated the difference in Clinical Global Impression–Improvement score. Only 2 patients receiving placebo (6.9%) had more than minimal global improvement, whereas 23 TBZ-treated patients (45.1%) were more than minimally improved (P = 0.0004). During a washout period at the end of the study, the TBZ-treated group worsened significantly in terms of chorea severity. Adverse effects were reported by 70% of patients receiving placebo and 91% of TBZ-treated patients, with fatigue and sleepiness being the most common. In the TBZ group, 5 serious adverse events were reported in 4 patients (drowning suicide, complicated fall, restlessness/suicidal ideation, and breast cancer) compared with 1 withdrawal and no serious adverse events in the placebo group. Overall, TBZ treatment resulted in clinically and statistically meaningful improvement in chorea and was well tolerated.

A second study cited as a pivotal for FDA approval was reported by Frank et al.[60] This 5-day study evaluated chorea re-emergence upon discontinuation of TBZ in a double-blind, placebo-controlled, staggered withdrawal study. Patients (n = 30) who had been responding to stable doses of TBZ for at least 2 months were randomized to either withdrawal of TBZ on day 1 (n = 12), withdrawal on day 3 (n = 12), or no withdrawal (n = 6). The primary outcome was change in UHDRS chorea score. At baseline, the mean duration of HD, duration of TBZ therapy, TBZ dosage, and chorea scores of the 3 groups were not significantly different. At day 3, the adjusted mean UHDRS chorea score in the group withdrawn on day 1 increased by 5.3 from baseline, compared with an increase of 3 in the 2 groups still receiving TBZ at that point (P = 0.0773). The only significant difference noted was a trend for re-emergent chorea noted in a post hoc analysis (P = 0.0486). Adverse effects associated with the abrupt discontinuation of TBZ were mild; those reported in >1 patient included anxiety and decreased appetite. The study results demonstrated a trend for re-emergence of chorea in patients withdrawn from TBZ. In addition, abrupt withdrawal from TBZ in patients undergoing chronic therapy was not associated with any significant negative effects (apart from worsening chorea). This study is unique in that the efficacy methods were based on TBZ withdrawal and re-emergence or worsening of chorea.

Table II. Summary of tetrabenazine (TBZ) published clinical studies for Huntington disease (HD) chorea.*

Study	Design	Treatment	TBZ Mean (SD) Dose, mg/d	Primary Outcome	Interpretation
HSG (TETRA-HD), 2006[59]	Randomized, double-blind, placebo-controlled; N = 84 adult	TBZ (n = 54) Placebo (n = 30) 12 weeks	Maximum allowable dose 100 mg/d	TBZ: Mean reduction in UHDRS chorea score of 5 (0.5) units† Placebo: Mean reduction in UHDRS chorea score of 1.5 (0.7) units	TBZ effective
Frank et al, 2008[60]	Randomized, double-blind, placebo-controlled; N = 30 adult	TBZ complete withdrawal (N = 12); partial withdrawal (N = 12); no withdrawal (N = 6); over 5 days	Withdrawal: 62.5 (38.1)‡ Partial withdrawal: 46.9 (18.6)‡ No withdrawal: 54.2 (24.6)‡	Withdrawal group with trend for worsened chorea vs combined partial withdrawal + no withdrawal groups (P = 0.0773); post hoc analysis of linear trend was positive for re-emergent chorea (P = 0.0486)	TBZ effective
Frank, 2009[61]	Open-label, long-term follow-up of HSG 2006 study; N = 75 adult	TBZ up to 80 weeks' treatment§	63.4	Mean reduction in UHDRS chorea score of 4.6 (5.55) units‖	TBZ effective

HSG = Huntington Study Group; UHDRS = Unified Huntington's Disease Rating Scale.

*Published clinical trials supporting the filing of a New Drug Application with the US Food and Drug Administration. There was a fourth study (unpublished) supporting the New Drug Application filing and consisted of a 48-week, open-label follow-up (N = 29) of patients enrolled in the study by Frank et al.[60] For complete reviews of all studies evaluating TBZ for HD chorea, see references 9 through 13.

†$P < 0.0001$ compared with placebo.

‡Mean baseline daily dose before drug withdrawal.

§Thirty patients discontinued long-term treatment; therefore, only 45 of 75 patients completed up to 80 weeks of treatment.

‖Longitudinal, $P < 0.0001$.

A third pivotal study was reported by Frank[61] with results of an 80-week, open-label extension phase of the TETRA-HD study. A total of 75 patients enrolled in this long-term study, but 30 patients discontinued treatment and only 45 patients were treated for up to 80 weeks. Reasons for discontinuation included adverse effects (n = 8), lack of efficacy (n = 1), patient/caregiver decision (n = 15), and protocol/site issues (n = 6). The maximum allowable TBZ daily dose was 200 mg. At week 80, chorea had significantly improved from baseline, with a mean (SD) reduction in the total maximal chorea score of 4.6 (5.55) units (longitudinal, $P < 0.0001$). The mean daily dose at week 80 was 63.4 mg (range, 12.5–175 mg).

In addition to these 2 double-blind studies[59,60] and the open-label follow-up study[61] evaluating TBZ for HD chorea, other recent studies include a small randomized, single-blind, cross-over study[62] and 3 observational studies.[63–65]

Brusa et al[62] evaluated TBZ and aripiprazole in 6 patients in a randomized, single-blind, crossover manner. Patients received 3 months of treatment with each drug with a 3-week washout between treatments. Both agents were similarly effective in improving chorea severity as assessed by using the UHDRS chorea score. Aripiprazole treatment was associated with an improvement of 5.2 UHDRS units in chorea severity ($P <$ 0.01 compared with baseline) and TBZ with an improvement of 5.4 UHDRS units in chorea severity ($P <$ 0.01 compared with baseline).

Kenney et al[63] assessed the acute effects of TBZ in a small observational study of 10 patients who were receiving stable doses of TBZ for HD chorea. Study protocol required patients to take their evening dose of TBZ and present the next day without taking the usual morning dose, which would allow the re-emergence of chorea. At the study site, the usual morning dose of TBZ was then administered, and patients were evaluated with serial UHDRS assessments (every 90 to 150 minutes) until re-emergence of baseline choreic movements, indicating wearing off of TBZ effects. A single dose of TBZ reduced the UHDRS chorea score a mean (SD) of 42.4% (17.8%) (*P* value not reported). The duration of effect varied from 3.2 to 8.1 hours (mean [SD] duration, 5.4 [13] hours). Although this was a small study, the results are consistent with the authors' clinical observation that TBZ necessitates multiple daily dosing (eg, 2 or 3 times daily) in many patients.

Fasano et al[64] retrospectively analyzed long-term outcomes in 68 patients with HD who had been treated with TBZ for a mean (SD) of 34.4 (25.2) months. At the first follow-up visit (mean, 9.7 [7.8] months), the UHDRS chorea score was improved by 21% ($P =$ 0.00005), and the mean daily dose of TBZ was 35.3 (14.7) mg. The UHDRS dystonia score also improved, but the change was not statistically significant. In 5 patients, TBZ was discontinued due to lack of efficacy. In the remaining patients, the authors noted that over time, TBZ benefit waned despite increasing dosages.

To evaluate long-term tolerability, Kenney et al[65] conducted a retrospective chart review of 448 patients with various hyperkinetic movement disorders. This cohort included 98 patients with HD chorea and other choreas. The mean (SD) age at onset of chorea symptoms was 45.7 (2.0) years (range, 0.1–78.4 years), whereas the mean age of initiation of TBZ was 52.6 (1.9) years (range, 3–80.2 years). Duration of TBZ therapy was a mean of 2.1 (0.2) years (range, 0.3–11.1 years). Follow-up was performed every 3 to 6 months. The percentage of chorea patients who experienced a moderate to marked improvement in abnormal movements plus a very good or excellent improvement in function at the first visit was 84.4%, and at the last visit it was 81.4% (*P* values not reported). Among the entire cohort, the most commonly reported adverse effects were drowsiness (25%), parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%). These adverse effects were dose related and managed by dose reduction. Overall, 17% discontinued treatment due to intolerability of adverse effects.

TBZ has also been shown to improve balance and postural stability in an open-label study of 10 patients (6 females).[66] The mean (SD) age was 58 (11) years (range, 43–73 years) and mean disease duration was 8.4 (3.5) years (range, 2–13 years). The mean TBZ maintenance dose was not reported. Patients were assessed via computerized dynamic posturography testing under 2 conditions: while receiving a stable TBZ maintenance dose and then after having stopped TBZ for 3 to 4 days. The mean composite equilibrium score was 34.1 (14.2) on treatment and 30 (15.5) off treatment ($P = 0.036$). There were no reported adverse events from withdrawing the medication except for worsening of chorea. TBZ moderately improved balance as determined by using computerized posturography.

Dystonia

Dystonia is characterized by involuntary sustained muscle contractions resulting in abnormal postures.[6] Dystonia can affect any part of the body or specific groups of muscles, with the most common areas affected being the cranial-cervical region. It may also affect the extremities, trunk, facial, and vocal muscles. Dystonia is often classified by anatomy (general, hemi-, segmental, multifocal, or focal). Generalized refers to widespread dystonia involving the legs and other areas. Hemi-dystonia affects the arm and leg on the same side. Segmental refers to dystonia affecting ≥2 adjacent focal areas but sparing the legs. Multifocal refers to dystonia affecting ≥2 separate focal areas, and focal refers to dystonia affecting only 1 specific focal area. Blepharospasm, cervical dystonia, oromandibular dystonia, spasmodic dystonia, and writer's cramp are examples of focal dystonias.

Relief of symptoms is the primary goal in the treatment of dystonia. For the management of generalized dystonia, anticholinergic agents and muscle relaxants are commonly used, and deep brain stimulation has been used for severe cases.[6,67] For the management of focal dystonias, injections of botulinum toxin are generally very effective and considered first-line therapy.

Eight studies have reported on the effectiveness of TBZ (**Table III**) for improving various types of dystonia in pediatric and adult patients.[65,68–74] One prospective, blinded, controlled study demonstrated that TBZ is effective for focal as well as generalized dystonias[70] and 2 single-blind, controlled studies demonstrated that TBZ was ineffective.[68,69] These blinded studies were limited by a small number of patients, with the largest evaluating only 12 patients.[70]

Of the 5 remaining studies,[65,71–74] which were retrospective evaluations, 4 reported a beneficial effect of TBZ for a variety of dystonias.[65,71–73] In a retrospective study, Jankovic and Beach[73] reported results of TBZ therapy in 400 patients (pediatric and adult) with severe hyperkinetic movement disorders. Within this cohort, 190 patients had various dystonias (idiopathic cranial, cervical, and generalized dystonic disorders; tardive dystonias). Clinical response to TBZ was rated on a global response scale (GRS) from 1 to 5 (1 = marked reduction in abnormal movements and excellent improvement in function; 2 = moderate reduction in abnormal movements, very good improvement in function; 3 = moderate improvement in abnormal movements, only mild or no improvement in function; 4 = poor or no response in abnormal movements or function; and 5 = worsening of movement disorders, deterioration in function, or both). Patients with idiopathic dystonia (n = 108) received TBZ for a mean (SD) of 29 (31.87) months and reached a maximum dose of 112.15 (58.94) mg/d. Patients with tardive dystonia (n = 82) received TBZ for a mean of 32.19 (39.28) months and reached a maximum dose of 125.15 (72.85) mg/d. Of the patients with idiopathic dystonia (47 with cranial distribution, 41 generalized, and 20 cervical), there was no difference in TBZ effectiveness based on affected area of dystonia (*P* values not reported). Patients with tardive dystonia showed more of an improvement than those with idiopathic dystonia. In patients with idiopathic dystonia, 62.9% had an initial response score of 1, and this finding fell to 45.3% at the final visit. In patients with tardive dystonia, 80.4% had a response score of 1 at the initial visit, with 73.1% having a score of 1 at the final visit.

Jankovic and Orman[72] also reported a retrospective analysis of 217 patients (pediatric and adult) with various hyperkinetic movement disorders. Of this group, 124 patients had dystonia and, overall, 76% of patients experienced moderate to marked improvement (assessed by using the GRS). The authors noted that a greater proportion of patients with generalized or tardive dystonia had improvement with TBZ compared with patients with cranial or other focal dystonias (*P* values not reported) (**Table III**).

In another retrospective analysis, Kenney et al[65] assessed the long-term efficacy of TBZ in 448 patients with various hyperkinetic movement disorders. Of this group, 132 patients (pediatric and adult) had dystonia. Mean (SD) age at initial TBZ treatment was 53.1 (1.7) years (range, 5.6–87.6 years), and mean duration of TBZ treatment was 3 (0.4) years (range, 0.3–21.6 years). Consistent with other studies,[72,73] 68% of patients with dystonia experienced a marked or moderate improvement (assessed by using the GRS).

TBZ has been used in pediatric and adult patients with various dystonias. Overall, based on the available prospective and retrospective data, TBZ demonstrates efficacy for dystonia but should be considered as an alternate treatment option to established therapies (eg, anticholinergics, botulinum toxin, muscle relaxants). Additional double-blind, placebo-controlled studies are warranted to better characterize TBZ efficacy against other agents as well as to better characterize

Table III. Summary of tetrabenazine (TBZ) published clinical studies for dystonias.

Study	Design	Treatment	TBZ Mean (SD) Dose, mg/d*	Primary Outcome†	Interpretation
Swash et al, 1972[68]	Single-blind,‡ prospective; N = 9 pediatric and adult	TBZ	128	TBZ: 3/8 (38%) improved	TBZ ineffective
Asher and Aminoff, 1981[69]	Single-blind,‡ placebo-controlled, crossover; N = 8 adult	TBZ for 3 weeks, followed by placebo for 3 weeks	175	TBZ: 2/8 (25%) patients with marked or moderate improvement	TBZ ineffective
Jankovic, 1982[70]	Randomized, double-blind, placebo-controlled, crossover; N = 12 adult	TBZ for 3 weeks, placebo for 3 weeks	162.5	TBZ: 11/12 (92%) patients improved	TBZ effective
Marsden et al, 1984[71]	Retrospective; N = 14 pediatric and adult	TBZ§	90 (adult), 75 (pediatric)	TBZ: 10/14 (71%) patients with improvement	TBZ effective
Jankovic and Orman, 1988[72]	Retrospective; N = 124 pediatric and adult	TBZ	Tardive dystonia (n = 15): 155.4‖ Generalized dystonia (n = 19): 114.5‖ Cranial dystonia (n = 57): 109‖ Focal dystonia (n = 25): 119‖ Essential blepharospasm (n = 5): 85‖ Hemidystonia (n = 3): 150‖	TBZ: 94/124 (76%) patients with marked, moderate, or fair improvement	TBZ effective
Jankovic and Beach, 1997[73]	Retrospective; N = 190 pediatric and adult	TBZ	Dystonia (n = 108): 112 (59)‖ Tardive dystonia (n = 82): 125 (73)‖	TBZ: 132/190 (69%) patients with marked or moderate improvement	TBZ effective
Paleacu et al, 2004[74]	Retrospective; N = 41 adult	TBZ	NR	TBZ: 20/41 (49%) patients with marked or moderate improvement	TBZ ineffective
Kenney et al, 2007[65]	Retrospective; N = 132 pediatric and adult	TBZ	NR	TBZ: ~68% with marked or moderate improvement	TBZ effective

NR = not reported.
*Not all studies reported SDs.
†Not all studies reported *P* values.
‡Blinded film/video analysis.
§In combination with pimozide and trihexyphenidyl.
‖Reported as an average maximum dose.

efficacy in the various types of dystonia (eg, generalized, segmental, focal).

Tardive Dyskinesia

TDk is a persistent drug-induced hyperkinetic movement disorder that is most commonly associated with use of central dopamine receptor–blocking agents (eg, metoclopramide, neuroleptic agents).[5,75] The term emphasizes the delayed or tardive onset of choreathetoid, stereotypic movements (ie, dyskinesias). Management of TDk is challenging. Interventions (none of which provide consistently satisfactory outcomes) include use of amantadine, atypical antipsychotic agents, baclofen, benzodiazepines, branched chain amino acids, calcium channel blockers (eg, verapamil), donepezil, gabapentin, levetiracetam, melatonin, methyldopa, ondansetron, pregabalin, vitamin B_6 (pyridoxine), and vitamin E.[5] In a meta-analysis of 45 randomized, placebo-controlled trials (up to December 2005), no single agent was identified as a definitive therapy for TDk.[5]

Table IV summarizes the results of 11 TBZ studies in TDk.[65,69,70,72–74,76–80] The majority of studies were conducted either retrospectively or prospectively with small numbers of patients. Only 2 studies reported statistical values.[70,80] However, overall, in 9 of 11 studies TBZ demonstrated a clinical benefit for TDk symptoms.[65,69,70,72,73,76,77,79,80]

The largest prospective, blinded study was by Ondo et al.[80] This was a single-blind study of 20 patients (15 were female) with TDk who had failed to respond to previous treatment. Mean (SD) age was 65.2 (10.8) years (range, 23–82 years). The mean duration of TDk was 43.7 (47.1) months (range, 2–420 months). The offending agents were metoclopramide (n = 7), haloperidol (n = 6), phenothiazine antipsychotics (n = 5), and amoxapine (n = 1). In addition to TDk, 5 patients displayed mild parkinsonism, and 5 reported akathisia. Patients were videotaped before and after receiving TBZ. Videotapes were blindly assessed in a randomized manner by using the Abnormal Involuntary Movement Scale (AIMS). The mean duration of TBZ treatment was 20.3 (10.4) weeks, and the mean dose was 57.9 (22.8) mg/d. The mean score on the AIMS motor subset (questions 1–7) improved 54.2% from pretreatment ($P < 0.001$), and the subjective scores (questions 8–10) improved 60.4% ($P < 0.001$). Seventeen patients rated themselves as markedly or moderately improved (assessed by using the GRS). In this study, TBZ provided clinically and statistically significant improvements.

In 2 large retrospective studies of patients with various hyperkinetic movement disorders, the effect of TBZ was reported in a subset total of 242 adult patients with TDk.[65,73] In 1 study of 149 patients with TDk, TBZ markedly or moderately improved symptoms (assessed by using the GRS) in 84% of patients.[65] In the other study of 93 adults with TDk, TBZ improved symptoms (moderately to markedly as assessed by using the GRS) in ~89% of patients.[73] The results of these and smaller studies are also summarized in Table III.

In the United States, no drug is FDA approved for the management of TDk. Another VMAT-2 inhibitor, NBI-98854 (Neurocrine Biosciences, San Diego, California), is currently in phase 2 clinical testing for the treatment of TDk.[81] Overall, the clinical data demonstrate that TBZ provides symptomatic benefit in TDk. Given that TDk is a challenge to manage, TBZ should be considered as a treatment option. However, additional randomized, placebo-controlled studies are warranted.

Tourette's Syndrome

TS is a childhood-onset neuropsychiatric disorder presenting with tics and a constellation of nonmotor symptoms that includes attention-deficit hyperactivity, impulsivity, and obsessive-compulsive behavior.[7,27] A defining feature of TS is the presence of brief, stereotyped, motor, or vocal tics. Accumulated evidence from pharmacology and functional-imaging studies suggests that abnormalities of dopaminergic neurotransmission (striatal and extrastriatal) play a role in the pathogenesis of TS.[82] Therapy for tics are indicated when symptoms start interfering with the patient's quality of life. Traditional agents include α-adrenergic agonists (eg, clonidine) for mild tics and various typical or atypical neuroleptics for more severe tics.[27] Deep brain stimulation is an emerging therapy for medication-refractory tics. Chronic neuroleptic therapy is associated with emergence of extrapyramidal adverse effects (eg, TDk) as well as metabolic abnormalities (eg, glucose and lipid dysregulation).

Although several studies have assessed the efficacy and tolerability of TBZ for tics in patients (pediatric and adult) with TS (Table V), none were randomized, controlled trials.[27,65,72–74,83–88] In an open-label, prospective study, Porta et al[27] reported on 120 consecu-

Table IV. Summary of tetrabenazine (TBZ) published clinical studies for tardive dyskinesia.

Study	Design	Treatment	TBZ Mean (SD) Dose, mg/d*	Primary Outcome†	Interpretation
Godwin-Austen and Clark, 1971[76]	Randomized, double-blind, crossover; N = 6 elderly	Placebo Diazepam TBZ; 1 week per treatment	100	TBZ: 3/6 (50%) patients improved with absence of movement Placebo or diazepam: 0/6 patients experienced absence of movements	TBZ effective
Kazamatsuri et al, 1972[77]	Open-label, crossover; N = 24 adult	TBZ for 6 weeks, followed by placebo for 2 weeks	122.5	TBZ: Abnormal movement disappeared in 8/24 (33%) patients; in 6/24 (25%) it was markedly reduced	TBZ effective
Kazamatsuri et al, 1973[78]	Randomized, placebo-controlled; N = 13 adult; 18 weeks	Haloperidol (n = 7) TBZ (n = 6)	100	TBZ: 2/6 with 100% disappearance of abnormal movements. Haloperidol: 2/7 with 100% disappearance of movements	TBZ and haloperidol similarly ineffective
Asher and Aminoff, 1981[69]	Single-blind,‡ placebo-controlled, crossover; N = 10 adult	TBZ for 3 weeks, followed by placebo for 3 weeks	175	TBZ: 6/10(60%) patients with marked or moderate improvement	TBZ effective
Jankovic, 1982[70]	Randomized, double-blind, placebo-controlled, crossover; N = 4 adult	TBZ for 3 weeks, placebo for 3 weeks	200	TBZ: 4/4 (100%) patients improved ($P < 0.005$)	TBZ effective
Jankovic and Orman, 1988[72]	Retrospective; N = 44 adult	TBZ	97.4§	TBZ: 31/44 (71%) patients improved	TBZ effective
Watson et al, 1988[79]	Open-label, case series; N = 23 adult	TBZ	91.3 (38.9)	TBZ: 23/23 (100%) patients improved from baseline	TBZ effective
Jankovic and Beach, 1997[73]	Retrospective; N = 93 adult	TBZ	96.9 (62)§	TBZ: 83/93 (89%) patients improved	TBZ effective
Ondo et al, 1999[80]	Open-label, single-blinded‡; N = 20	TBZ	57.9 (22.8)	TBZ: 17/20 (85%) markedly or moderately improved; AIMS motor subset score 54.2% improvement ($P < 0.001$)	TBZ effective
Paleacu et al, 2004[74]	Retrospective; N = 17 adult	TBZ	NR	TBZ: 7/17 (41%) marked or moderate improvement	TBZ ineffective
Kenney et al, 2007[65]	Retrospective; N = 149 adult	TBZ	NR	TBZ: Approximately 84% with marked or moderate improvement	TBZ effective

AIMS = Abnormal Involuntary Movement Scale; NR = not reported.
*Not all studies reported SDs.
†Not all studies reported *P* values.
‡Blinded film/video analysis.
§Reported as an average maximum dose.

Table V. Summary of tetrabenazine (TBZ) published clinical studies for Gilles de la Tourette syndrome.

Study	Design	TBZ Mean (SD) Dose, mg/d*	Primary Outcome†	Interpretation
Sweet et al, 1974[83]	Nonrandomized, prospective, open-label, crossover‡; N = 7 pediatric and adult	270§	TBZ: 2/5‡ (40%) patients improved. The other 3 received no benefit whatsoever	TBZ ineffective
Jankovic et al, 1984[84]	Retrospective; N = 9 pediatric and adult	82	TBZ: 4/9 (44%) patients with marked improvement lasting >6 months; 3/9 (33%) with mild or transient <6 months improvement	TBZ effective‖
Jankovic and Rohaidy, 1987[85]	Retrospective; N = 15 pediatric and adult	NR	TBZ: 12/15 (80%) patients improved	TBZ effective
Jankovic and Orman, 1988[72]	Retrospective; N = 17 pediatric and adult	81.6§	TBZ: 16/17 (94%) patients improved	TBZ effective
Jankovic and Beach, 1997[73]	Retrospective; N = 47 adult	83.5 (41.9)§	TBZ: 27/47 (57%) improved	TBZ effective
Vuong et al, 2004[86]	Retrospective; N = 53 pediatric	NR	TBZ: 38/53 (72%) patients improved	TBZ effective
Paleacu et al, 2004[74]	Retrospective; N = 9 adult	NR	TBZ: 3/9 (33%) patients improved	TBZ ineffective
Jain et al, 2006[87]	Retrospective; N = 10 pediatric	78.3	TBZ: 7/10 (70%) patients improved	TBZ effective
Kenney et al, 2007[65]	Retrospective; N = 92 pediatric and adult (86 with adequate follow-up)	NR	TBZ: 66/86 (77%) with marked or moderate improvement	TBZ effective
Kenney et al, 2007[88]	Retrospective; N = 77 pediatric and adult	50.4 (27)	TBZ: 64/77 (83%) improved	TBZ effective
Porta et al, 2008[27]	Open-label, prospective; N = 120 pediatric and adult	70.5	TBZ: 91/120 (76%) improved	TBZ effective

NR = not reported.
*Not all studies reported SDs.
†*P* values not reported.
‡TBZ compared with α-methyl-para-tyrosine. Five patients received TBZ; 4 of whom previously received α-methyl-para-tyrosine.
§Reported as an average maximum dose.
‖Three patients also underwent sleep studies and experienced reduction in nocturnal tics and sleep arousals.

tive patients (age range, 5–55 years) with TS treated with TBZ. Patients received TBZ (mean daily dose, 70.5 mg) for a mean of 19 months. At baseline, 93% of patients were receiving a serotonin reuptake inhibitor, antipsychotic, and/or tricyclic antidepressant, and TBZ was added. At the final visit, 76% of patients were rated as improved on the Clinical Global Impression of Change scale (*P* value not reported). Adverse effects such as asthenia, akathisia, depression, parkinsonism, and somnolence were seen in 2% to 5% of patients.

In another retrospective study, Kenney et al[65] reported on the efficacy of TBZ in 92 patients (pediatric and adult) with tic disorders. Of the 92 patients, 86 provided adequate follow-up. The mean (SD) age at initiation of TBZ was 24.1 (1.7) years (range, 8.2–72.2 years), and the mean duration of TBZ treatment was 1.6 (0.3) years (range, 0.3–20.4 years). On follow-up, ~77% of patients had either marked or moderate improvement in tic movements (assessed by using the GRS; *P* value not reported).

These results are consistent with another retrospective study by the same investigators who evaluated the efficacy and tolerability of TBZ in 77 pediatric and adult patients with TS.[88] Mean age at TBZ initiation was 14.8 (17.4) years (range, 2–71.4 years). The mean TBZ treatment period was 23.7 (41.1) months. Patients were followed up every 3 to 6 months. The mean dose of TBZ at last visit was 50.4 (27) mg/d. At the last follow-up visit, 83.1% of patients had moderate to marked reduction of abnormal movements with functional improvement (assessed by using the GRS; *P* value not reported). The results were comparable to the benefits noted after the initial visit, suggesting an enduring benefit. The most common adverse effects were drowsiness/fatigue (36.4%), nausea (10.4%), depression (9.1%), insomnia (7.8%), and parkinsonism (6.5%) and were managed by dose reduction. Because neuroleptic agents are commonly used for TS, the authors noted that with TBZ treatment, there was no instance of TDk or dystonic reactions.[88] Approximately 20% of patients reported no adverse effects during the study period.

In a retrospective chart review, Vuong et al[86] reported on the tolerability profile and efficacy of TBZ in a group of 448 patients with various hyperkinetic movement disorders. Of these 448 patients, 76 were pediatric (mean age,12.4 years; range, 3–17.9 years) at the time of TBZ initiation. For the pediatric cohort, the mean follow-up period was 18.7 months, and the mean total daily TBZ dose was 49.3 mg (range, 6.25–150 mg). Of the 76 pediatric patients, 53 were being treated for tics, and improvement (assessed by using the GRS) occurred in 72% (*P* value not reported). The most common adverse effects among the entire cohort were drowsiness or fatigue (35.5%), nausea (10.5%), depression (9.2%), akathisia (6.5%), and insomnia (3.9%). Approximately 37% reported no adverse effects.

Results of these and other smaller retrospective studies are summarized in **Table V**. Overall, TBZ has been studied in pediatric and adult patients with TS and demonstrates clinically significant benefits and seems well tolerated for motor and vocal tics. However, because none of the studies were double-blind and randomized, TBZ should be considered as an alternative agent to standard therapies (eg, clonidine, neuroleptic agents). Unlike neuroleptic agents, TBZ has not been associated with development of TDk. There is a need for randomized controlled trials to assess the efficacy and tolerability of TBZ for tic disorders.

Miscellaneous Hyperkinetic Movement Disorders

TBZ has also been used in a variety of other abnormal involuntary hyperkinetic movement disorders (eg, hemiballism, myoclonus, stereotypies) and often with dramatic success.[65,73,89–91] Because the published data consist of case reports or small case series, a summary review of TBZ for these other hyperkinetic movement disorders is beyond our intended scope. However, clinicians should be aware that TBZ has been used in patients presenting with unusual hyperkinetic movement disorders or when other therapies are unsatisfactory.

DRUG INTERACTIONS, SAFETY PROFILE, AND TOLERABILITY CONSIDERATIONS

Overall, TBZ is well tolerated, although fatalities and severe reactions (eg, hyperthermia, neuroleptic malignant syndrome, severe dysphagia, suicide) have been reported.[59,73,92–95] In the clinical studies we reviewed and in clinical practice, TBZ is initiated at a subtherapeutic dose and titrated to a dose that provides the best efficacy with tolerable adverse effects. Dose-limiting adverse effects to be expected (10%–30% occurrence), beginning with the most common, include somnolence, insomnia, fatigue, depression, akathisia, anxiety, nausea, and parkinsonism.[9,10] These adverse effects can be managed by dose reduction. Elderly patients with baseline striatal dopamine deficiency may be at greater risk for experiencing TBZ-induced

parkinsonism and patients with a history of depression at greater risk of TBZ-induced depression.

In the United States, the manufacturer labeling for TBZ includes a black box warning regarding depression and suicidality.[96] TBZ can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with HD. Anyone considering the use of TBZ must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in HD. TBZ is contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression.

Before the initiation of TBZ therapy, patients should be screened and treated for depression when warranted. Kenney et al[97] evaluated the frequency of depression in a retrospective chart review of 518 patients with hyperkinetic movement disorder treated with TBZ. Of 246 patients with no history of depression, 28 (11.4%) developed depression while taking TBZ. Of the 272 patients with a documented history of depression, 50 (18.4%) experienced an exacerbation of depression. In a post hoc analysis, data from the TETRA-HD study were used to evaluate the incidence of depressed mood either as an adverse event or as a 2 points or greater worsening on the "depressed mood" item of the UHDRS.[98] In the TETRA-HD study, 56% of the TBZ-treated patients (who completed the trial) were taking an antidepressant.[59,98] The incidence of depressed mood did not differ between those taking and not taking an antidepressant (15% and 5%, respectively; $P = 0.37$), and the percentage experiencing a worsening on the "depressed mood" item did not differ (7% and 10%, respectively; $P = 1.00$). Therefore, among patients taking antidepressants, TBZ was not associated with a worsening of depressed mood.

Several hyperkinetic movement disorders are traditionally managed with neuroleptic agents, which are associated with the development of TDk and metabolic abnormalities.[75] Of note, the development of TDk has not been associated with TBZ use despite up to 21 years of exposure in some cases.[10,65]

Coadministration with a strong CYP2D6 inhibitor (eg, fluoxetine, paroxetine, quinidine) may increase levels of some active metabolites, and TBZ dosage reduction may be warranted. TBZ does not seem to have clinically significant interactions with other CYP inhibitors.[9]

DOSING, ADMINISTRATION, AND PHARMACOECONOMICS

Dosing of TBZ is very patient specific and needs to be titrated to the lowest dose that controls symptoms and is tolerated. It possesses considerable interindividual dose-response variability, possibly due to differences in carbonyl reductase and CYP2D6 metabolic activity. In the literature reviewed within this article, TBZ was used in pediatric and adult patients with a therapeutic daily dose ranging from 6.25 to 300 mg. The manufacturer recommends a starting dose of 12.5 mg once daily with weekly titration by 12.5 mg.[96] For doses >37.5 mg, administration should be divided into 3 doses. The maximum recommended daily dose, according to the manufacturer, is 100 mg.

Table VI. Key points regarding use of tetrabenazine.

- Tetrabenazine is a reversible, selective, central nervous system monoamine reuptake inhibitor, resulting in depletion of intravesicular dopamine
- Consider as first-line agent for the management of Huntington chorea
- Consider as an option for reducing severity of other hyperkinetic movement disorders (eg, dystonias, tardive dyskinesia, tics)
- Efficacy and tolerability has been studied in pediatric and adult populations
- Common adverse effects are depression, parkinsonism, and somnolence.
- Not associated with development of tardive dyskinesia
- Dose is titrated weekly up to 100 mg daily. Higher doses have been used
- Wide interindividual dosage variability
- Improvements may be seen within days of therapy initiation

The manufacturer recommends obtaining CYP2D6 genotyping in patients who require daily doses >50 mg.[96] However, no published research has been found on the correlation of CYP2D6 genotyping and TBZ dose-response.

There were no published reports on the pharmacoeconomics of TBZ for HD chorea or other hyperkinetic movement disorders. The 2012 average wholesale price for TBZ 12.5-mg and 25-mg tablets are $51.85 and $103.70, respectively.[99]

CONCLUSIONS

TBZ is effective for a variety of hyperkinetic movement disorders such as chorea of HD, dystonias, TDk, and tic disorders (eg, TS) and has been studied in pediatric and adult populations. However, for dystonia, TDk, and TS, only a small number of studies are randomized and controlled, with the majority of data derived from retrospective studies. Therefore, for off-label uses, we believe TBZ should be considered as an alternative to other therapies. The common adverse effects of TBZ include somnolence, insomnia, fatigue, depression, akathisia, anxiety, nausea, and parkinsonism.

Based on the literature reviewed, we concluded that clinicians should be aware of several considerations and key points that are important for the use of TBZ (**Table VI**). Concomitant depression should be treated before initiation of TBZ, and the dose must be titrated properly with monitoring.

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CONFLICTS OF INTEREST

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Address correspondence to: Jack J. Chen, PharmD, FCCP, BCPS, CGP, Movement Disorders Clinic, Loma Linda University, Schools of Medicine and Pharmacy, 11262 Campus Street—West Hall, Loma Linda, CA 92350. E-mail: jjchen@llu.edu