Tetrabenazine in Huntington’s Disease Chorea

Shilpa Chitnis and Cherian Abraham Karunapuzha
Assistant Professor of Neurology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, J3.134 E, Dallas, Texas 75390-9036, USA. Chief Resident, Adult Neurology, UT Southwestern Medical Center, Dallas, Texas, USA.
Email: shilpa.chitnis@utsouthwestern.edu

Abstract: Huntington’s disease (HD) is a heredodegenerative neurological disorder with chorea and other hyperkinetic movement disorders being part of the disease spectrum. These along with cognitive and neurobehavioral manifestations contribute significantly to patient’s disability. Several classes of drugs have been used to treat the various symptoms of HD. These include typical and atypical neuroleptics along with dopamine depletors for treatment of chorea and antidepressants, GABA agonists, antiepileptic medications, cholinesterase inhibitors, antiglutamatergic drugs and botulinum toxin for treatment of other manifestations. Tetrabenazine (TBZ), a dopamine depleting medication was recently approved by the US FDA for treatment of chorea in HD. The purpose of this article is to briefly review information regarding HD and current treatments for chorea and specifically focus on TBZ and review the literature related to its use in HD chorea.

Keywords: Huntington’s disease, chorea, tetrabenazine
Introduction
Huntington’s disease (HD) was described in 1872 by George Huntington initially based on his observations in patients from multiple generations on Long Island, New York. It is an autosomal dominant, neuropsychiatric disorder causing degeneration of neurons predominantly in the caudate, putamen and cortical areas. It has a distinct phenotype consisting of a combination of various movement disorders.

The genetic defect on the short arm of chromosome 4 leads to alteration of the protein huntingtin, resulting in toxic gain of function and subsequent neuronal loss. The onset of symptoms is generally between the ages of 30–50 years with some individuals developing symptoms before the age of 20 (juvenile HD) and some in the later years of life. A genetic test has been available for diagnosis of HD since the early 1990s and measures the number of trinucleotide (cysteine-adenine-guanine) (CAG) repeats.

The movement disorder typically associated with HD is chorea associated with bradykinesia, dystonia and rigidity and a complicated gait disorder predisposing to falls. The typical antipsychotics have been used to treat chorea in HD for many years but their undesirable side effects have lead to use of newer, atypical antipsychotics which are now widely used to treat HD. Recently the US FDA approved the use of TBZ, a dopamine depleting drug for treatment of chorea associated with HD. TBZ is thought to have good efficacy in clinical studies but the use of this drug must be balanced with the risk of new or worsening depression, suicidality as well as parkinsonism.

Epidemiology of HD
There is a correlation between age of onset of symptoms and the number of CAG repeats. Patients can present between the age of 35 and 45 years, but the age of onset can range anywhere between 2–80 years. The prevalence of HD is about 7–10 cases per 100,000 in white population with lesser prevalence in mixed white, black and asian populations. The island of Tasmania and the Lake Maracaibo region in Venezuela have a high prevalence due to a founder effect where an earlier settler or ancestor carried the abnormal gene.

Genetics of HD
In a normal person, the huntingtin gene has less than 36 repeats which encode glutamine. HD is an autosomal-dominant disorder with an abnormal gene carrying an expanded CAG repeat on the short arm of chromosome 4. If the expansion has 40 or more repeats, the disease is fully penetrant; between 36–40 repeats, it has variable penetrance; and with 35 repeats or less, disease does not occur. The expanded CAG repeat is unstable and this instability begins at repeat size of 29 or greater. In gametogenesis, these CAG repeats are prone to further expansion, which explains the phenomenon of anticipation, where the age of onset of the disease tends to get younger with succeeding generations.

Pathology of HD
Striatal medium spiny neurons are selectively vulnerable with prominent cell loss seen in the caudate and putamen. Neurons containing enkephalin and those that project to the globus pallidus externa are more involved than neurons that contain substance P and project to globus pallidus interna with sparing of interneurons. Other brain areas affected in patients with HD include substantia nigra, cortical layers 3, 5, 6 and the CA1 region of the hippocampus, the angular gyrus in the parietal lobe, purkinje cells of the cerebellum, lateral tuberal nuclei of the hypothalamus and the centromedial-parafascicular complex of the thalamus. There is appearance of nuclear and cytoplasmic inclusions that contain the mutant huntingtin and polyglutamine.

Pathogenesis – Table 1
Clinical Features of HD
The median age of onset of the disease is in the mid 40s to early 50s. Early and late onset disease is also seen. The disease is initially characterized by insidious and slow deterioration of intellectual function and mild personality changes. Minor motor abnormalities include generalized restlessness, abnormal eye movements, hyperreflexia, and mild dysarthria. In early stages patients have problems with planning, organizing and scheduling day to day activities. Middle stage brings about the motor disorder classically associated with the disease. Chorea is the major motor sign of Huntington disease. It is present during waking hours, cannot be voluntarily suppressed, and is worsened by stress, anxiety and depression. Motor impersistance results in inability to apply steady pressure during
handshake—milkmaid’s grip. There can be impaired attention, decreased verbal fluency, poor motor programming, and difficulty with abstraction. Also seen are deficits in learning, retention and retrieval of information and visuo-motor performance. This disease has prominent affective disorders including depression, feeling of worthlessness, guilt, apathy, loss of energy, appetite and change in sleep patterns. Some patients have mania displaying elevated mood, over activity, decreased need for sleep, impulsiveness and grandiosity. Also seen are signs of irritability and bad-tempered outbursts, aggressiveness, angry or violent behavior. With disease progression, chorea is replaced by bradykinesia, rigidity and dystonia. Impairment of voluntary motor function causes clumsiness in day to day activities, decreased motor speed, fine motor control and gait disturbances. There is delayed initiation of voluntary saccades and eventual slowing of saccades, impairment of gaze fixation and ability to suppress blinking. There can be severely impaired speech and communication, along with impaired swallowing requiring PEG tube placement. Loss of ability to walk due to gait disturbance leads to confinement to wheelchair or bed and eventual loss of independence requiring full nursing care. There may be onset of secondary illnesses such as pneumonia, choking, nutritional deficiencies, and skin ulcers. Emotional withdrawal and blunting will be seen in some patients as well as the increased potential for death by suicide.

Genetic Testing, Radiographic Findings and Diagnosis of HD
Fewer than 5% of individuals at risk for HD choose to actually pursue predictive genetic testing. Many elect not to test because of absence of effective treatment but some may undergo testing to assist in making career and especially family choices. Predictive testing is not without its risk and there is a risk of suicide in patients after finding out a positive result. The overall experience tends to be positive for those individuals who undergo extensive pretest counseling. A positive genetic test provides confirmation for individuals who manifest signs and symptoms consistent with HD. MRI and CT imaging in moderate to severe HD show a loss of striatal volume and increased size of the frontal horns of the lateral ventricles. Data from PET and functional MRI studies reveal that changes in affected brains can take place before symptom onset with caudate atrophy apparent 11 years before and putaminal atrophy 9 years before the estimated onset of the disease.
Management Considerations in HD – Table 3

Tetrabenazine

Pharmacology
TBZ is a synthetic benzoquinolizine derivative. TBZ is available in Europe and Australia as Xenazine® and in Canada as Nitoman® for the treatment of hyperkinetic movement disorders. It has been granted orphan drug status by the FDA for chorea in people with Huntington’s disease and was approved in the United States for the treatment of chorea in people with Huntington’s disease in August 2008.

Pharmacodynamics
TBZ is a selective, reversible, centrally-acting dopamine depleting drug that works by inhibiting
vesicular monoamine transporter 2 (VMAT2). TBZ depletes presynaptic dopamine, norepinephrine, and serotonin storage and antagonizes in vitro postsynaptic dopamine D2 receptors. D2 receptor blockade occurs at micromolar levels, while VMAT2 inhibition occurs at nanomolar concentrations. Brain concentrations tend to occur at nanomolar levels, after extrapolation from animal studies, therefore, unlikely to cause D2 receptor blockade in vivo.

The effect of a single 25 or 50 mg dose of TBZ on the QT interval was studied in a randomized, double-blind, placebo controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 50 mg, TBZ caused an approximately 8 m sec mean increase in QTc (90% CI: 5.0, 10.4 m sec). Additional data suggest that inhibition of CYP2D6 in healthy subjects given a single 50 mg dose of TBZ does not further increase the effect on the QTc interval. Effects at higher exposures to either TBZ or its metabolites have not been evaluated.

Pharmacokinetics

TBZ is administered orally. Food has no effect on mean plasma concentrations, Cmax, or the area under the concentration time course (AUC) of alpha-DTBZ or beta-DTBZ. Absorption following oral administration is at least 75% of the dose. Plasma concentrations of TBZ will likely be below detectable levels after single doses up to 50 mg due to extensive and rapid hepatic metabolism. TBZ is rapidly metabolized via first-pass metabolism into two main metabolites known as alpha- and beta-dihydrotetrabenazine (DTBZ). Of these two compounds, alpha-DTBZ is pharmacologically active, whereas beta-DTBZ is pharmacologically inert. DTBZ is highly bioavailable and is approximately 44% to 59% protein-bound, compared with TBZ, which is approximately 85% protein-bound. Peak plasma concentrations of alpha-DTBZ and beta-DTBZ are achieved within one to 1.5 hours following an oral dose, and these compounds have a half-life of approximately 10 hours. In contrast, TBZ exhibits a half-life of about six hours. One study showed that TBZ and DTBZ follow linear kinetics between 37.5 mg and 112.5 mg/day. PET-scan studies in humans show that the highest binding is in the striatum and lowest binding in the cortex. DTBZ is further metabolized by CYP2D6 to O-dealkylated DTBZ, which is subsequently excreted via the urine and feces. The metabolites are primarily renally eliminated. In a mass balance study in 6 healthy volunteers, approximately 75% of the dose was excreted in the urine and fecal recovery accounted for approximately 7%–16% of the dose.

The results of in vitro studies do not suggest that TBZ, alpha-DTBZ, or beta-DTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. Their effect on CYP2B6 has not been evaluated. In vitro studies suggest that neither TBZ nor its alpha- or beta-DTBZ metabolites is likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19. Although the pharmacokinetics of TBZ and its metabolites in subjects who do not express the drug metabolizing enzyme CYP2D6 (poor metabolizers, PMs) have not been systematically evaluated, it is likely that the exposure to alpha-DTBZ and beta-DTBZ would be increased compared to subjects who express the enzyme (extensive metabolizers), with an increase similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively).

Dosing Considerations and Side Effects

Initial dosing of the drug starts at 12.5 mg per day. The dose can be increased by 12.5 mg per week based on tolerability and effect on chorea. The doses should be broken into a twice or thrice daily regimen. If a dose of 37.5 mg per day or greater is needed, it should be given in a 3-times daily regimen. If daily doses of greater than 50 mg are necessary, patients should first be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate
metabolizers (EMs or IMs) of CYP2D6. For PMs, the maximum recommended single dose is 25 mg, and the maximum recommended daily dose is 50 mg. For IMs or EMs, the maximum recommended single dose is 37.5 mg and the maximum recommended daily dose is 100 mg. Patients already on strong CYP2D6 inhibitors (like fluoxetine, paroxetine, quinidine) should be dosed as a PM. Also when adding a CYP2D6 inhibitor to patients already receiving a stable dose of TBZ, the daily dose of TBZ should be halved. TBZ is also contraindicated in patients who have impaired hepatic function or are taking monoamine oxidase inhibitors or reserpine. At least 20 days should elapse after stopping reserpine before starting TBZ. Serious side effects include; depression and suicidal ideation, neuroleptic malignant syndrome, parkinsonism, akathisia, dysphagia, arrhythmia secondary to QTc prolongation, orthostatic hypotension and tardive dyskinesia. Common side effects include sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, and nausea. Some adverse events such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism, and akathisia may be dose-dependent. If the adverse effect does not resolve or decrease, consideration should be given to lowering or discontinuing TBZ.\textsuperscript{14}

**Clinical Studies of Tetrabenazine in HD Chorea**

Since the 1960s evidence for TBZ in the treatment of chorea (various hyperkinetic movement disorders including Huntington’s) have been shown through numerous case reports and clinical trials, most of them open-label, retrospective or using a small sample size.
A study by Paleacu et al\textsuperscript{18} showed that TBZ is a moderately effective treatment of a large variety of hyperkinetic movement disorders, with excellent effects in a subgroup with chorea and facial dystonia/dyskinesias. The study was aimed at assessing the efficacy of TBZ in a retrospective chart review in 3 tertiary care movement disorders centers over long-term treatment. Of 150 patients to whom TBZ was prescribed, 118 were followed up and assessed using the Clinical Global Impression of Change (CGIC), ($−3$ to $+3$), a composite grade from a patient and caregiver scale over variable periods. The patients had a variety of hyperkinetic movement disorders including dystonia (generalized and focal, axial, Meige syndrome, torticollis, blepharospasm, bruxism), Huntington disease (HD) or other choreas, tardive dyskinesia (TD) or akathisia, and Tourette syndrome. Mean patient age was $48.8 ± 18.7$ years; 48 were men ($40.7\%$) with mean disease duration of 93 months. The mean follow-up time was 22 months and the mean TBZ dose was $76.2 ± 22.5$ mg/d (median 75 mg, range 25–175 mg/d). The mean CGIC score was $+1$ (mild improvement). The group of patients who scored $+3$ on the CGIC (very good improvement) represented $18.6\%$ ($n = 22$) of all patients. They had HD or other types of chorea $7.6\%$ ($n = 9$), facial dystonia/dyskinesia ($n = 7$, $5.9\%$), 1 with TD, 2 with trunk dystonia, 2 with Tourette syndrome, and 1 with tardive akathisia. This group had the longest treatment duration and received a mean TBZ dose of $70.5$ mg/d (median $75$ mg/d) for a mean of $25.4 ± 21.3$ months.

Bonelli et al\textsuperscript{19} conducted an evidence based review of treatment studies from 1965 to 2005 in Huntington’s disease, which showed poor evidence and no concrete treatment recommendations could be ascertained. Randomized controlled trials (RCTs) were classified as Level-I-studies, Level-II evidence was assigned to non-randomized, controlled clinical studies, while Level-III-studies comprised open label trials excluding case reports. They identified 218 publications on pharmacological interventions in HD since 1965 and among them were 20 level-I, 55 level-II, 54 level-III trials, and 89 case reports. Chorea was the primary end point in all level-I and level-II symptomatic intervention trials. There is some evidence for treating chorea with haloperidol or fluphenazine, and less evidence for olanzapine. These three drugs have been considered “possibly useful”
Table 4. Commonly used medications in the management of HD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Indication</th>
<th>Side effects</th>
<th>Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine</td>
<td>Binds vesicular monamine transporters, inhibiting uptake of monoamines into synaptic vesicles; also blocks postsynaptic dopamine receptors</td>
<td>Hyperkinetic movement disorders</td>
<td>Drowsiness, Parkinsonism (around 30%), depression, insomnia, anxiety, acute dystonia, rarely confusion, orthostatic hypotension, hallucinations. NB No reports of tardive dyskinesia, but neuroleptic malignant syndrome has been reported.</td>
<td>12.5 mg bd, increased slowly to 12.5–25 mg tds (max 200 mg/day)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Serotonin-dopamine (D₂) antagonist</td>
<td>Hyperkinetic movement disorders; Mood swings; psychosis</td>
<td>Prolonged QT interval, postural hypotension, hyperglycemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), fatigue, gastrointestinal</td>
<td>2 mg od, initially then usually 2–3 mg bd, max 16 mg/day, Liquid available</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Serotonin-dopamine (D₂) antagonist</td>
<td>Hyperkinetic movement disorders; Mood swings; psychosis; Depression; weight loss</td>
<td>Prolonged QT interval, postural hypotension, hyperglycemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), marrow depression, hepatitis, fatigue. Caution with prostatic hypertrophy</td>
<td>10 mg od adjusted as required to 5–20 mg od. Max 20 mg/day</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Selective serotonin reuptake inhibitor (SSRI)</td>
<td>Depression</td>
<td>Gastrointestinal, anorexia, hypersensitivity, drowsiness, syndrome of inappropriate antidiuresis (SIADH), postural hypotension, confusion</td>
<td>20 mg, increasing to 60 mg max</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>Depression</td>
<td>Less sedating than citalopram, gastrointestinal, anorexia, hypersensitivity, SIADH, blood dyscrasia</td>
<td>20 mg, increasing to 60 mg max</td>
</tr>
<tr>
<td>Mirtazepine</td>
<td>Presynaptic α₂-antagonist, increases central noradrenaline and serotonin activity</td>
<td>Depression, weight loss</td>
<td>Drowsiness, tremor, myoclonus, reversible agranulocytosis</td>
<td>15 mg nocte, increasing to 45 mg (max) as required</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Alters GABA, glutamatergic activity, and T-type calcium channel and potassium channel conductance</td>
<td>Mood swings</td>
<td>Hyperammonemia, drowsiness, blood dyscrasia, hepatitis, dizziness, gastrointestinal, cognitive disturbance, endocrine</td>
<td>200 mg tds, increasing to 2.5 g max if required</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Inhibition of voltage-gated sodium channels. Action on monoamine, acetylcholine, and NMDA receptors</td>
<td>Mood swings, weight loss</td>
<td>Drowsiness, blood dyscrasia, hepatitis, hyponatremia, dizziness, gastrointestinal</td>
<td>Usually 200–1,600 mg in 2–3 daily doses (max 2 g)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Inhibition of voltage-gated sodium channels</td>
<td>Mood swings</td>
<td>Hypersensitivity, blood dyscrasia, dizziness, gastrointestinal, depression</td>
<td>25 mg/day increasing to 250 mg bd (max) if required</td>
</tr>
</tbody>
</table>

for the treatment of chorea in this analysis. Other substances (e.g. amantadine, riluzole, and TBZ) are considered “investigational” for chorea. A well-controlled dose-finding study of TBZ for the treatment of Huntington’s chorea was published by the Huntington Study Group (TETRA-HD) in 2006.20 84 ambulatory HD patients with chorea (total maximal chorea ≥10 on the Unified Huntington’s Disease Rating Scale [UHDRS]) were randomly allocated to receive TBZ (n = 54) or placebo (n = 30) for 12 weeks. Over the first 7 weeks, TBZ was titrated up to 100 mg/day or until the desired antichoreic effect occurred or intolerable adverse effects supervened. For the last 5 weeks, patients received a consistent dose unless adverse events prevented a patient from remaining at that dose. The primary outcome was the change from baseline in the unified Huntington disease rating scale (UHDRS) chorea score. The change from baseline on the Clinical Global Impression (CGI) scale (range 0–7, with a higher score indicating a worse outcome) was also evaluated, and adverse events were recorded throughout the study. TBZ treatment resulted in a reduction of 5.0 units in chorea severity compared with a reduction of 1.5 units on placebo treatment (adjusted mean effect size = −3.5 ± 0.8 UHDRS units [mean ± SE]; 95% CI: −5.2, −1.9; p < 0.0001). The improvement in chorea at week 12 was greater in patients who received TBZ doses of 50 mg/day or less (adjusted mean treatment effect −6.24, 95% CI −8.56 to −3.93) than in patients who received more than 50 mg/day (−3.65, 95% CI −5.70 to −1.60). TBZ-treated patients measured more favorably compared with the placebo cohort on the CGI Improvement scale (improvement of −0.7 vs placebo patients; 95% CI −1.3, 0.2). There were five study withdrawals in the TBZ group and five serious adverse events (SAEs) in four subjects (drowning suicide, complicated fall, restlessness/suicidal ideation, and breast cancer) compared with one withdrawal and no SAEs in the placebo group. This trial showed that TBZ was effective in reducing chorea symptoms and improving global outcome in HD patients. However the dose should be individually titrated based on tolerability and adverse effects.

A study by Fasano et al21 showed that TBZ was well tolerated and produced long-term improvement of motor symptoms in Huntington disease patients, although a slight reduction of benefit occurred during the course of treatment. 68 Huntington disease patients (mean disease duration, 55.8 ± 34.7 months) were analyzed who had been treated with TBZ for a mean period of 34.4 ± 25.2 months (median, 34 months; mode, 48 months; range, 3–104 months). They measured the variation from pretreatment of the motor score of UHDRS at the first follow-up visit and at the latest. Mean UHDRS-chorea underscore at the time of the pretreatment visit was 10.4 ± 4.1 (range, 0–28). At the first follow-up, 9.7 ± 7.8 months after the prescription of TBZ (mean dose, 35.3 ± 14.7 mg), mean score of chorea was 8.2 ± 4.1 (−21% compared with baseline), whereas at the latest follow-up visit (mean dose, 57.5 ± 14.7 mg), it was 9.5 ± 5.0 (9%). During the follow-up, the clinical benefit persisted, but the magnitude was reduced despite a progressive increase of the doses (up to 60%). Motor improvement was not influenced by sex, or doses or duration of therapy; age at onset was the only predictor of a good outcome (patients with later onset have a better outcome). Five patients (7%) did not gain any improvement, and TBZ was discontinued. There were 2 withdrawals because of side effects (rapid worsening of psychiatric disturbance and disabling asthenia); 34 patients reported at least 1 side effect.

There are hardly any studies comparing TBZ versus typical neuroleptics in regards to efficacy and safety. In one non-randomized single crossover study of 11 Huntington's disease patients,22 TBZ was not superior to haloperidol in improving chorea. There are a few studies in regards to pharmacodynamics of TBZ such as the duration of action.

Kenney et al23 conducted an observational study on the short-term clinical effects of TBZ on choreic movements in Huntington’s disease patients. A total
of 10 patients on stable doses of TBZ presented without taking the usual morning dose (last dose was last evening). They were assessed using UHDRS motor assessment and Beck Depression Inventory. The usual morning dose of TBZ was then administered and patients were followed with serial UHDRS motor examinations approximately every 2 hours until choreic movements subsided and then returned. The UHDRS chorea score decreased on average 42.4% ± 17.8% after administration of TBZ. The duration of effect varied from a minimum of 3.2 hours to a maximum of 8.1 hours (mean = 5.4 ± 1.3). No patient experienced an adverse event related to TBZ or its withdrawal. The study concluded that during short-term follow-up after a single dose, TBZ improves chorea for approximately 5 hours.

A study by Frank et al.24 showed the effectiveness of TBZ in reducing chorea as well as the short duration of action, by evaluating the change in Huntington disease-

**Table 5. Pharmacology of tetrabenazine (TBZ).**

**Compound:**
- Monoamine depletor for oral administration
- Molecular weight: 317.43, pKa: 6.51. Formula: C_{19}H_{27}NO_{3}
- White to yellow crystalline powder, sparingly soluble in water
- 12.5 or 25 mg of TBZ as active ingredient

**Pharmacodynamics:**
- Precise mechanism of action unknown
- Reversible depletor of monoamines from nerve terminals
- Reversibly inhibits human vesicular monoamine transporter 2

**Pharmacokinetics:**
- Extent of absorption on oral administration is at least 75%
- Peak plasma concentration reached within 1–1.5 hrs post dose
- Food has no effect on mean plasma concentrations and TBZ can be given with or without food
- TBZ protein binding ranges from 82%–85%

**Metabolism and Excretion:**
- Two major circulating metabolites with half lives of 4–8 hrs and 2–4 hrs
- These are formed by carbonyl reductase in the liver
- At least 19 metabolites have been identified
- Neither TBZ nor its major metabolites are likely to inhibit or induce any of the major CYP450 enzymes
- Metabolites are primarily renally eliminated
- Unchanged TBZ has not been found in human urine

**Special populations:**
- Pharmacokinetics have not been studied in pediatric patients
- Pharmacokinetics have not been studied in geriatric patients
- Effect of renal insufficiency on TBZ pharmacokinetics have not been studied
- Contraindicated in patients with hepatic impairment since it is not possible to adjust the dose of TBZ in hepatic impairment to ensure safe use

**Drug interactions:**
- not significant since TBZ and metabolites are not enzyme inhibitors or inducers

**Indications and Contraindications:**
- Treatment of chorea associated with Huntington’s disease
- Contraindicated (CI) in patients who are actively suicidal or with uncontrolled or inadequately controlled depression
- CI in patients with impaired hepatic function
- CI in patients taking monoamine oxidase inhibitors (MAOIs) and reserpine

**Warnings:**
- Periodically evaluate need for TBZ and distinguish between side effects and symptoms due to progression of HD
- Need for careful titration of TBZ, some side effects may be dose-dependent
- Doses above 50 mg may require CYP2D6 genotyping
- Increase risk of depression and suicide in HD which are aggravated by TBZ
- Risk of neuroleptic malignant syndrome (NMS)

**Drug interactions:**
- Concomitant use with neuroleptic drugs may increase risk of QTc prolongation, NMS and extrapyramidal disorders
- Concomitant use of alcohol may worsen sedation
- No other significant drug interactions noted
- Caution while switching from reserpine to TBZ, at least 20 days should elapse after stopping reserpine before starting TBZ

**Adverse Events (AE):**
- Commonly reported AE are sedation, fatigue, depression, nausea
- Extrapyramidal reactions such as akathisia, parkinsonism
- Increase risk of dysphagia, irregular heart beat, orthostatic hypotention
- No drug abuse and dependence is seen
- Overdose with acute dystonia, oculogyric crisis, nausea, vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, tremor

of TBZ. The duration of effect varied from a minimum of 3.2 hours to a maximum of 8.1 hours (mean = 5.4 ± 1.3). No patient experienced an adverse event related to TBZ or its withdrawal. The study concluded that during short-term follow-up after a single dose, TBZ improves chorea for approximately 5 hours.
associated chorea resulting from TBZ treatment withdrawal. Thirty patients treated in the long term were randomized to 1 of 3 groups assigned to withdraw from TBZ in a double-blind, staggered fashion during a 5-day period. The UHDRS chorea scores of subjects withdrawn from TBZ treatment increased by 5.3 units from days 1 to 3, whereas the scores of the group with partial or no withdrawal of TBZ treatment increased by 3.0 units (P = 0.0773). A post hoc analysis of the linear trend was positive for re-emergent chorea (P = 0.0486). No serious adverse events were reported after abrupt withdrawal of TBZ treatment.

There are few studies on the adverse effects of TBZ. Jankovic et al\textsuperscript{25} published a paper in 1997 which studied the long term treatment effects of TBZ in 400 patients who had various hyperkinetic movement disorders. The average duration of TBZ treatment was 28.9 months (+/-31.1; range, 0.25 to 180 months). The response was rated on a scale of 1 to 5 (1 = marked improvement, 4 = no response, 5 = worsening) and was assessed initially and at the last clinic visit. The global response rating of 1 (marked improvement) was recorded in 89.2% of 93 patients with tardive stereotypy, 83.3% of 12 with myoclonus, 82.8% of 29 with Huntington’s disease, 80.5% of 82 with tardive dystonia, 79.3% of 29 with other movement disorders, 62.9% of 108 with idiopathic dystonia, and in 57.4% of 47 with Tourette’s syndrome. The most common side effects included drowsiness (36.5%), parkinsonism (28.5%), depression (15.0%), insomnia (11.0%), nervousness or anxiety (10.3%), and akathisia (9.5%). The side effects were controlled with reduction in the dosage. TBZ was shown to be effective and safe in various hyperkinetic disorders and unlike typical neuroleptics did not cause tardive dyskinesia.

Kenney et al\textsuperscript{26} conducted a retrospective chart review to ascertain the long-term tolerability of TBZ and seek determinants of tolerability in the treatment of hyperkinetic movement disorders. The review was performed on patients treated with TBZ between 1997 and 2004. Efficacy of TBZ was assessed by a 1 to 5-point response scale (1 = marked reduction in abnormal movements, 5 = worsening). A total of 448 patients (42% male) were treated for a variety of hyperkineties, including tardive dyskinesia (n = 149), dystonia (n = 132), chorea (n = 98), tics (n = 92), and myoclonus (n = 19). The mean age at onset of the movement disorder was 43.0 ± 24.2 years, with TBZ starting at a mean age of 50.0 ± 22.3 years. Patients remained on treatment for a mean of 2.3 ± 3.4 years. An efficacy response rating of 1 or 2 was sustained in the majority of patients between the first and last visit. Common AEs included drowsiness (25.0%), Parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%). Comparison of log-likelihood ratios revealed that age was a reliable predictor of Parkinsonism (P < 0.0001). They concluded that TBZ is a safe and effective drug for the long-term treatment of hyperkinetic movement disorders.

Rarely, neuroleptic malignant syndrome has been reported with TBZ usage in Huntington’s disease.\textsuperscript{27-29} Kenney et al\textsuperscript{30} retrospectively reviewed the charts of 518 patients treated with TBZ to determine whether a history of depression predisposes hyperkinetic patients treated with TBZ to a recurrence or worsening of this symptom. Of those patients with no history of depression, 28 (11.4%) of 246 were newly diagnosed with depression. Patients with a documented history of depression experienced a significantly higher rate of worsening in 50 (18.4%) of 272 cases (P = 0.03). So depression is more likely to occur or worsen in patients with a preexisting history of depression. However, patients with a history of depression experienced more improvement of their hyperkinesia compared to those without a history of depression (P < 0.01).

Discussion

There have been several approaches to treating chorea in Huntington’s disease. These are dopamine antagonism to counter the hyperkinetic state by depleting dopamine (reserpine, TBZ), receptor blockade (neuroleptics, TBZ) or inhibition of presynaptic release (apomorphine). Among dopamine depletors, TBZ tends to have less systemic side-effect profile when compared to reserpine. This is probably because TBZ acts selectively towards VMAT2 (found mostly in neurons), whereas reserpine acts on both VMAT2 and VMAT1 (found in the periphery). It is not entirely clear as to why TBZ works well in chorea as opposed to reserpine. Perhaps it could be due to the reversible inhibition of VMAT2 as well as the dual action of TBZ at the pre and post synapse. Since we have some data that post synaptic D\textsubscript{2} antagonism occurs at higher concentrations, TBZ is probably more effective at higher doses, but the dose related side-effects would increase as well. The higher concentrations required could also mean that the post

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synaptic D₂ receptor blockade might be inconsistent for TBZ, which is probably why long term side effects (like tardive dyskinesia) are less common unlike neuroleptics. Lithium has been shown to have a potentiating effect on anti-dopaminergic drugs.⁴³ There have been some studies on lithium modulating the effect of TBZ,²⁵,⁴¹,⁴² with possible reduction in the required effective dose of TBZ in combination with lithium which helps decrease dose related side effects.²⁵ Chorea and tremors secondary to lithium will need to be kept in mind. A randomized controlled trial would be useful to properly assess this combination, safety and efficacy. While there has been a randomized controlled trial for TBZ in the treatment of chorea, there has hardly been any level 1 study in regards to neuroleptics except clozapine. This is surprising given that neuroleptics are very often used in the clinical setting to treat chorea. There is some evidence for treating chorea with typical neuroleptics such as haloperidol or fluphenazine. However, these neuroleptics may accelerate functional decline⁴⁴ and may induce tardive dystonia.⁴⁵ Atypical neuroleptics have had less success, for example clozapine showed poor results,⁴⁶,⁴⁷ but there is some evidence for olanzapine.⁴⁸–⁵⁰ Also it would be interesting to have comparative studies between TBZ and neuroleptics. Apomorphine at low dose may cause inhibition of dopamine release by dopaminergic autoreceptor stimulation. It proved effective in a non-randomized double blinded crossover study.⁵¹ The possible excitotoxic neuronal death mechanism of pathogenesis has given rise to another approach, which is to use anti-glutaminergic drugs. However the drugs tried, including amantadine,⁵¹,⁵² remacemide,⁵³,⁵⁴riluzole,⁵⁴ lamotrigine,⁵⁵ showed none or poor benefit. Among the side effects of TBZ, depression and suicidal nature are of concern. A pre-existing diagnosis of depression did not seem to be an absolute contraindication, although worsening is likely to be expected. Working closely with the patient’s psychiatrist in known cases of depression, and a psychiatric screening of all patients to be tried on TBZ is prudent.

To summarize, there are currently no therapies available that slow the progression of neurodegeneration in HD. Chorea can have a considerable impact on daily functioning and availability of numerous symptomatic therapies and their judicious use serves to improve the quality of life for HD patients. Traditionally, neuroleptics have been considered to be first line therapy for HD chorea. However treatment with neuroleptics carries a considerable risk for adverse events such as dystonia, parkinsonism and tardive dyskinesia and their use needs to be carefully monitored. TBZ is effective in reducing the burden of chorea and improving global outcome in HD patients. The dose should be adjusted for each individual patient depending upon their tolerance and clinical response. Appropriate clinical studies and post-marketing surveillance will be required to assess the long term benefits and risks of TBZ therapy in HD. The potential for serious adverse events such as depression and suicide must be carefully weighed against the clinical benefits of TBZ in HD patients.

Conflict of Interest Disclosures
Shilpa Chitnis is a consultant for Medtronic and a speaker for Medtronic, Teva Neuroscience, IPSPU and Lundbeck.

References
Tetrabenazine in Huntington’s disease chorea


