



# LONG-TERM SAFETY AND EFFICACY OF TETRABENAZINE IN THE TREATMENT OF CHOREA ASSOCIATED WITH HUNTINGTON'S DISEASE

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## ABSTRACT (UPDATED)

**Objective:** To assess long-term safety and efficacy of tetrabenazine (TBZ) for chorea associated with Huntington's disease (HD).

**Background:** Although TBZ was not approved by the FDA (for chorea associated with HD) until 2008, it has been used at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine (BCM) since 1979.

**Methods:** In an open-label, Phase IIIb study conducted through an Investigational New Drug Application (IND) granted to Dr. Jankovic in 1979, patients with hyperkinetic movement disorders were evaluated at PDCMDC. TBZ was used as a "last resort" when other medications failed to provide satisfactory symptom control. For HD-chorea patients, all previous chorea treatments were discontinued before TBZ initiation. Patients were initially hospitalized and TBZ was started at 12.5 mg/day (≤300 mg/day maximum). Dosage was increased every 3 days until a troublesome adverse event (AE) occurred. TBZ was then down-titrated to the optimal dosage, defined as dosage that provided best possible efficacy with no or tolerable AEs. Visits were 6 weeks after hospitalization and every 3 months thereafter. Responses were rated on a scale of 1–5, with 1 = marked chorea reduction, excellent improvement in function; 2 = moderate chorea reduction, very good improvement in function; 3 = fair chorea improvement, only mild improvement in function; 4 = poor or no response for chorea and function; and 5 = worsening chorea and some functional deterioration.<sup>1</sup> Dosage, efficacy, and AEs were collected at each visit.

**Results:** By 2004, 98 HD-chorea patients had been treated with TBZ for a mean of 3.1±2.5 years (range: <1 to 11.4 years on TBZ); 54% had received TBZ >2 years. The 5 most common AEs possibly/probably related to TBZ were somnolence (31%), insomnia (14%), depression (13%), akathisia (11%), and nervousness (10%). Of those patients with valid ratings, 75% had a "marked or moderate" response to TBZ at their optimal dosage.

**Conclusions:** TBZ provided sustained improvement in chorea and function with AE rates comparable to those that have been previously reported.

## BACKGROUND

- Tetrabenazine (TBZ) selectively and reversibly depletes monoamines from nerve terminals by inhibiting the vesicular monoamine transporter type 2 (VMAT2)<sup>2</sup>
- Prior to approval of TBZ by the US Food and Drug Administration (FDA) for the treatment of chorea associated with Huntington's disease (HD), some US patients were able to obtain the drug from abroad, while others received TBZ under physician Investigational New Drug Applications (INDs)
- The Parkinson's Disease Center and Movement Disorder Clinic (PDCMDC) at Baylor College of Medicine administered TBZ under Dr. Jankovic's IND, issued in 1979<sup>3,4</sup>
- Patients were enrolled and treated at the PDCMDC under Protocol H-721, "Compassionate Use of TBZ in the Treatment of Hyperkinesias," a single-center, open-label, individualized-dosage study<sup>3,4</sup>
- From January 1979 through February 2004, 165 patients received TBZ for chorea
- During this 25-year period, 98 patients with chorea associated with HD were treated from <1 to >11 years and had complete records available for analysis<sup>2</sup>
- The PDCMDC has the longest history with TBZ for the treatment of chorea associated with HD and the largest patient database for this population

## OBJECTIVE

- To assess long-term safety and efficacy of TBZ treatment of chorea associated with HD

## METHODS

### Patients

- Patients with hyperkinetic disorders underwent a detailed neurologic examination and a video recording designed to capture the phenomenology and severity of the disorder
- Male and female patients with HD-associated chorea were eligible for treatment with TBZ if their chorea interfered with activities of daily living, occupational activities, and/or academic activities
- Patients were also required to have failed available conventional treatments or not derived satisfactory relief from these treatments

### Treatment

- Treatment with TBZ was started at 12.5 mg/day and the dosage was gradually increased by 12.5-mg/day increments every 3–7 days until satisfactory improvement of the chorea was achieved or troublesome adverse events (AEs) occurred. If a troublesome AE occurred, the dosage was down-titrated to the optimal dosage, defined as dosage that provided the best possible efficacy with no or tolerable AEs.<sup>2</sup>

### Assessments

- From 1980–1991, patients were initially admitted to hospital for TBZ treatment and were monitored for postural hypotension and other potential AEs. After 1991, because of the low incidence of AEs, TBZ treatment was administered in the outpatient clinic.
- Outpatient visits were scheduled 6 weeks after treatment initiation and every 3 months thereafter
- Dosage, efficacy, and AEs were collected at each clinic visit and entered on a Case Report Form (CRF)
- Response to treatment was rated on a scale of 1–5<sup>1</sup>
  - 1 = marked chorea reduction, excellent improvement in function
  - 2 = moderate chorea reduction, very good improvement in function
  - 3 = fair chorea improvement, only mild improvement in function
  - 4 = poor or no response for chorea and function
  - 5 = worsening chorea and some functional deterioration

### Data Extraction

- Data were extracted from the Baylor PDCMDC CRFs into a database
- The data transfer was audited and the data analyzed
- Of the 165 patients listed in the Clinic Log as having received TBZ after being diagnosed with chorea, 98 patients had chorea associated with HD and were used for this analysis

### Statistical Analysis

- Descriptive statistics were employed to summarize demographic and illness characteristics, response to treatment, and AEs

## RESULTS

### Demographics and Patient Disposition

- Patient demographics are shown in Table 1
- By 2004, 17 patients had withdrawn because of AEs

**Table 1. Demographics and Patient Disposition**

Demographic	N=98
Female, n (%)	58 (59)
Age at study entry, mean (range), years	55 (31–79)
<b>Ethnic origin, n (%)</b>	
African-American	7 (7)
Asian	1 (1)
Caucasian	78 (80)
Hispanic or Latino	6 (6)
Native Hawaiian or Pacific Islander	2 (2)
Other	3 (3)
Missing	1 (1)
Time since symptom onset, mean (range), years	8 (0–35)
Length of study participation <sup>a</sup> , mean (range), years	3 (<1–11.4)
Cumulative TBZ treatment duration >2 years, n (%)	53 (54)
<b>Treatment status, n (%)</b>	
Continuing treatment	19 (19)
Withdrawn from treatment	79 (81)
Death	6 (6)
Adverse event	17 (17)
Lack of efficacy	4 (4)
Disorder resolved spontaneously	1 (1)
Travel/financial reasons	7 (7)
Other	44 (45)

<sup>a</sup>Length of participation for 1 patient is unknown.

- Depression (n=3) and parkinsonism (n=3) were the most common AEs leading to withdrawal (Table 2)

**Table 2. AEs Leading to Study Withdrawal**

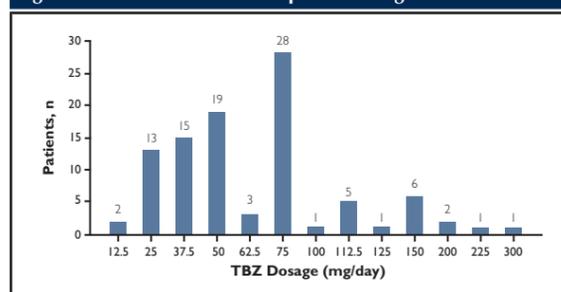
Adverse event	n
Depression	3
Parkinsonism	3
Agitation	2
Nausea	2
Akathisia	1
Anxiety	1
Constipation	1
Cough increased	1
Dehydration	1
Dizziness	1
Dyspepsia	1
Dysphagia	1
Emotional lability	1
Headache	1
Hostility	1
Insomnia	1
Nervousness	1
Somnolence	1
Vomiting	1

AE=adverse event.

### TBZ Dosage

- The average daily dosage of TBZ was 68.3 (±38.1) mg/day
- Dosing was highly individualized and ranged from 12.5 to 300 mg/day (Figure 1)

**Figure 1. Distribution of TBZ Optimal Dosage**

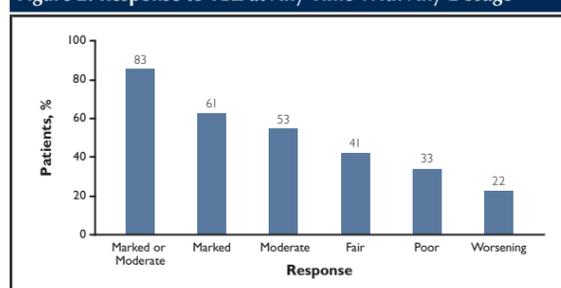


TBZ=tetrabenazine.  
Data missing for 1 patient.

### Efficacy

- 92 of 98 patients had complete efficacy data
- At any time/dosage during the entire study, 83% of patients had a "marked or moderate" improvement in chorea and function (Figure 2)
- 22% of patients had worsening of symptoms at any time/dosage

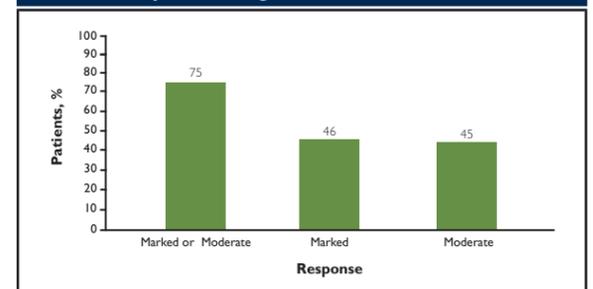
**Figure 2. Response to TBZ at Any Time With Any Dosage**



Patients could be counted more than once depending upon response to treatment.

- At optimal dosage (dosage that provides the greatest efficacy with tolerable AEs), 75% of patients had a "marked or moderate" response to TBZ (Figure 3)

**Figure 3. Patients With "Marked" and/or "Moderate" Response to TBZ With Optimal Dosage**



TBZ=tetrabenazine.  
Patients could be counted more than once depending upon response to treatment.

### Safety

- The 5 most commonly reported AEs possibly or probably related to TBZ were somnolence, insomnia, depression, akathisia, and nervousness (Table 3)
- As there was no placebo control, we have provided safety data from the TETRA-HD trial<sup>5</sup> for comparison
- AEs were similar between these studies

**Table 3. Incidence of AEs Possibly or Probably Related to TBZ**

AE, n (%)	Baylor (N=98)	TETRA-HD <sup>5</sup> (N=54)
Somnolence	30 (31)	17 (31) <sup>a</sup>
Insomnia	14 (14)	14 (26)
Depression	13 (13)	8 (15) <sup>b</sup>
Akathisia	11 (11)	—
Nervousness	10 (10)	5 (9)
Parkinsonism	7 (7)	—
Nausea	7 (7)	7 (13)
Asthenia	6 (6)	—

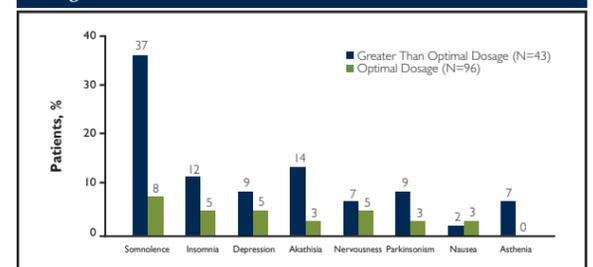
AE=adverse event; TBZ=tetrabenazine.

<sup>a</sup>Combined drowsiness/somnolence.

<sup>b</sup>Depression here applies to a description of mood, rather than a formal diagnosis.

- AEs were reported more frequently at dosages greater than optimal dosage (Figure 4)

**Figure 4. Incidence of AEs at Greater Than Optimal vs. Optimal Dosage**



AE=adverse event.

## LIMITATIONS

- Although the data were prospectively collected, the analysis was retrospective
- Not a double-blind, placebo-controlled, randomized study

## CONCLUSIONS

- As the largest and longest trial, the data from Baylor's PDCMDC trial provides valuable insight into the long-term safety and efficacy of TBZ treatment of HD-related chorea
- TBZ provided sustained improvement in chorea and function
- The most frequent AEs (somnolence, insomnia, depression, akathisia, nausea, and parkinsonism) and their rates reported here are comparable to other reports of TBZ<sup>4,5</sup>
- No TBZ-related tardive dyskinesia has been documented in this or other studies
- At their optimal dosage, 75% of patients had "marked or moderate" improvement with minimal dosage-related AEs

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## ACKNOWLEDGMENTS

The authors thank Statistics Collaborative, Inc. in Washington, DC, for providing the requested statistical summaries.