

Articles

Safety and Efficacy of Tetrabenazine and Use of Concomitant Medications During Long-Term, Open-Label Treatment of Chorea Associated with Huntington's and Other Diseases

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Abstract

Background: Although tetrabenazine, a drug that depletes presynaptic dopamine by inhibiting vesicular monoamine transporter 2 (VMAT2), was approved by the U.S. Food and Drug Administration in 2008 for the treatment of chorea associated with Huntington's disease (HD), there is a paucity of data on its long-term efficacy and safety.

Methods: Approximately 2,000 patients with a variety of hyperkinetic movement disorders had been treated with open-label tetrabenazine at the Movement Disorders Clinic, Baylor College of Medicine, since 1979. Tetrabenazine was usually started at 12.5 mg/day, and the dosage was gradually increased (up to 300 mg/day). Responses were rated by the investigator 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, some functional deterioration. Efficacy and safety were analyzed retrospectively.

Results: By 2004, 98 HD chorea patients had received tetrabenazine for a mean of 3.1 years (range ≤1–11.4 years). Of those with valid ratings, 75% had either marked or very good responses (rating 1 or 2) at their optimal dosages. The most common adverse events occurring in ≥5% of the patients were somnolence (39%), insomnia (33%), depression (31%), accidental injury (26%), and dysphagia (19%). Efficacy and safety were comparable to results for non-HD chorea patients.

Discussion: Tetrabenazine treatment was associated with long-term improvement in chorea. Adverse event rates were comparable to those reported from controlled trials.

Keywords: Huntington's disease, tetrabenazine, chorea, VMAT2 inhibition, monoamines, clinical trial

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Introduction

Tetrabenazine is a potent, selective, reversible, and short-lasting depletor of nerve terminal monoamines, especially dopamine.^{1,2} It directly inhibits the presynaptic vesicular monoamine transporter 2 (VMAT2), which, in humans, is expressed almost exclusively in the brain. Following oral administration, it is nearly completely absorbed from the digestive tract and rapidly transformed through first-pass metabolism in the liver by the enzyme carbonyl reductase into a pair of stereoisomeric metabolites, α -dihydro-tetrabenazine (α -HTBZ) and

β -HTBZ, which, in turn, are metabolized, again in the liver, primarily by cytochrome P450 CYP2D6. Tetrabenazine and α -HTBZ (but not β -HTBZ) are potent VMAT2 inhibitors. Circulating concentrations of the two primary, first-pass metabolites vary markedly from patient to patient, which may account for the substantial optimal dosing variability observed between patients. The parent compound and its two metabolites do not inhibit the major CYP450 isoforms, and, therefore, concomitant administration of tetrabenazine with drugs that are CYP450 substrates should not affect their metabolism. On the

other hand, α -HTBZ and β -HTBZ are CYP2D6 substrates, and their metabolism may be affected by CYP2D6 inhibitors.

Results from four controlled clinical trials,^{1,2,3-5} including the pivotal, randomized controlled TetraHD study,³ supported the U.S. Food and Drug Administration's (FDA) approval of tetrabenazine for chorea associated with Huntington's disease (HD) in August 2008.^{1,2} Prior to the FDA approval, U.S. patients were able to obtain the drug through physician Investigational New Drug (IND) Applications. These IND studies typically made tetrabenazine available as a "last resort" therapy, when other medications had failed to provide satisfactory control. Tetrabenazine was administered to selected patients with a wide range of hyperkinetic disorders at the Parkinson's Disease Center and Movement Disorder Clinic (PDCMDC) at the Baylor College of Medicine (BCM) under Dr. Jankovic's IND study, beginning in 1979.^{6,7}

This is the first full report of all patients with chorea that spans the entire study period. Previous reports included those with other hyperkinetic disorders and spanned only part of the full study periods.^{6,7} Through this open-label, observational study of patients treated between 1979 and 2004, we evaluated the long-term efficacy and safety effects of tetrabenazine at optimal and other dosages, and sought to determine whether efficacy and safety varied by subgroups of patients based on the use of concomitant medications, particularly antidepressants and neuroleptics, as well as chorea severity, all in a less restrictive, real-world setting.

Methods

Patients were enrolled and treated at the PDCMDC under Protocol H-721, "Compassionate Use of Tetrabenazine in the Treatment of Hyperkinesias," a single-center, open-label, individualized-dosage, observational study.^{6,7} This study protocol was conducted in accordance with FDA regulations for investigational new drugs outlined in 21 Code of Federal Regulations (CFR), Sections 312, 50, and 56, "Good Clinical Practice." All patients signed an informed consent approved by the BCM Institutional Review Board and were videotaped before tetrabenazine therapy was begun.^{6,7}

Patients

Patients with chorea were approached and offered the opportunity to participate in the study if their chorea had been troublesome (i.e., chorea had to have interfered with activities of daily living, occupational activities, and/or academic activities). Further, conventionally available treatments for chorea had to have failed to provide satisfactory symptomatic relief. Patients were excluded if they were unwilling to comply with study requirements or were unable to provide informed consent.

From 1980 to 1991, study patients were initially admitted to the hospital for the start of tetrabenazine treatment and were monitored for postural hypotension and other potential adverse effects. After 1991, because of the low incidence of adverse effects, all participants began tetrabenazine therapy in the outpatient clinic.

At entry into the study, chorea severity generally ranged from moderate to severe/disabling. We analyzed data from two subgroups

of HD patients to determine if there were differences in tetrabenazine safety and efficacy for those with moderate chorea versus those with severe/disabling chorea.

Dosing

Prior to 1991, tetrabenazine dosage was initiated at 25 mg/day, and increased by 25 mg every several days until a total dosage of 150–200 mg was achieved, or an adverse event occurred. The treatment regimen was modified as the PDCMDC gained experience with tetrabenazine. Beginning in 1991, tetrabenazine dosage was titrated (by either 12.5- or 25-mg increments every 3–7 days) to achieve a response without troublesome adverse events. If a troublesome adverse event occurred, the dosage was down-titrated to the last greatest tolerated dosage.

Outpatient visits were scheduled 6 weeks post treatment initiation and every 3 months thereafter. Dosage, efficacy, and adverse events were collected at each clinic visit and recorded on case report forms.

Disease severity and response ratings

Disease severity was determined by the investigator and rated on a scale of 1–4: 1 = mild, 2 = moderate, 3 = severe, and 4 = disabling.

Efficacy responses to tetrabenazine were rated on a scale of 1–5: 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, some functional deterioration.⁸ Functional improvement was assessed by the ability to perform activities of daily living and was based on information obtained from patients or their caretakers.⁸

A hierarchical algorithm was used to derive the "standard or best dosage" a patient received. If the last dosage was received for at least 21 days, then this was considered the "standard or best dosage" for that patient. If the last dosage was received for fewer than 21 days, then the "standard or best dosage" was defined as the most recent dosage received for at least 21 days. If neither of those criteria could be met, then the "standard or best dosage" was that dosage received for the greatest duration.

Concomitant medication use

Because patients with HD also exhibit neuropsychiatric symptoms, they are often treated with antidepressants and neuroleptics. During the study, participants were treated, when necessary, with other drugs (including psychotropic drugs), as determined by the investigator. Concomitant medications were recorded with start date (as month) relative to the start of tetrabenazine. Length of time on the concomitant medication was recorded in days. Analyses in relation to other concomitant medications or adverse events were not conducted.

Safety evaluations

Safety and tolerability were evaluated primarily by documentation of adverse events, which were elicited and recorded at each follow-up visit. For each event, the investigator determined its relationship to

tetrabenazine (probable, possible, unlikely, none), and categorized it as “severe” or “not severe.” The original terms used to identify adverse events in the case report forms were translated into Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)⁹ dictionary-coded preferred terms at the time of the 2004 analysis. The number and percentage of patients experiencing one or more adverse events was tabulated by the onset date of the event (i.e., elapsed time since start of treatment) and “standard or best dosage” of tetrabenazine.

Results

Patient disposition

From January 1979 through February 2004, 165 patients received open-label tetrabenazine for the treatment of chorea. Complete records were available for 145 patients. Of those, 98 had chorea associated with HD. Analyses of these 145 patients were conducted to assess long-term safety and efficacy of tetrabenazine for both HD and non-HD chorea. In 2004, data were extracted from the BCM case report forms into a database. The data transfer was audited, and the data analyzed. Of the 165 patients listed in the PDCMDC clinic log as having received tetrabenazine after being diagnosed with chorea, three were subsequently found to have been misclassified. Full patient disposition is provided in Figure 1.

Baseline demographics and clinical characteristics

Descriptive statistics were employed to summarize demographics, dosing, and clinical variables for all 145 patients (Table 1) and patient subsets (Table 2). Overall, patients with HD chorea and those with non-HD chorea shared similar characteristics. The major difference between the two groups was age. The HD chorea patients were, on average, older (54.8 years, range 31–79 years) than the non-HD chorea patients (mean age 44 years, range 3–80 years).

At study entry, of the entire group of 145 patients, chorea severity, as determined by the investigator (J.J.), was rated as mild for one, moderate for 69, severe for 59, and disabling for 16. Ninety-eight patients had chorea associated with HD, and were categorized by either moderate chorea (44) or severe/disabling chorea (54) at baseline. Overall, no notable differences were observed between the two groups in sex, age, time since symptom onset, length of study participation, and cumulative tetrabenazine treatment. In addition, baseline demographics and clinical characteristics, as well as time since first symptom onset, did not appear to be different for patients who had received concomitant antidepressants and neuroleptics compared with those who had not.

Etiologies of chorea for the non-HD chorea patients included Sydenham’s chorea (7), tardive chorea (7), hemi-chorea (6), cerebrovascular chorea (4), congenital chorea (3), post-infection chorea (3),

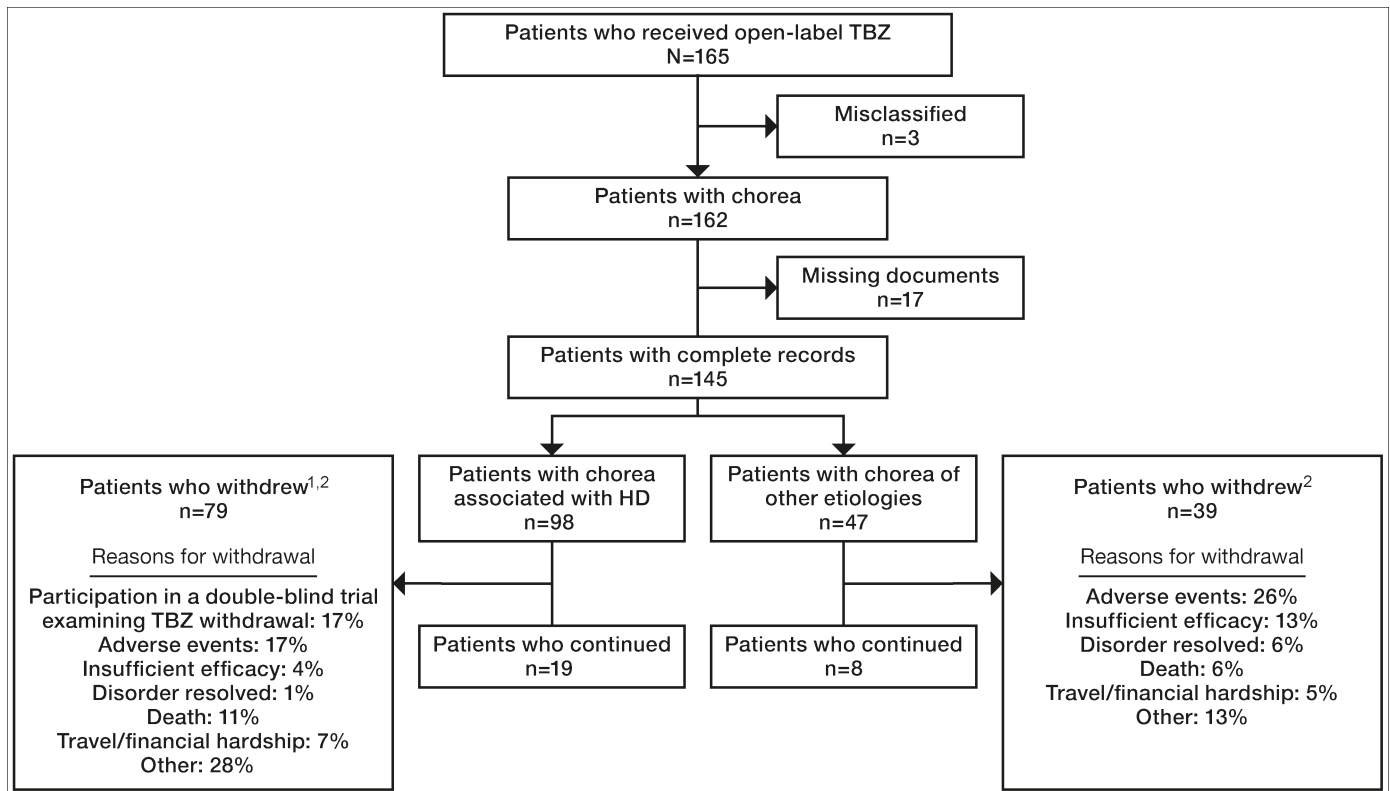


Figure 1. Patient Disposition. ¹At study cutoff on February 29, 2004, 118 of the 145 patients had withdrawn from treatment. Reasons for withdrawal included participation in a double-blind clinical trial examining withdrawal from tetrabenazine (TBZ) (12%), adverse events (20%), insufficient efficacy (7%), disorder resolved (3%), death (10%), travel/financial hardship (8%), and other (23%). Other reasons included the patient transferred care to another physician, the patient entered hospice or nursing home, inadequate follow-up information, progression of Huntington’s Disease (HD), and surgical treatment of movement disorder. ²See Table 3.) TBE, tetrabenazine; HD, Huntington’s Disease.

Table 1. Demographics and Patient Disposition

| Demographic | All Participants | HD Chorea | Non-HD Chorea |
|--|------------------|---------------|---------------|
| | N=145 | N=98 | N=47 |
| Sex, n (%) | | | |
| Female | 87 (60) | 58 (59) | 29 (62) |
| Age at study entry, mean (range), years | 51.3 (3–80) | 54.8 (31–79) | 44 (3–80) |
| Ethnic origin, n (%) | | | |
| African-American | 10 (7) | 7 (7) | 3 (6) |
| Asian | 3 (2) | 1 (1) | 2 (4) |
| Caucasian | 112 (77) | 78 (80) | 34 (72) |
| Hispanic or Latino | 12 (8) | 6 (6) | 6 (13) |
| Native Hawaiian or Pacific Islander | 3 (2) | 2 (2) | 1 (2) |
| Other | 4 (3) | 3 (3) | 1 (2) |
| Missing | 1 (1) | 1 (1) | |
| Time since symptom onset, mean (range), years | 7.9 (0–55) | 8.1 (0–35) | 7.4 (0–55) |
| Length of study participation, mean (range), years | 2.6 (<1–13.1) | 3.1 (<1–11.4) | NA |
| Cumulative TBZ treatment duration >2 years, n (%) | 70 (48) | 53 (54) | NA |

HD, Huntington's Disease; NA, Not Available; TBZ, Tetrabenazine.

autoimmune chorea (2), static encephalopathy (2), unknown etiology (3), and other (10).

Tetrabenazine dosage

Dosage was highly individualized and ranged from 12.5–300 mg/day for HD chorea patients (Figure 2), which was similar for those with non-HD chorea (12.5–150 mg/day). In addition, dosing was independent of chorea severity. The average daily dosages for HD patients with moderate chorea and severe/disabling chorea at baseline were 60.5 mg/day (range 16.9–138.1 mg/day) and 74.8 mg/day (range 21.4–225.5 mg/day), respectively.

Efficacy of tetrabenazine

Of the 145 total patients, 137 had valid response ratings. At any time and dosage during the entire study, 59% were judged to have had a marked response (efficacy rating 1), 49% had a very good response (efficacy rating 2), 40% had a mild response (efficacy rating 3), 31% had a poor response (efficacy rating 4), and 18% had worsened (efficacy rating 5). (Some patients had different scores at different visits,

thus the total percentage exceeds 100%.) Responses for those with HD chorea were 61% with marked, 53% with very good, 41% with mild, and 33% with poor responses. In addition, 22% had worsened. Of those with non-HD chorea, 56% had marked, 40% had very good, 38% had mild, and 27% had poor responses, while 11% had worsened.

Optimal tetrabenazine dosage

At any time/dosage during the entire study, 83% of patients with HD chorea had “marked or very good” improvement in chorea symptoms and functioning (Figure 3A). At optimal dosage (dosage that provided the greatest efficacy with tolerable adverse events), 75% of patients had a “marked or very good” response to tetrabenazine (efficacy ratings 1 and 2, respectively) (Fig. 3B).

Moderate versus severe/disabling HD chorea

Forty-two of 44 patients with moderate HD chorea and 50 of 54 with severe/disabling HD chorea had valid response ratings. At any

Table 2. Demographics and Patient Disposition for Subsets of Patients with HD Chorea

| Demographic | Moderate Chorea at Baseline (N=44) | Severe/Disabling Chorea at Baseline (N=54) | Concomitant Use of Antidepressant (N=71) | No Antidepressant (N=27) | Concomitant Use of Neuroleptic (N=53) | No Neuroleptic (N=45) |
|--|------------------------------------|--|--|--------------------------|---------------------------------------|-----------------------|
| Sex, n (%) | | | | | | |
| Female | 21 (48) | 37 (69) | 44 (62) | 14 (52) | 29 (55) | 29 (64) |
| Age at study entry, mean (range), years | 53 (31–75) | 56 (32–79) | 53 (31–73) | 60 (34–79) | 54 (31–78) | 55 (31–79) |
| Time since symptom onset, mean (range), years | 7 (<1–20) | 9 (<1–35) | 8.6 (<1–35) | 6.7 (<1–18) | 8.8 (<1–35) | 7.2 (<1–24) |
| Length of study participation, mean (range), years | 3.0 (<1–11) | 3.2 (<1–9) | 3.5 (<1–9) | 2.1 (<1–11) | 3.4 (<1–11) | 2.7 (<1–8) |
| Cumulative TBZ treatment duration >2 years, n (%) | 20 (45) | 33 (61) | 43 (61) | 10 (37) | 30 (57) | 23 (51) |

HD, Huntington's Disease; TBZ, Tetrabenazine.

dosage and time during the trial, of those with moderate chorea, 52% were judged to have had a marked response to tetrabenazine, 52% had a very good response, 45% had a mild response, 29% had a poor response, and 17% had worsened. (Because of the length of the study [25 years], some participants could have had more than one rating, and, thus, one patient could be represented by multiple response ratings. Hence, the total percentage exceeds 100%). Similarly, of those with severe/disabling chorea, 68% were judged to have had a marked

response to tetrabenazine, 54% had a very good response, 38% had a mild response, 36% had a poor response, and 26% had worsened. (Some patients may have been counted more than once.) Overall, 79% and 86% of those with moderate chorea and severe/disabling chorea, respectively, had achieved a “marked or very good” response. At “standard or best dosage” at any time during the trial, 71% of patients with moderate chorea had achieved a “marked or very good” response compared with 78% for those with severe/disabling chorea.

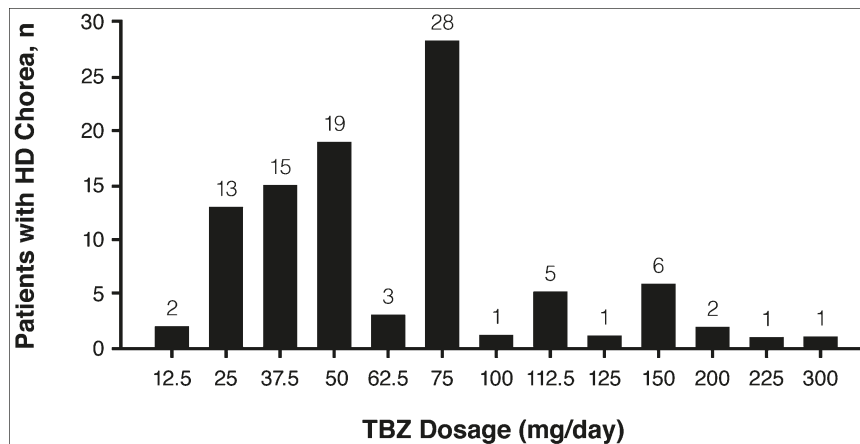


Figure 2. Distribution of Tetrabenazine Optimal Dosage. Data are missing for one patient. TBZ, Tetrabenazine.

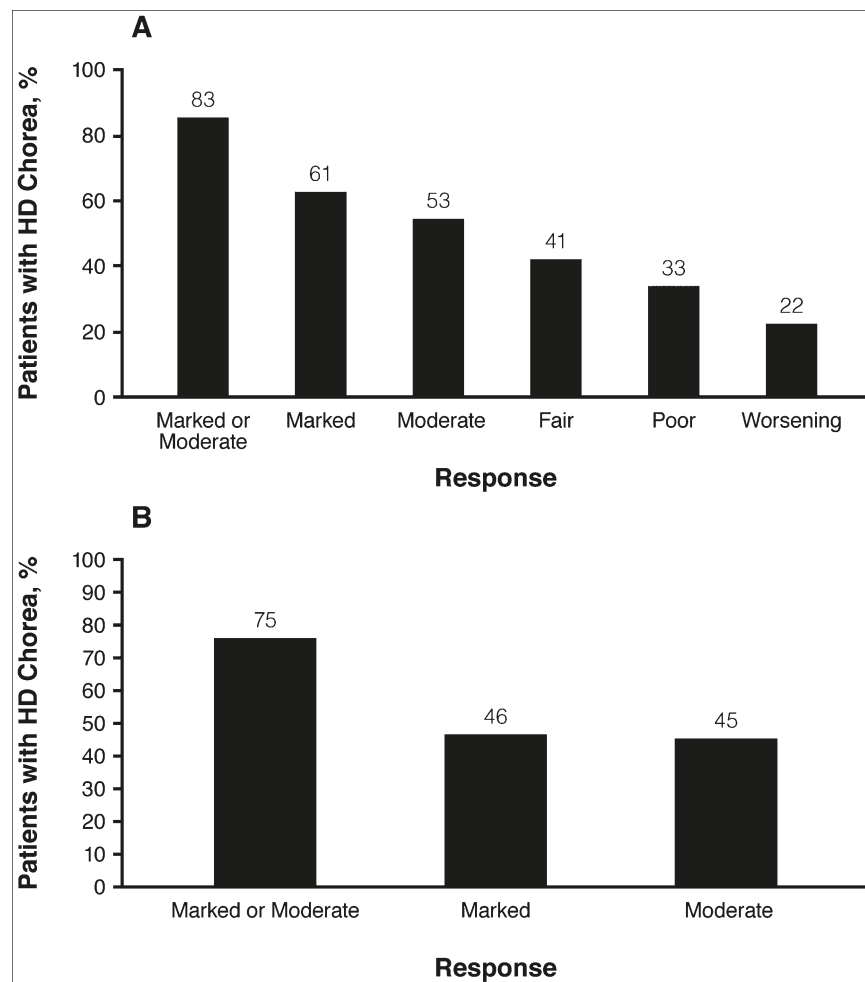


Figure 3. Response to Tetrabenazine. (A) Response to tetrabenazine at any time with any dosage; (B) patients with “marked” and/or “moderate” response to tetrabenazine with optimal dosage. For (A) and (B), patients could have been counted more than once, depending on response to treatment.

Concomitant medications

Other concomitant medications, including psychotropic medications, were used when necessary during the study, as determined by the investigator (Table 3). For most patients, concomitant treatment with an antidepressant or a neuroleptic was not maintained for the entire length of the study. Neither concomitant antidepressants nor neuroleptics appear to have affected the duration of tetrabenazine treatment or reasons for discontinuations (Table 4). A total of 34 patients received an antidepressant and neuroleptic at some point during tetrabenazine therapy. However, concomitant use of both types of medications did not always overlap. Concomitant medication use in the HD chorea group at baseline and during the study is detailed in Table 5.

Maximum anti-chorea responses to tetrabenazine were similar across groups, whether or not HD chorea patients were receiving concomitant antidepressants (Figure 4A) or neuroleptics (Fig. 4B) at any time during the study.

Safety

Overall, 125 of the 145 (86%) patients in the safety analysis group reported an adverse event, and most of these events were within the nervous system (76%). A list of most common adverse events ($\geq 5\%$) reported in the trial is provided in Table 6. Adverse events were reported more frequently at tetrabenazine dosages greater than optimal dosage than at optimal dosage (Table 7).

Fourteen patients died during the study period, and 11 of those had a diagnosis of HD. Others included two patients with tardive chorea and one with systemic lupus erythematosus. Seven of the patients with HD had end-stage HD/presumed end-stage HD listed as cause of death. Other causes of death included gastrointestinal hemorrhage (1), metastatic lung carcinoma (1), myocardial infarction (2), pneumonia and respiratory failure, and unknown (2). Most deaths were thought not to be a result of the study drug. For one patient, causes of death are listed as end-stage HD and pneumonia (with preceding adverse event

Table 3. Concomitant Medication Use During Study for All Patients and Subsets of Patients With and Without HD Chorea

| | All Participants | HD Chorea | Non-HD Chorea |
|--|------------------|-----------|---------------|
| | N=145 | N=98 | N=47 |
| Received ≥1 concomitant medication during study, n (%) | 141 (97) | 95 (97) | 46 (98) |
| Antidepressants | 90 (62) | 71 (72) | 19 (40) |
| Benzodiazepines | 67 (46) | 45 (46) | 22 (47) |
| Neuroleptics | 68 (47) | 53 (54) | 15 (32) |

HD, Huntington's Disease.

of excessive salivation and pneumonia possibly related to tetrabenazine). There were no recorded deaths attributed to suicide.

A total of 40 of 145 (28%) patients reported depression during the study period. Of these, 30 of 98 (31%) were patients with HD chorea and 10 of 47 (21%) were patients with non-HD chorea. Depression was judged to be related to tetrabenazine for 13 of 98 HD patients (13%), and for 6 of 45 non-HD patients (13%). Three cases of suicidal ideation were reported during the study period, two of which involved patients with chorea associated with HD. Tetrabenazine was discontinued for one of these three patients because of insufficient efficacy. Tetrabenazine was continued uneventfully in the two remaining patients (suicidal ideation eventually resolved in both). The third patient was judged to have made a suicidal gesture. All three

patients were receiving concomitant antidepressants. In the case of the suicidal gesture, the patient was hospitalized, antidepressants were initiated, and tetrabenazine therapy was continued. The event resolved, and the patient was eventually discharged from the hospital. There were no completed suicides in this study.

Additional safety information is provided in Table 8.

Discussion

This observational, open-label study represents the largest and longest running database of patients with HD and non-HD chorea who received long-term tetrabenazine therapy. This study permits, for the first time, indirect comparisons between the response to tetrabenazine in patients with HD-associated chorea and the response

Table 4. Treatment Status and Reasons for Tetrabenazine Discontinuation for Subsets of Patients with HD Chorea

| End of Study Disposition, n (%) | Moderate Chorea at Baseline (N=44) | Severe/Disabling Chorea at Baseline (N=54) | Concomitant Use of Antidepressant (N=71) | No Antidepressant (N=27) | Concomitant Use of Neuroleptic (N=53) | No Neuroleptic (N=45) |
|---------------------------------|------------------------------------|--|--|--------------------------|---------------------------------------|-----------------------|
| Continuing treatment | 9 (20) | 10 (19) | 14 (20) | 5 (19) | 10 (19) | 9 (20) |
| Withdrawn from treatment | 35 (80) | 44 (81) | 57 (80) | 22 (81) | 43 (81) | 36 (80) |
| Death | 5 (11) | 6 (11) | 8 (11) | 3 (11) | 7 (13) | 4 (9) |
| Adverse events | 9 (20) | 8 (15) | 12 (17) | 5 (19) | 11 (22) | 6 (13) |
| Lack of efficacy | 1 (2) | 3 (6) | 3 (4) | 1 (4) | 4 (8) | 0 |
| Disorder resolved spontaneously | 0 | 1 (2) | 0 | 1 (4) | 0 | 1 (2) |
| Travel/financial reasons | 1 (2) | 6 (11) | 5 (7) | 2 (7) | 3 (6) | 4 (9) |
| Other | 25 (55) | 20 (37) | 31 (44) | 13 (48) | 19 (36) | 25 (56) |

HD, Huntington's Disease.

Table 5. Antidepressant and Neuroleptic Use by Patients with HD Chorea at Baseline and During Study

| HD, N=98 | Antidepressants | No Antidepressants | Unknown | Neuroleptics | No Neuroleptics | Unknown |
|---------------------|----------------------|--------------------|---------|--------------|----------------------|---------|
| Baseline, n (%) | 32 (33) | 52 (53) | 14 (14) | 12 (12) | 73 (75) | 13 (13) |
| During study, n (%) | 71 (72) ¹ | 27 (98) | 0 | 53 (54) | 45 (46) ² | 0 |

HD, Huntington’s Disease.

¹Some participants were receiving several antidepressants.

²Concomitant neuroleptic use ranged from an as-needed basis to concomitant use for 2,839 days for one patient.

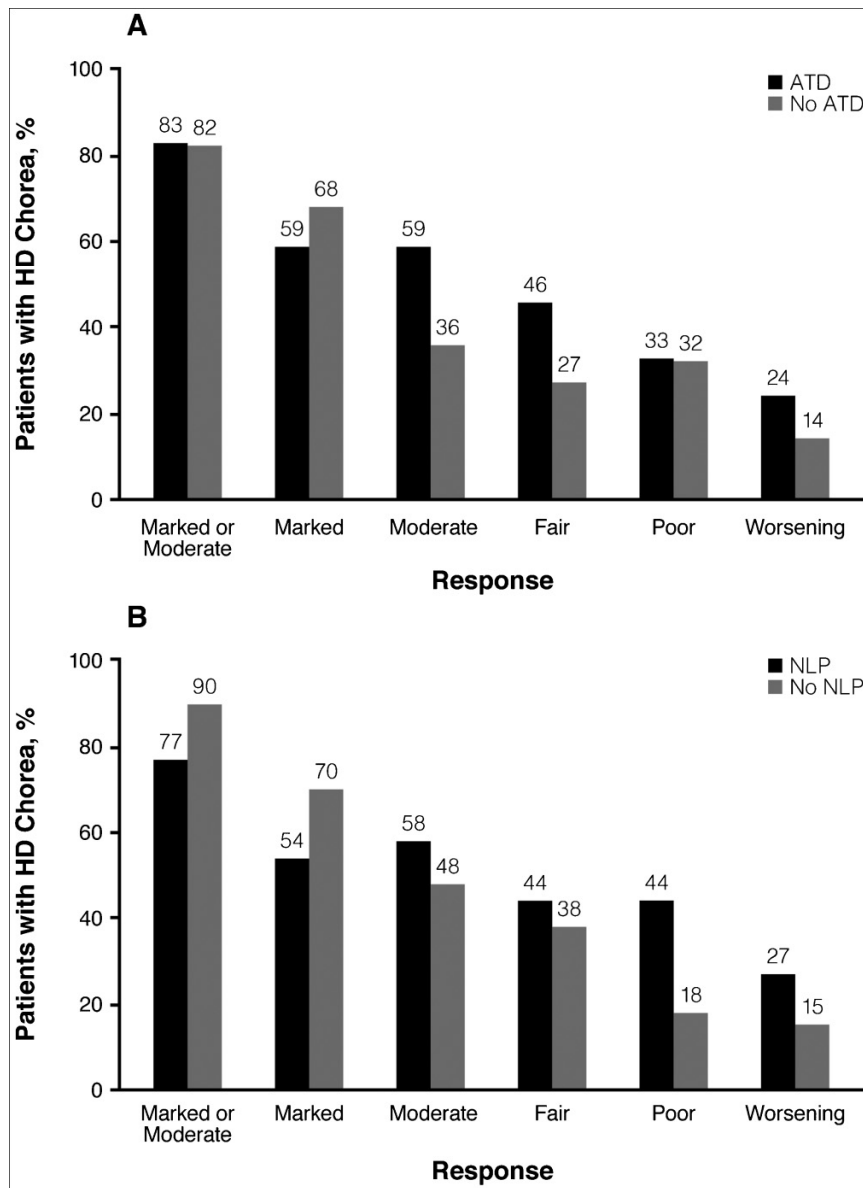


Figure 4. Tetrabenazine Efficacy Ratings. (A) Tetrabenazine efficacy ratings for patients with or without antidepressant treatment. Patients either received an antidepressant at any time during the study or never received an antidepressant during the study. (B) Tetrabenazine efficacy ratings for patients with or without neuroleptic treatment. Patients either received a neuroleptic at any time during the study or never received a neuroleptic during the study. For (A) and (B), patients could have been counted more than once. ATD, Antidepressant; NLP, Neuroleptic.

Table 6. Adverse Events Reported for $\geq 5\%$ of 145 Patients in Trial

| Adverse Event, n (%) | All Patients | HD | Non-HD |
|----------------------|--------------|---------|---------|
| | N=145 | N=98 | N=47 |
| Somnolence | 65 (45) | 38 (39) | 27 (57) |
| Insomnia | 41 (28) | 32 (33) | 9 (19) |
| Depression | 40 (27) | 30 (31) | 10 (21) |
| Accidental injury | 30 (21) | 25 (26) | 5 (11) |
| Dysphagia | 22 (15) | 19 (19) | 3 (6) |
| Parkinsonism | 20 (14) | 11 (11) | 9 (19) |
| Weight loss | 21 (14) | 17 (17) | 4 (8) |
| Increased salivation | 19 (13) | 12 (12) | 7 (15) |
| Akathisia | 17 (12) | 12 (12) | 5 (11) |
| Nervousness | 16 (11) | 11 (11) | 5 (11) |
| Anxiety | 15 (10) | 11 (11) | 4 (8) |
| Asthenia | 15 (10) | 10 (10) | 5 (11) |
| Diarrhea | 13 (9) | 12 (12) | 1 (2) |
| Nausea | 13 (9) | 10 (10) | 3 (6) |
| Pain | 12 (8) | 5 (5) | 7 (15) |
| Constipation | 11 (8) | 9 (9) | 2 (4) |
| Dizziness | 10 (7) | 8 (8) | 2 (4) |
| Urinary incontinence | 10 (7) | 9 (9) | 1 (2) |
| Agitation | 9 (6) | 8 (8) | 1 (2) |
| Ataxia | 9 (6) | 7 (7) | 2 (4) |
| Headache | 9 (6) | 4 (4) | 5 (11) |
| Amnesia | 8 (6) | 5 (5) | 3 (6) |
| Dysarthria | 8 (6) | 8 (8) | 0 |
| Speech disorder | 8 (6) | 5 (5) | 3 (6) |

HD, Huntington's Disease.

in patients with other types of chorea with data from the full report of all patients with chorea that spanned the entire study period (1979–2004). Of the 145 patients included in the study, 98 had chorea associated with HD, and 47 had chorea associated with other diseases.

The results suggest that tetrabenazine was comparably efficacious and well-tolerated over the long run in the treatment of a variety of choreas.

A total of 145 patients were followed during this open-label trial for a period ranging from 1 to 11 years, much longer than other studies. Further, 53 patients with HD were treated for more than 2 years, and 26 were treated for more than 4 years. By contrast, during TetraHD, the pivotal double-blind, placebo-controlled study of tetrabenazine for HD chorea,³ 54 of the 84 patients received tetrabenazine for only 12 weeks. The long-term efficacy and safety data from this database compares favorably with the short-term results from the TetraHD study³ and provides evidence that tetrabenazine exerts long-term benefits in patients with chorea. Of the 84 patients in TetraHD,³ 75 (89%) continued into an open-label extension study for up to 80 weeks⁴ (approximately half the time of the BCM IND study). A more recent open-label observational study, the Cooperative Huntington Observational Research Trial (COHORT),¹⁰ included 149 participants receiving tetrabenazine at some time for the treatment of HD chorea. Efficacy and tetrabenazine-related safety data from COHORT have not yet been fully analyzed and published.

Of the 145 patients in this long-term observational study, 98 (67.5%) had a diagnosis of HD. Limitations of this database include its open-label design and retrospective analyses. In addition, although the data were captured prospectively, the analyses were conducted retrospectively, and baseline depression status and knowledge of specific reasons for concomitant medication use were unknown, especially for antidepressants and neuroleptics. Further, the patients who respond to and tolerate the drug the best tend to remain in open-label studies the longest. Finally, for some patients, the records did not indicate precisely when they started receiving concomitant medications, when they stopped receiving them, and what adverse events occurred during their concomitant medication periods.

Dosing was similar in all groups and, in keeping with previous reports of tetrabenazine's use, was highly individualized. It has been hypothesized that, because of interindividual variations in carbonyl reductase, tetrabenazine may be metabolized into varying ratios of the alpha and beta metabolites. Currently, there have been no studies that correlated the "optimal dosage" of tetrabenazine to circulating metabolites. A recent retrospective study from BCM PDCMDC sought to correlate the CYP2D6 genotype and the response to tetrabenazine.¹¹ The number of patients was too small to make any correlations between CYP2D6 genotype and response, but the authors concluded that knowledge of a patient's CYP2D6 status (i.e., poor, intermediate, extensive, or ultrarapid metabolizer) was not required to manage that patient's condition, as the dosage or titration adjustments were individualized and made according to the observed response or emergence of adverse events.¹¹

Efficacy response rates did not differ between subgroups in this long-term observational study, suggesting that response to tetrabenazine does not seem to be affected by either severity of chorea, or use of concomitant antidepressants or neuroleptics. While chorea was measured differently, these data are consistent with what was observed

Table 7. Adverse Events at Best Dosage vs. Dosages Greater Than Best Dosage, All Possibly/Probably Related to Tetrabenazine

| Adverse Event, n (%) | At Best Tetrabenazine Dosage | | | At Greater Than Best Tetrabenazine Dosage | | |
|----------------------|------------------------------|--------|----------|---|----------|---------|
| | All | HD | Non-HD | All | HD | Non-HD |
| | N=142 | N=96 | N=46 | N=65 | N=43 | N=22 |
| Somnolence | 20 (14%) | 8 (8%) | 12 (26%) | 23 (35%) | 16 (37%) | 7 (32%) |
| Insomnia | 9 (6%) | 5 (5%) | 4 (9%) | 6 (9%) | 5 (12%) | 1 (5%) |
| Depression | 7 (5%) | 5 (5%) | 2 (4%) | 6 (9%) | 4 (9%) | 2 (9%) |
| Akathisia | 4 (3%) | 3 (3%) | 1 (2%) | 8 (12%) | 6 (14%) | 2 (9%) |
| Parkinsonism | 6 (4%) | 3 (3%) | 3 (7%) | 9 (14%) | 4 (9%) | 5 (23%) |
| Nervousness | 7 (5%) | 5 (5%) | 2 (4%) | 4 (6%) | 3 (7%) | 1 (5%) |
| Asthenia | 1 (1%) | 0 | 1 (2%) | 5 (8%) | 3 (7%) | 2 (9%) |
| Nausea | 4 (3%) | 3 (3%) | 1 (2%) | 1 (2%) | 1 (2%) | 0 |

HD, Huntington's Disease.

in TetraHD,³ in which tetrabenazine-related decreases in chorea scores were found to be not related to baseline chorea severity (as measured by Clinical Global Impression of severity³), or chorea score (as measured by the Unified Huntington's Disease Rating Scale).

In all groups, there were slightly fewer patients reporting marked or very good responses at their optimal dosages than when analyzed at any dosage and time. This suggests that some individuals may have had to decrease their dosages of tetrabenazine because of intolerable adverse events, resulting in some loss of chorea control. Limitations in assessing efficacy for those receiving or not receiving concomitant medications stem from the inability to determine the concurrence of the initiation, dosage change, and discontinuation of antidepressants or neuroleptics with efficacy results. Of note, while concomitant antidepressants were permitted during TetraHD,³ and could be initiated during the trial, concomitant neuroleptics were not allowed at any point during TetraHD,³ in contrast to this open-label observational study. Concomitant medications, including neuroleptics, were added if the investigator felt they were required, reflecting a more real-world clinical setting.

Overall, rates and types of adverse events were consistent with those previously published in the placebo-controlled TetraHD trial.³ Adverse events occurred more frequently at greater than "optimal" dosages. Insomnia, depression, akathisia, nervousness, and parkinsonism appeared to have occurred more frequently in patients who had received antidepressants during the study. Nervousness, asthenia, and parkinsonism were more frequent in patients who had received a neuroleptic. Interpretation of these results is complex, as adverse events may not have occurred at the same time as when a concomitant medication was received. For example, greater incidence of depression in those who had received antidepressants may simply reflect the reason why antidepressant treatment was initiated in these patients in

the first place. Indeed, antidepressants were often used effectively to improve mood in patients with suspected tetrabenazine-induced depression. Similarly, dopaminergic drugs were sometimes used to treat tetrabenazine-induced parkinsonism. Furthermore, stimulants (particularly modafinil and armodafinil) have been used to counteract the sedative effects of tetrabenazine. Finally, anxiolytics and zolpidem can be very useful in the treatment of tetrabenazine-induced nervousness (anxiety) and akathisia.¹²

An ongoing concern with tetrabenazine, a monoamine depletor, has been the potential for an increased risk of depression. The HD population, as a whole, is at a greater risk of developing depression than the general population, possibly as a result of underlying depression, obsessive-compulsive behavior, and increased impulsivity.¹³ In TetraHD,³ there were eight adverse event reports of depressed mood in those on the study drug, and no reports for those on the placebo. Based on *post-hoc* analyses of TetraHD,³ the incidence of depressed mood with tetrabenazine did not differ between those who were receiving an antidepressant and those who were not.¹⁴ In this open-label, observational chorea patient sample, there were 30 (31%) reported adverse events of depression in the HD chorea group, while 10 (21%) of the non-HD chorea group reported depression. In consideration of an adverse event of depression considered by the investigator as being possibly or probably related to tetrabenazine, the rate of depression was the same in both groups (13%). This suggests that depression in some individuals with HD chorea receiving tetrabenazine may be a result of underlying disease.

Another concern with the HD population is the risk of suicide. The HD population, as a whole, is at a 10-times greater risk for suicide than the general population.¹⁵ Moreover, it is the third most common cause of death for patients with HD,¹⁶ and suicidal ideation has been reported for 21.6% of those in Stage 2 HD.¹⁷ There was one suicide in

Table 8. Adverse Events for Subsets of Patients With and Without HD Chorea, with Moderate vs. Severe/Disabling HD Chorea, and by Concomitant Antidepressant or Neuroleptic Use for Those with HD Chorea.

| | HD | Non-HD |
|---|----------------------|----------------------------|
| | N=98 | N=47 |
| Serious adverse event, n (%) | 19 (19) ¹ | 5 (11) |
| | Moderate HD chorea | Severe/disabling HD chorea |
| Adverse event probably or possibly related to TBZ, n (%) | n=44 | n=54 |
| Somnolence | 19 (43) | 12 (22) |
| Insomnia | 7 (16) | 8 (15) |
| Depression | 10 (23) | 6 (11) |
| Akathisia | 3 (7) | 8 (15) |
| Nervousness | 3 (7) | 7 (13) |
| | HD | HD |
| | N=98 | N=98 |
| Received ≥1 concomitant antidepressant during study | Yes | No |
| n (%) | 71 (72) | 27 (28) |
| Adverse events probably or possibly related to TBZ, n (%) | | |
| Somnolence | 21 (30) | 10 (37) |
| Insomnia | 14 (20) | 1 (4) |
| Depression | 14 (20) | 2 (7) |
| Akathisia | 10 (14) | 1 (4) |
| Nervousness | 9 (13) | 1 (4) |
| Parkinsonism | 8 (11) | 1 (4) |
| Nausea | 5 (7) | 2 (7) |
| Asthenia | 6 (8) | 0 |
| Received ≥1 concomitant antidepressant during study | Yes | Yes |
| n (%) | 71 (72) | 71 (72) |

| Received paroxetine or fluoxetine ² | Yes | No |
|---|-------------|-------------|
| n (%) | 34 (48) | 37 (52) |
| Adverse event (may or may not have been related to TBZ) | | |
| Somnolence | 19 (56) | 9 (24) |
| Depression | 18 (53) | 14 (38) |
| Insomnia | 16 (47) | 13 (35) |
| Accidental injury | 11 (32) | 11 (30) |
| Dysphagia | 8 (24) | 8 (22) |
| Weight loss | 9 (26) | 6 (16) |
| Akathisia | 9 (26) | 2 (5) |
| Increased salivation | 6 (18) | 3 (8) |
| Diarrhea | 7 (21) | 2 (5) |
| Anxiety | 5 (15) | 6 (16) |
| Parkinsonism | 5 (15) | 5 (14) |
| Nervousness | 1 (3) | 9 (24) |
| Urinary incontinence | 7 (21) | 2 (5) |
| | HD | HD |
| | N=98 | N=98 |
| Received ≥ 1 concomitant neuroleptic during study | Yes | No |
| n (%) | 53 (54) | 45 (46) |
| Adverse events probably or possibly related to TBZ, n (%) | | |
| Somnolence | 19 (36) | 12 (27) |
| Insomnia | 8 (15) | 7 (16) |
| Depression | 9 (17) | 7 (16) |
| Akathisia | 4 (8) | 7 (16) |
| Nervousness | 8 (15) | 2 (4) |
| Parkinsonism | 6 (11) | 3 (7) |
| Nausea | 5 (9) | 2 (4) |
| Asthenia | 6 (11) | 0 |

HD, Huntington's Disease; TBZ, Tetrabenazine.

¹Two patients had serious adverse events thought to be related to tetrabenazine: accidental injury (one patient); and psychosis, hallucinations, and insomnia (one patient). Otherwise, serious adverse events were most commonly associated with the primary illness, such as HD, or a co-morbid medical condition such as lung cancer, gastric ulcer, or accidental injury. Accidental injuries included falls, dislocated hip, lacerations, abrasions, and lip biting.

²Strong CYP2D6 inhibitors.

TetraHD³ for a patient on the study drug. In this database, there was one case of suicidal gesture in the HD chorea group (which resolved), and there were three cases of suicidal ideation: two in the HD chorea group and one in the non-HD chorea group. There were, however, no suicides reported in our study of individuals treated with tetrabenazine for chorea. A recent analysis of the COHORT database analyzed 1,413 individuals for more than 5 years.¹⁸ Of these, 149 individuals were receiving tetrabenazine. For those exposed to tetrabenazine, there were no suicide attempts or suicides completed.¹⁸ Of those 1,264 individuals not exposed to tetrabenazine, there were 17 suicide attempts and four suicides, and suicidal ideation was either not captured or not reported.¹⁸ Suicide and suicide attempts, while more common for those with HD than for the general population, remain rare events.

Although there were limitations in interpreting data from this database, efficacy and rates of adverse events were consistent with those observed in the double-blind, placebo-controlled study TetraHD.³ Efficacy and safety were comparable for HD and non-HD chorea; for moderate and severe/disabling HD chorea; and for those receiving or not receiving an antidepressant or a neuroleptic. We conclude that tetrabenazine is efficacious and well-tolerated for the treatment of chorea over both the short and the long terms.

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