Tetrabenazine as antichorea therapy in Huntington disease

A randomized controlled trial

Huntington Study Group*

Abstract—*Background:* Tetrabenazine (TBZ) selectively depletes central monoamines by reversibly binding to the type 2 vesicular monoamine transporter. Open-label reports indicate TBZ is effective in treating chorea. *Objective:* To examine the safety, efficacy, and dose tolerability of TBZ for treating chorea in Huntington disease (HD). *Methods:* The authors randomized 84 ambulatory patients with HD to receive TBZ (n = 54) or placebo (n = 30) for 12 weeks. TBZ was increased over 7 weeks up to a maximum of 100 mg/day or until the desired antichoreic effect occurred or intolerable adverse effects supervened. The primary outcome was the change from baseline in the chorea score of the Unified Huntington's Disease Rating Scale (UHDRS) *Results:* 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; $p < 0.0001$). There was also a significant benefit on ratings of clinical global improvement. 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. *Conclusion:* Tetrabenazine (TBZ), at adjusted dosages of up to 100 mg/day, effectively lessens chorea in ambulatory patients with Huntington disease. TBZ should be dosed individually based on ongoing assessment of possible adverse side effects.

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Although there is no established treatment to delay the onset or forestall the progression of illness associated with Huntington disease (HD), symptomatic treatment of chorea may be beneficial in selected individuals.[1,2] Neuroleptics reduce chorea but are associated with extrapyramidal side effects. Several reports have suggested that tetrabenazine (TBZ) ameliorates hyperkinetic movement disorders,[3-9] but controlled studies have been limited.[10-12] TBZ is currently marketed in nine countries including Canada, but it has been available in the United States only for research purposes.

TBZ binds with high affinity (K_d = 2.4 nM) and selectivity to the CNS vesicular monoamine transporter (VMAT2),[13-18] effectively depleting monoamines and serotonin (5HT) from nerve terminals by inhibiting their transport into presynaptic vesicles.[14,19-21] TBZ depletes dopamine (IC_{50} = 0.4 mg/kg) preferentially over norepinephrine or 5HT (IC_{50} = 2 mg/kg), whereas reserpine, the only currently available monoamine depleter, is less selective and also binds to VMAT1 expressed in the periphery.[22-25] The highest binding density for TBZ is in the caudate nucleus, putamen, and nucleus accumbens, areas known to bear the brunt of pathology in HD.[26,27] VMAT binding and monoamine depletion by TBZ are reversible, last hours, and are not modified by chronic treatment, whereas those by reserpine are irreversible and last days to weeks.[28,29] Unlike reserpine, TBZ has therefore not been associated with troublesome peripheral side effects such as hypotension.

We report the first multicenter, prospective, double-blind, placebo-controlled dose-finding study of TBZ for the treatment of chorea in HD.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 14 issue to find the title link for this article.

Methods. *Subjects.* Eligible subjects had HD as confirmed by the presence of a characteristic movement disorder (chorea), a family history, and an expanded CAG repeat (n ≥ 37). All participants were required to be independently ambulatory, to have a screening total functional capacity (TFC) of >5,[30] and a total maximal chorea of ≥10 (sum of the maximal chorea scores for facial,

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buccal–oral–lingual, trunkal, and each extremity from the motor subscale of the Unified Huntington's Disease Rating Scale [UHDRS]).[31] Patients were excluded if they had disabling depression, dysphagia, or dysarthria. Eligible participants could not have been treated in the past with TBZ or currently with dopamine-depleting medications, dopamine D2 receptor blockers, selective or nonselective monoamine oxidase inhibitors, levodopa, dopamine agonists, amantadine, or memantine. Patients previously treated with dopamine D2 receptor blockers were enrolled, provided they had been off these medications for at least 4 weeks. Patients were permitted to take existing antidepressant or benzodiazepine medication if receiving stable dosages for at least 8 weeks prior to the randomization visit. Subjects needed to be accompanied by a caregiver.

Study design. This randomized, double-blind, placebo-controlled study was carried out at 16 Huntington Study Group (HSG) sites in the United States. The primary purpose was to study the efficacy, dosing, tolerability, and safety of TBZ in two parallel groups of HD subjects with clinically manifest chorea, allocated 2:1 to receive TBZ or placebo. The study protocol received institutional review board approval at each participating center prior to subject enrollment.

A data and safety monitoring committee consisting of two physicians experienced in clinical research and a biostatistician, who were not otherwise involved in the conduct of the study, convened on three occasions during the course of the trial to assess safety, including unblinded analysis of accrued adverse events and laboratory tests.

Study procedures. Consenting research participants who satisfied the eligibility criteria were randomized (2:1) to receive either TBZ or placebo for 12 weeks. Treatment assignment was concealed from subjects and investigators, and randomization was performed through a computerized module developed in the Department of Biostatistics at the University of Rochester. TBZ was formulated in 12.5-mg tablets and was identical in appearance to matching placebo tablets. During the first 7 weeks of the study, dosage was titrated in blinded fashion by providing 1 tablet on the first day, then 1 tablet twice daily for the remainder of the first week. Subsequently, the number of tablets was increased by 1 per week up to 8 tablets per day in three divided doses or until a desired antichoreic effect was achieved or intolerable adverse effects occurred. To reduce intolerable side effects, the number of tablets was reduced to the participant's previously well-tolerated level or lower if necessary. Participants were permitted one suspension of study drug for up to 7 days. By the end of the first 7 weeks of the study, participants were on their "best dose," and during the last 5 weeks of the study, the dosage remained constant unless reduced because of intolerable adverse effects. After 12 weeks, study drugs were withdrawn, and subjects returned for a follow-up visit 1 week later.

Assessments. Subjects were examined at baseline and at the end of weeks 1, 3, 5, 7, 9, 12, and 13. At each examination, the investigator rated the UHDRS total maximal chorea score. The Clinical Global Impression (CGI) was done at weeks 1, 3, 5, 7, 9, and 12. A full UHDRS, including motor, cognitive, behavioral, and functional components, was completed at baseline, at the end of the titration phase, and at the end of the maintenance phase.[31] Complete blood count and general chemistry profiles were obtained at screening and at the end of week 12.

Participants were also evaluated for adverse events, parkinsonism subscore of the UHDRS (sum of finger taps, pronate/supinate hands, rigidity arms, bradykinesia–body, gait, tandem walking, and retropulsion pull test), akathisia as measured by the Barnes Akathisia Scale,[32] speech and swallowing as measured by Unified Parkinson's Disease Rating Scale Part II, item 5 (UPDRS speech) and item 7 (UPDRS swallowing),[33] depression as measured by the 17-item Hamilton Depression Scale (HAM-D),[34] sleepiness as measured by the Epworth Sleepiness Scale (ESS),[35] vital signs (systolic and diastolic blood pressure, radial artery pulse rate) while sitting, and a 12-lead EKG. We also piloted a new instrument, the Functional Impact Scale (FIS), to assess the degree of difficulty with bathing, dressing, feeding, social isolation, and toileting. FIS information was obtained from the accompanying caregiver, and each item was graded on a scale of 0 to 3 (see appendix E-1 on the *Neurology* Web site; go to www.neurology.org).

An amendment to the initial protocol, adding a videotape to document subjects' chorea at the end of the maintenance phase (week 12) and after withdrawal (week 13), was instituted during the course of the study. An independent movement disorder expert who was blinded to subjects' treatment assignments, as well as to whether a given tape had been done at the conclusion of the maintenance phase or the conclusion of the washout phase, rated each tape as to chorea severity using the UHDRS and overall clinical improvement using the CGI Improvement Scale.

Statistical analysis. The primary prespecified efficacy outcome measure was the difference between the baseline total maximal chorea score and the average of the score at week 9 (midmaintenance phase) and week 12 (end of maintenance phase). Analysis of covariance (ANCOVA) was used to assess the treatment effect. The model included the site and baseline score. The treatment-by-site interaction was not significant and was therefore not included in the final model. Primary analyses were based on intention to treat. If either the week 9 or the week 12 data were missing for a given subject, the missing data were imputed as the one available score. If both week 9 and week 12 data were missing, the subject's last available score (after baseline) was carried forward.

Power calculations were based on the results obtained in the subgroup of patients whose baseline total maximal chorea score was at least 10 in a previous 12-week HSG trial. Given a 2:1 randomization (TBZ/placebo), an estimated dropout rate of 15%, and an estimated baseline chorea score of 14.5 ± 3.5 (mean $\pm$ SD), a total sample size of 72 subjects gave >80% power to detect an effect size of at least 2.7-unit change in the total maximal chorea score. The study sample provided a probability of >90% for detecting an adverse event that occurred with a frequency of 10% or more in the population from which the participants were drawn and a power of >99% for detecting an absolute difference in tolerability of 50% between the placebo group and the TBZ group.

Because of the large number of potential outcome measures, the analysis plan prespecified that four secondary endpoints (CGI Global Improvement score, change in total motor score, change in functional checklist, change in gait score) be analyzed in descending hierarchy, with definitive analyses ceasing when the significance level reached $\alpha \geq 0.05$. The CGI Global Improvement score was analyzed using only data from week 12, as prespecified in the analysis plan. ANCOVA procedures comparable with those in the primary efficacy analysis were used for the change from baseline in the other measures. Exploratory analyses of other outcome measures were undertaken after the hierarchical analyses reached a stopping point. Baseline characteristics were compared using t tests or χ^2 tests, as appropriate. Group comparisons on tolerability measures and adverse events were made with continuity-corrected χ^2 tests or F tests.

Results. *Baseline comparability.* Figure 1 outlines the flow of participants in the study. Ninety-one individuals were screened and 84 eligible subjects were randomized between July and December 2003. Table E-1 lists the baseline demographic and outcome variable scores for all participants. The groups were comparable with regard to age, CAG repeat length, gender, duration of illness, and proportion with a history of depression. Subjects randomized to TBZ scored worse at baseline on the Symbol Digit Test of the UHDRS cognitive battery ($p = 0.018$), as well as on the pilot FIS ($p = 0.035$). Although the other individual UHDRS measures were not statistically different across treatment groups, subjects randomized to TBZ tended to score somewhat more poorly at baseline on most UHDRS measures of severity with the notable exception of chorea score (see table E-1). There was a strong inverse correlation between CAG repeat length and the age at symptom onset in our study sample ($r = -0.63$, $p < 0.0001$), as observed in other studies of HD patients.[36,37]

Outcome summaries. Table 1 shows the adjusted mean changes in treatment-related outcome measures from baseline to the prespecified study endpoint (average of week 9 and week 12 scores), including the adjusted treat-

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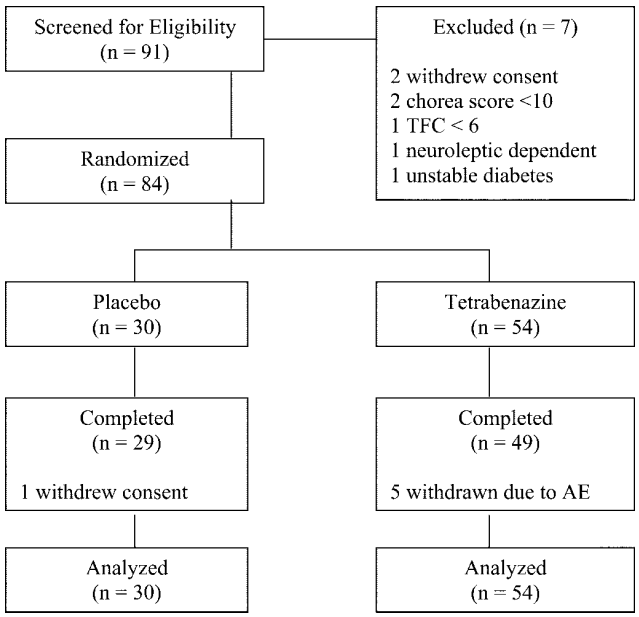

Figure 1. Flow of study subjects.

ment effect with 95% CIs, the effect sizes as a function of the average baseline scores, and the effect sizes as a function of the total scale range for each variable.

Primary efficacy outcome: Impact of TBZ on chorea. Although there was a mild reduction in total maximal chorea in the placebo group between baseline and the average of the week 9 and week 12 assessments (−1.5 ± 0.7 UHDRS units; adjusted mean ± SE), the impact of TBZ on chorea severity was larger: −5.0 ± 0.5 UHDRS units ($p < 0.0001$). The adjusted effect size of −3.5 UHDRS units (95% CI: −5.2, −1.9), represents a 23.5% average reduction in baseline chorea severity due to TBZ (figure 2). Whereas only 20% of placebo subjects had a reduction in chorea of at least 3 UHDRS units, 69% of TBZ-treated subjects had a reduction of at least this magnitude (adjusted odds ratio = 9.9; 95% CI: 3.2, 29.9; $p < 0.0001$). The TBZ-related reduction in chorea was not related to age, gender, trinucleotide repeat length, gender of affected parent, baseline CGI of severity, or baseline chorea score.

Secondary efficacy outcomes. TBZ was superior to placebo on the CGI Global Improvement Scale, with an adjusted effect size (improvement) of −0.7 CGI unit (95% CI: −1.3, −0.2) on this 7-point scale. Figure 3 shows the distribution of CGI Global Improvement scores at week 12 by treatment group. Twenty-four percent of subjects in the placebo group achieved a CGI Global Improvement score of ≤3 (corresponding to at least minimal global improvement) compared with 69% of TBZ subjects ($p = 0.0001$). Only two participants receiving placebo (6.9%) had more than minimal global improvement, whereas 23 TBZ partic-

Table 1 *Change in outcome variables (adjusted mean ± SE) from baseline to average of week 9 and week 12 scores (ITT/LOCF analyses)*

	Direction of favorable change	Placebo, n = 30	TBZ, n = 54	p Value < 0.05	Adjusted mean TE, scale units	TE 95% CI, scale units	TE, % baseline mean score	TE, % scale range
Primary outcome variable								
Δ UHDRS tot max. chorea	−	−1.5 ± 0.7	−5.0 ± 0.5	0.0001*	−3.5†	−5.2, −1.9	−23.5	−12.5
Secondary outcome variables								
CGI Global Improvement‡		3.7 ± 0.2	3.0 ± 0.2	0.007*	−0.7	−1.3, −0.2		−10.0
Δ UHDRS total motor	−	−3.5 ± 1.5	−6.8 ± 1.1		−3.3	−7.0, 0.3	−7.1	−2.7
Exploratory outcome variables								
Δ UHDRS functional checklist	+	0.4 ± 0.4	−0.8 ± 0.3	0.02§	−1.2	−2.2, −0.2	−6.3	−4.8
Δ 17-item HAM-D	−	−2.4 ± 0.4	−0.7 ± 0.3	0.003§	1.6	0.6, 2.7	33.8	3.1
Δ Epworth Sleepiness	−	−0.3 ± 0.6	1.5 ± 0.5	0.02§	1.8	0.3, 3.4	47.7	7.5
Δ Stroop test								
Word reading	+	1.8 ± 2.1	−4.8 ± 1.5	0.01§	−6.6	−11.8, −1.5	−12.1	—
Color naming	+	1.3 ± 1.7	−1.7 ± 1.2		−2.9	−7.3, 1.4	−6.6	—
Interference	+	1.5 ± 1.2	−1.5 ± 0.9		−3.0	−6.0, 0.0	−12.9	—

Per the prespecified hierarchical analysis plan (see text), only changes in total maximal chorea and CGI Global Improvement scores achieved definitive significance.

* Favors TBZ over placebo.
† The study was powered to detect an effect size of 2.7 UHDRS units.
‡ CGI Global Improvement analysis based on week 12 rating per analysis plan. For CGI Global Improvement, a score of <4 = improvement, 4 = no change, >4 = worsening.
§ Favors placebo over TBZ.

ITT = intention-to-treat analysis; LOCF = last observation carried forward analysis; TBZ = tetrabenazine; TE = treatment effect (TBZ compared with placebo); UHDRS = Unified Huntington's Disease Rating Scale; HAM-D = Hamilton Depression Scale; CGI = Clinical Global Impression; UPDRS = Unified Parkinson's Disease Rating Scale.

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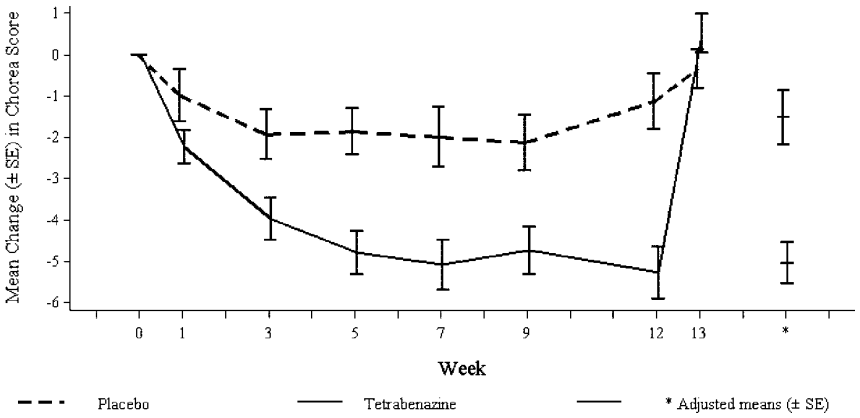

Figure 2. Mean change from baseline in Unified Huntington's Disease Rating Scale total maximal chorea score by treatment group (last observation carried forward [LOCF] except for week 13). Change from baseline to week 12 favors tetrabenazine ($p = 0.0001$; analysis of covariance, intention to treat, LOCF, side panel). There was blinded washout of study drug after week 12. Scale range: 0 to 28.

ipants (45.1%) were more than minimally improved ($p = 0.0004$). There was a correlation between improvement in chorea and the CGI Global Improvement score at week 12 ($r = 0.58$, $p < 0.0001$, n = 80). A similar correlation was found between improvement in total motor score and CGI Global Improvement score at week 12 ($r = 0.41$, $p = 0.0001$).

Although there was a trend toward an improvement, the impact of TBZ on the UHDRS total motor score did not reach significance (adjusted mean treatment effect = −3.3 UHDRS units; 95% CI: −7.0, 0.3; $p = 0.08$). Per the sequential hierarchy of analyses prespecified in the study protocol, all further analyses of secondary outcomes were considered exploratory rather than definitive once this result was established.

Exploratory outcome measures. There was an adverse impact of TBZ on the UHDRS Functional Checklist, with the placebo group improving by 0.4 unit on this 25-point scale and the TBZ worsening by 0.8 unit ($p = 0.02$). There was no impact of TBZ on UHDRS gait assessment, UHDRS parkinsonism score, or any of the other exploratory outcome measures (TFC, FIS, Independence Scale). There was a small but significant correlation between worsening UHDRS Functional Checklist scores and worsening UHDRS parkinsonism scores ($r = 0.24$; $p = 0.027$). Subjects in the TBZ group reported more sleepiness on the ESS (adjusted mean effect size = 1.8 ESS units; 95% CI: 0.3, 3.4; $p = 0.02$). There was no significant impact of TBZ on the Barnes Akathisia Scale, UHDRS Behavioral Assessment (calculated as the sum of all items), UPDRS swallowing, or UPDRS speech items. TBZ had an adverse impact on Stroop word reading, but not on other UHDRS measures of cognitive function. Subjects in both the placebo and the TBZ groups improved on the 17-item HAM-D over the course of the trial, but those in the placebo group did so to a slightly greater degree, with a relatively smaller improvement seen in the TBZ group (adjusted mean effect size = 1.6 HAM-D units; 95% CI: 0.6, 2.7; $p = 0.003$). As the mean HAM-D score across all subjects at baseline was only 4.7, the net TBZ effect was clinically insignificant in the context of the threshold score of >12 for a diagnosis of depression. There was, however, a small but significant correlation between worsening HAM-D scores and worsening UHDRS Functional Checklist scores ($r = 0.30$; $p = 0.006$).

Washout period. There were no differences between TBZ and placebo at the conclusion of the washout phase (week 13), compared with baseline, with regard to motor, cognitive, behavioral, or global measures of illness severity. Chorea in subjects on TBZ worsened more than placebo subjects in the period following withdrawal of medication at week 12 (adjusted effect size = 4.4 UHDRS units; 95% CI: 2.8, 6.0; $p < 0.0001$). These results were confirmed by analysis of chorea ratings and CGI ratings made by the independent movement disorder expert on a subset of 23 subjects for whom videotapes at weeks 12 and 13 were available. Video chorea worsening attributable to the washout from TBZ vs placebo was estimated at 4.08 UHDRS units (ANCOVA, 95% CI: 0.55, 7.62; $p = 0.03$). Seventy-one percent (10/14) of the TBZ patients were at

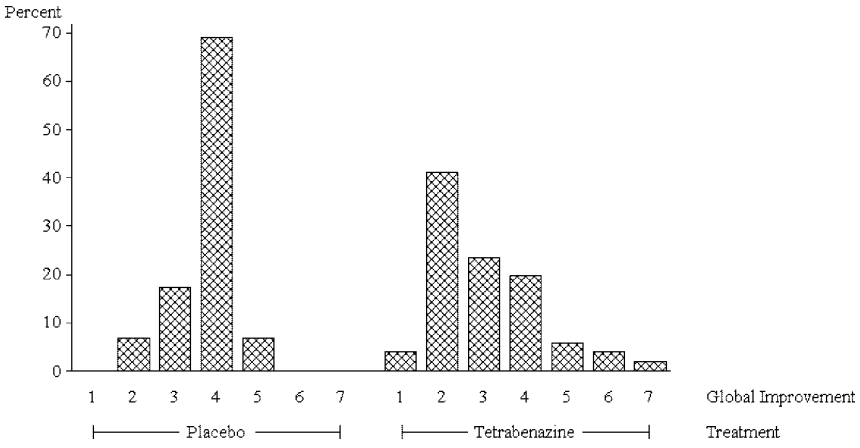

Figure 3. Distribution of Clinical Global Impression Global Improvement ratings at week 12 (end of active treatment phase) by treatment group. Scores are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. There is a shift of the curve to the left (improvement) in the tetrabenazine group ($p = 0.0001$ for proportion achieving score of ≤3; χ^2 intention to treat).

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Table 2 *Tolerability analyses*

Variable	Placebo, n (%), n = 30	TBZ, n (%), n = 54	*p* Value
Subjects withdrawn (see text)	1 (3.3)	5 (9.3)	NS
Subjects experiencing at least one SAE (see text)	0 (0)	4 (7.4)	NS
New AEs per subject, mean ± SD			
All	1.5 ± 1.8	3.8 ± 3.1	0.0005
Excluding mild	0.6 ± 0.9	1.9 ± 2.0	0.0007
Subjects reporting AEs			
All	21 (70.0)	49 (90.7)	0.01
Excluding mild	10 (33.3)	37 (68.5)	0.002
Subjects with week 12 reduced dosage due to intolerability	1 (3.3)	24 (44.4)	<0.0001

TBZ = tetrabenazine; SAE = serious adverse event.

least minimally worse on the CGI after withdrawal of drug compared with 22% (2/9) of the placebo patients (Cochran—Armitage trend test, $p = 0.01$). There was strong correlation between the independent rater's assessment of chorea severity by video and investigators' reports of chorea severity in the clinic at both week 12 ($r = 0.76$; $p < 0.0001$) and at week 13 ($r = 0.68$; $p = 0.0004$).

Tolerability and serious adverse events. Seventy-eight (93%) of the 84 subjects completed the full 13 weeks of the study. One subject in the placebo group was lost to follow-up. Five withdrawals occurred in the TBZ group: four due to serious adverse events (SAEs), and one due to akathisia. Four participants receiving TBZ experienced five SAEs. There was one death by drowning due to suicide. Neither the investigator nor the subject's caregiver had detected signs of depression at a study visit conducted 2 weeks prior to the event, and no abnormality was detected on the HAM-D at that time. There was a premature disclosure of treatment assignment to the site investigator consequent to this SAE. One TBZ-treated subject had an intracerebral hemorrhage consequent to a fall and subsequently returned to baseline level of function. One participant was hospitalized for restlessness that resolved within 48 hours of dosage reduction and treatment with clonazepam, but 2 weeks later developed depressive symptoms, irritability, and suicidal ideation when motor symptoms worsened. The subject was continued on TBZ, rehospitalized, and treated with mirtazapine, with resolution of suicidal ideation within a day of rehospitalization. One subject had been aware of a breast lump prior to screening but did not bring it to the investigator's attention until after she was enrolled; she was diagnosed with breast cancer during the study. There were no SAEs in the placebo group.

All AEs. Table 2 summarizes the number of withdrawals, dosage reductions due to intolerability, subjects experiencing at least one AE, and number of AEs per subject. Twenty-one (70%) of placebo and 49 (91%) of TBZ participants experienced an AE (World Health Organization preferred coding; $p = 0.01$). Table E-2 lists AEs reported in four or more participants (approximately 5% of the total study population). By the conclusion of the maintenance phase, when subjects were presumably on optimal dosage, there were no significant differences between TBZ and placebo with regard to specific AEs that had not been reported at baseline (coding based on the AE log using World Health Organization preferred term). Among subjects completing the study, the most common AE at week 12 was fatigue, reported by seven subjects on TBZ (14.3%) and two subjects on placebo (6.9%).

Dosage adjustments. Figure E-1 on the *Neurology* Web site gives the distribution of dosages achieved by each group at the end of the titration and maintenance phases. Twenty-seven (55%) of the 49 TBZ subjects and 4 (14%) of the 29 placebo subjects completing the study were taking less than the maximum allowed dosage at the end of the maintenance phase (week 12). Of these, one TBZ and two placebo subjects had early washouts during the maintenance phase (unrelated to adverse events), whereas two TBZ and one placebo subject achieved desirable antichoreic effect at less than maximal dosage. Dose-limiting symptoms (based on the dosage adjustment log) in the TBZ-treated group included sedation in 13 (27%), akathisia in 4 (8%), parkinsonism in 2 (4%), depression as description of mood rather than a formal diagnosis in 2 (4%), and other in 3 (6%). One placebo-treated subject (3%) reported light-headedness as a dose-limiting symptom.

Vital signs and laboratory results. There were no significant treatment differences in blood pressure or weight between baseline and the end of the maintenance phase. There was an increase in pulse in the TBZ group (5.9 ± 2.7 beats/min, adjusted mean effect ± SE; $p = 0.03$). There were no clinically relevant EKG changes during the course of the study. All participants had laboratory values less than grade 3 by National Cancer Institute guidelines at screening, with the exception of lipid profiles. Three subjects receiving TBZ developed alanine aminotransferase (ALT) increases that were not associated with elevated bilirubin values or clinical symptoms. Of these three patients, two were classified as grade 2 and resolved with continued therapy in an open extension trial. The patient who developed a grade 3 increase had an abnormal value at baseline and acknowledged binge drinking at the time of the increase; this patient's ALT normalized on withdrawal of therapy after which he tolerated retreatment at a lower dose in an open extension trial. There were no other clinically meaningful differences between the groups with regard to changes in laboratory values during the course of the study, and the groups did not differ statistically with regard to the occurrence of ALT elevation.

Medications. The most common concomitant medications at study entry included antidepressants (60%) and

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