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Long-Term Tolerability of Tetrabenazine in the Treatment of Hyperkinetic Movement Disorders

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Abstract: We sought to review the long-term tolerability of tetrabenazine (TBZ) and seek determinants of tolerability in the treatment of hyperkinetic movement disorders. A retrospective chart 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). All adverse events (AEs) were captured according to their relationship with study drug. A total of 448 patients (42% male) were treated for a variety of hyperkinesias, 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 ($P < 0.0001$). TBZ is a safe and effective drug for the long-term treatment of hyperkinetic movement disorders. © 2006 Movement Disorder Society

Key words: tetrabenazine; tolerability; chorea; tardive dyskinesia; tics

Tetrabenazine (TBZ) acts as an inhibitor of vesicular monoamine transporter 2 (VMAT2), leading to depletion of dopamine and other monoamines (norepinephrine and serotonin) in the central nervous system.[1–3] Although in vitro studies have shown that TBZ blocks dopamine D2 receptors, as suggested by its ability to inhibit [^{3}H]spiperone binding to striatal membranes with a Ki of approximately 2.1×10^{-6} M, this affinity is 1,000-fold lower than its affinity for VMAT2.[4,5] Furthermore, TBZ only weakly inhibits the pharmacologic action of apomorphine, a dopamine agonist.[6] Therefore, it is unlikely that the weak D2 receptor antagonism is responsible for TBZ clinical effects and probably explains the absence of reports of TBZ-induced tardive dyskinesia (TD).

TBZ ameliorates a variety of involuntary movements, including chorea,[7–13] TD,[14–16] tics,[17–19] and other hyperkinetic movement disorders.[12] Two recent double-blind, placebo-controlled studies confirmed the efficacy of TBZ in the treatment of chorea associated with Huntington disease (HD).[10,11] Although not yet available in the United States, there is a growing demand for TBZ, largely because of its demonstrated efficacy and safety. Whereas adverse events (AEs) associated with TBZ are similar to those seen with other neuroleptics, including sedation, Parkinsonism, depression, and akathisia, TBZ has never been reported to cause TD. This is a major advantage of TBZ over typical neuroleptics, as up to 25% of those chronically treated with these dopamine receptor blocking drugs eventually develop TD.[20] Even the newer "atypical" neuroleptics have been reported to have a risk of TD, and this may increase with more chronic exposure.[21–23]

Over a thousand patients suffering from hyperkinetic movement disorders have been treated with TBZ at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic since we received Notice of Claimed Investigational Exemption for a New

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TABLE 1. *Demographic/treatment information*

	Hyperkinetic Movement Disorder									
	Dyskinesia 149		Dystonia 132		Chorea 98		Tics 92		Myoclonus 19	
N	Mean (SE)	Range	Mean (SE)	Range	Mean (SE)	Range	Mean (SE)	Range	Mean (SE)	Range
Age, years										
Symptom onset	59.8 (1.2)	2.8–82.7	44.6 (1.8)	0.2–78.7	45.7 (2.0)	0.1–78.4	12.9 (1.6)	2.0–65.8	47.4 (5.3)	1.2–82.2
Initial tetrabenazine treatment	65.0 (1.1)	29.2–86.4	53.1 (1.7)	5.6–87.6	52.6 (1.9)	3.0–80.2	24.1 (1.7)	8.2–72.2	49.3 (5.3)	4.3–82.6
Duration, years										
Initial symptom	5.2 (0.6)	0.0–46.4	8.5 (0.9)	0.2–57.5	7.0 (0.7)	0.0–37.2	11.3 (1.3)	0.1–64.3	1.9 (0.5)	0.1–7.5
Tetrabenazine treatment	2.5 (0.2)	0.3–11.3	3.0 (0.4)	0.3–21.6	2.1 (0.2)	0.3–11.1	1.6 (0.3)	0.3–20.4	1.7 (0.8)	0.3–9.0

Drug (IND) in 1979. In 1997, we described our open-label experience in 400 patients.[7] This study represents an analysis of longitudinal data focusing on safety of TBZ in our Clinic between 1997 and 2004.

PATIENTS AND METHODS

All patients included in this study had involuntary movements that were troublesome or disabling despite optimal conventional therapy. After signing an informed consent approved by the Baylor Institutional Review Board, TBZ was administered following a regimen described earlier with an emphasis on tailoring dosage to the individual's needs and tolerance.[7] Patients were subsequently followed every 3 to 6 months by 1 of 2 experienced movement disorder specialists, at which time their response was assessed using a 1 to 5 response rating (1 = marked reduction in abnormal movements, excellent improvement in function; 2 = moderate reduction in abnormal movements, very good improvement in function; 3 = moderate improvement in abnormal movements, only mild or no improvement in function; 4 = poor or no response; 5 = worsening).[7]

AEs were captured by an open-ended question at each visit ("Have you noted any new symptoms since the last visit?"). This question was followed by specific questions related to level of alertness, mood, and motor function. The patients were also examined for any evidence of Parkinsonism and other neurological abnormalities. For each AE, the investigator assigned a level of relationship to TBZ as probable, possible, or unlikely. Complete blood counts and liver function tests were screened at least once a year. For the purpose of this analysis, patient data were extracted from the outpatient and hospital records onto Case Report Forms and then entered into a database. Completeness and accuracy were verified by the principal investigator during an audit of 25% of the records.

To seek determinants of long-term tolerability, we separately assessed AEs in a subset of patients (n = 354) in whom TBZ was initiated between 1997 and 2002 and excluded those patients who initiated TBZ more recently (since 2002) and, therefore, had only a short-term follow-up. Sequential logistic regression analysis was performed with SPSS v10 to predict the likelihood of experiencing an AE as outcome, first on the basis of eight diagnostic and four treatment predictors (Model 1), and then after addition of age at initial TBZ treatment (Model 2). The diagnostic predictors were the presence or absence of Parkinsonism, tremor, dystonia, stereotypy, tics, chorea, myoclonus, and other movement disorders. Treatment predictors included the initial and last stable dosages, disease severity, and duration of TBZ treatment. Each of the seven most common AEs (drowsiness, Parkinsonism, depression, akathisia, nausea/vomiting, nervousness/anxiety, and insomnia) were then assessed using the Hosmer–Lemeshow Goodness-of-Fit Test.[24]

RESULTS

Between January 1997 and January 2004, a total of 448 patients (42% male) received TBZ for the treatment of hyperkinetic movement disorders including TD, HD, and other choreas, Tourette's syndrome, secondary tics, dystonia, and myoclonus (Table 1). The majority of patients had a moderate to severe movement disorder (Table 2). With the exception of a greater proportion of males to females with tics ($\chi^2 = 0.11$; $P < 0.0001$) and

TABLE 2. *Disease severity by diagnosis*

		Baseline Severity (Prior to TBZ Treatment)			
Indication	N	Mild (%)	Moderate (%)	Severe (%)	Disabling (%)
Dyskinesia	149	1.3	40.3	50.3	8.1
Dystonia	132	0.0	37.4	45.8	16.8
Chorea	98	0.0	40.8	46.9	12.2
Tics	92	1.1	47.8	46.7	4.3
Myoclonus	19	5.3	52.6	26.3	15.8

TBZ, tetrabenazine.

a greater proportion of females to males with TD (χ^2 = 0.08; $P < 0.0001$), there was an equal sex distribution across the five hyperkinetic movement disorder categories. The mean age at onset of the movement disorder was 43.0 ± 24.2 years (range, 0.1–82.7 years). TBZ was started at a mean age of 50.0 ± 22.3 years (range, 3.0–87.6 years), and the treatment was maintained for a mean of 2.3 ± 3.4 years (up to 21.6 years). At the last visit, the mean daily dose was 60.4 ± 35.7 mg. In most cases, patients were treated with 50 to 75 mg of TBZ per day; 18.2% of patients required doses greater than 75 mg/day (range, 12.5–300 mg/day). As of January 2004, a majority of patients with either TD (60.4%) or chorea (63.3%) remained on TBZ treatment. A smaller proportion of patients with dystonia (43.9%), tics (48.9%), and myoclonus (52.6%) continued treatment with TBZ.

Most patients improved with TBZ and response rates did not vary over time across the five hyperkinetic movement disorders (Fig. 1). The percentage of patients presenting with a response rating of 1 or 2 was virtually identical at the first and last visit (TD = 83.5%, 85.7%; chorea = 84.4%, 81.4%; tics = 76.7%, 77.8%; myoclonus = 76.5%, 71.4%; and dystonia = 67.2%, 69.5%) with TD and chorea being most responsive to the effects of TBZ. Of the 190 patients in whom TBZ therapy was temporarily suspended (2–3 days) to determine whether the patient's underlying hyperkinetic movement disorder had spontaneously improved, 69.5% experienced rebound worsening (χ^2 = 0.12; $P < 0.0001$).

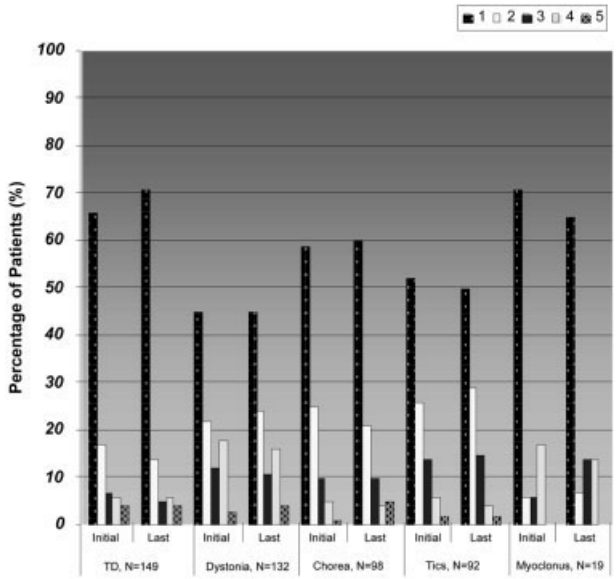

FIG. 1. Efficacy response at initial and last visit by indication. 1 = marked reduction in abnormal movements, excellent improvement in function; 2 = moderate reduction in abnormal movements, very good improvement in function; 3 = moderate improvement in abnormal movements, only mild or no improvement in function; 4 = poor or no response; 5 = worsening. TD, tardive dyskinesia.

TABLE 3. *Adverse event profile*

Adverse event[a]	Number of adverse events (N = 441) n	%	Number of patients (N = 448) n	%
Drowsiness	114	25.9	112	25.0
Parkinsonism	71	16.1	69	15.4
Depression	35	7.9	34	7.6
Akathisia	34	7.7	34	7.6
Nausea/Vomiting	26	5.9	25	5.6
Nervousness/Anxiety	23	5.2	23	5.1
Insomnia	22	5.0	22	4.9
Salivation	12	2.7	12	2.7
Dizziness	11	2.5	11	2.5
None reported	—	—	207	46.2

[a]Incidence of reported adverse event ≥ 2.5%

Safety

The most frequently reported AEs (Table 3) were drowsiness (25.0%) and Parkinsonism (15.4%), followed by depression (7.6%) and akathisia (7.6%). Less common AEs included nausea/vomiting, nervousness/anxiety, and insomnia. All AEs were dose-related and abated when dosage was reduced. In some cases, the patients were willing to tolerate the AEs, including Parkinsonism, although amantadine, levodopa, or dopamine agonists were sometimes used to treat the parkinsonian symptoms with variable success. No patient experienced TD, despite up to 21 years of exposure in some cases. Of the varied reasons for treatment discontinuation, intolerability of AEs (17.0%), lack of efficacy (8.5%), and travel/financial difficulties (7.6%) were predominant.

There was no significant difference in the profile of AEs experience by the cohort of 354 patients: drowsiness (25.1%), Parkinsonism (17.2%), depression (7.9%), and akathisia (6.8%). For each of the seven most common AEs, the Hosmer–Lemeshow Goodness-of-Fit Test revealed a good model fit on the basis of the eight diagnostic and four treatment predictors alone, as well as after the addition of age into the model. Comparison of log-likelihood ratios for models with and without age showed that age is a reliable predictor of Parkinsonism as an AE ($\chi^2(1)$ = 18.89; $P < 0.0001$).

DISCUSSION

This analysis of 448 patients with moderate to severe hyperkinetic movement disorders treated with TBZ, at a mean daily dose of 60.4 ± 35.7 mg, for up to 21.6 years (mean, 2.3 ± 3.4 years) provides evidence that the drug is safe and well-tolerated. Whereas this is not an efficacy

trial, patients with TD and chorea appear to respond slightly better than those with tics, myoclonus, or dystonia, although not to a statistically significant degree. As noted by others,[25,26] the high response rate of TBZ has been sustained over the duration of treatment, which for some patients has exceeded 2 decades. In most patients in whom TBZ was discontinued, the involuntary movement returned and again improved when TBZ was reinstated. This study extends our observations of the effects of TBZ in over thousand patients treated at Baylor College of Medicine since 1979.

Consistent with other reports, drowsiness, Parkinsonism, depression, and akathisia were the most common side effects noted in our patients.[9,11,12,27] No patient in our cohort experienced TD. All side effects improved with dosage adjustment and were minimized by a slow titration. The dose-dependent nature of side effects is an important point to keep in mind when discussing the AE profile of TBZ.[7,26] As an example of short-term tolerability, Kidd and McLellan described an overdose in a 27-year-old woman without any significant sequelae, except for sedation, after taking approximately 1 gram of TBZ.[28] On the other hand, potentially serious side effects of TBZ described in the literature include severe hyperthermia,[29] neuroleptic malignant syndrome,[30–33] acute dystonic reaction,[34] pneumonia,[35,36] dysphagia,[7,37] and suicide.[38] With regard to determinants of tolerability, we find that older patients are more prone to develop Parkinsonism. This finding suggests that there is an underlying age-related dopamine deficiency that becomes clinically manifest with the use of TBZ. No other predictors of AEs were statistically significant.

Of the various movement disorders, TBZ has been most extensively studied in chorea. We demonstrated the efficacy of TBZ in chorea associated with HD in a single-blind study of 19 patients, based on blinded rating of videos using a modified Abnormal Involuntary Movement Scale.[8] Additional analysis of TBZ usage in our Clinic between 1997 and 2004, showed that over 80% of patients experienced a complete or marked amelioration of chorea.[39] The Huntington Study Group recently completed a Phase III study assessing the safety, efficacy, and dose-tolerability of TBZ for ameliorating chorea in patients with HD (TETRA-HD).[11] A total of 84 patients were randomly assigned to placebo (n = 30) or TBZ (n = 54) up to 100 mg/day for 12 weeks. Based on the chorea score of the Unified Huntington Disease Rating Scale (UHDRS), TBZ was found to significantly reduce chorea. Likewise, the Clinical Global Impression of Change improved significantly more in patients treated with TBZ when compared to placebo. In another study, 30 HD subjects with a clinical response to TBZ were randomly assigned into three groups: 12 subjects stopped TBZ on day 1 (group 1, withdrawal), 12 on day 3 (group 2, partial withdrawal), and 6 subjects continued on TBZ (group 3, nonwithdrawal).[10] Subjects were withdrawn in a double-blind manner by replacing TBZ with identically appearing placebo tablets. The primary outcome measure was the difference between the day 1 UHDRS chorea score and the chorea score at day 3. Adjusted mean chorea scores for subjects withdrawn on day 1 increased by 5.3 units, while those remaining on TBZ increased by 3.0 units ($P = 0.0773$). Although the investigators showed only a trend toward a statistically significant difference in the primary outcome measure, a post hoc analysis showed a positive linear trend for re-emergent chorea ($P = 0.0486$). For these reasons, we believe TBZ to be the most appropriate first-line treatment for chorea; approval by the Food and Drug Administration is expected in the near future.

The most important limitations of our study relate to the retrospective and open-label nature. Nevertheless, as this is not an efficacy study, we believe that the conclusions from our data analysis are justified[40,41] and provide important information about the long-term tolerability of TBZ. Because all our patients before starting TBZ had troublesome and often disabling symptoms, it would have been problematic to conduct a study comparing patients treated with TBZ with those without TBZ therapy. Some clinicians have, in fact, argued that open trials more accurately reflect clinical practice than the usual short-term, double-blind, placebo-controlled trials.[42] Furthermore, TBZ has already proven effective in several double-blind, controlled studies in a variety of movement disorders.[11,35,36,43–46] Despite the limitation of a retrospective study, we believe that our data support the conclusion that TBZ is safe, well-tolerated, and effective in the chronic treatment of hyperkinetic movement disorders.

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REFERENCES

1. Quinn GP, Shore PA, Brodie BB. Biochemical and pharmacological studies of RO 1-9569 (tetrabenazine), a nonindole tranquilizing agent with reserpine-like effects. J Pharmacol Exp Ther 1959; 127:103–109.
2. Pettibone DJ, Totaro JA, Pflueger AB. Tetrabenazine-induced depletion of brain monoamines: characterization and interaction with selected antidepressants. Eur J Pharmacol 1984;102:425–430.
3. Scherman D. Dihydrotetrabenazine binding and monoamine uptake in mouse brain regions. J Neurochem 1986;47:331–339.
4. Login IS, Cronin MJ, MacLeod RM. Tetrabenazine has properties of a dopamine receptor antagonist. Ann Neurol 1982;12:257–262.
5. Reches A, Burke RE, Kuhn CM, Hassan MN, Jackson VR, Fahn S. Tetrabenazine, an amine-depleting drug, also blocks dopamine receptors in rat brain. J Pharmacol Exp Ther 1983;225:515–521.

6. Pletscher A, Brossi A, Gey K. Benzoquinolizine derivatives: a new class of monoamine decreasing drugs with psychotropic action. Int Rev Neurobiol 1962;4:275–306.
7. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997;48:358–362.
8. Ondo WG, Tintner R, Thomas M, Jankovic J. Tetrabenazine treatment for Huntington's disease-associated chorea. Clin Neuropharmacol 2002;25:300–302.
9. Paleacu D, Giladi N, Moore O, Stern A, Honigman S, Badarny S. Tetrabenazine treatment in movement disorders. Clin Neuropharmacol 2004;27:230–233.
10. Frank S, Ondo W, Hunter C, et al. A randomized, double-blind, placebo-controlled, staggered withdrawal study in patients with Huntington's disease treated with tetrabenazine. Mov Disord 2005; 20:1244.
11. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 2006;66:366–372.
12. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. Expert Rev Neurother 2006;6:7–17.
13. Kenney C, Hunter C, Davidson A, Jankovic J. Short-term effects of tetrabenazine on chorea associated with Huntington disease. Mov Disord 2006; DOI 10.1002/mds.21161.
14. Fahn S. A therapeutic approach to tardive dyskinesia. J Clin Psychiatry 1985;46:19–24.
15. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. Am J Psychiatry 1999;156:1279–1281.
16. Tarsy D. Tardive dyskinesia. Curr Treat Options Neurol 2000;2: 205–214.
17. Jankovic J, Glaze DG, Frost JD Jr. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology 1984; 34:688–692.
18. Jankovic J, Rohaidy H. Motor, behavioral and pharmacologic findings in Tourette's syndrome. Can J Neurol Sci 1987;14:541–546.
19. Jimenez-Jimenez FJ, Garcia-Ruiz PJ. Pharmacological options for the treatment of Tourette's disorder. Drugs 2001;61:2207–2220.
20. Jankovic J. Tardive syndromes and other drug-induced movement disorders. Clin Neuropharmacol 1995;18:197–214.
21. Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1. Pathophysiology and mechanisms of induction. Can J Psychiatry 2005;50:541–547.
22. Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R, Annable L. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 2. Incidence and management strategies in patients with schizophrenia. Can J Psychiatry 2005;50:703–714.
23. Ghaemi S, Hsu D, Rosenquist K, Pardo T, Goodwin F. Extrapyramidal side effects with atypical neuroleptics in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:209–213.
24. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106.
25. Kazamatsuri H, Chien CP, Cole JO. Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine. Am J Psychiatry 1973;130:479–483.
26. Mikkelsen BO. Tolerance of tetrabenazine during long-term treatment. Acta Neurol Scand 1983;68:57–60.
27. Kenney C, Hunter C, Mejia N, Jankovic J. Is history of depression a contraindication to treatment with tetrabenazine. Mov Disord 2006 (in press).
28. Kidd DW, McLellan DL. Self-poisoning with tetrabenazine. Br J Clin Pract 1972;26:179–180.
29. Stevens E, Roman A, Houa M, Razavi D, Jaspar N. Severe hyperthermia during tetrabenazine therapy for tardive dyskinesia. Intensive Care Med 1998;24:369–371.
30. Burke RE, Fahn S, Mayeux R, Weinberg H, Louis K, Willner JH. Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. Neurology 1981;31: 1022–1025.
31. Mateo D, Munoz-Blanco JL, Gimenez-Roldan S. Neuroleptic malignant syndrome related to tetrabenazine introduction and haloperidol discontinuation in Huntington's disease. Clin Neuropharmacol 1992;15:63–68.
32. Ossemann M, Sindic CJ, Laterre C. Tetrabenazine as a cause of neuroleptic malignant syndrome. Mov Disord 1996;11:95.
33. Petzinger GM, Bressman SB. A case of tetrabenazine-induced neuroleptic malignant syndrome after prolonged treatment. Mov Disord 1997;12:246–248.
34. Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. Ann Neurol 1985; 17:200–202.
35. McLellan DL. The suppression of involuntary movements with tetrabenazine. Scott Med J 1972;17:367–370.
36. Shoulson I, Goldblatt D. Huntington's disease (HD): effect of tetrabenazine and antipsychotic drugs on motoric features. Neurology 1981;31:79.
37. Huang CY, McLeod JG, Holland RT, Elliot C. Tetrabenazine in the treatment of Huntington's chorea. Med J Aust 1976;1:583–584.
38. Gimenez-Roldan S, Mateo D. Huntington disease: tetrabenazine compared to haloperidol in the reduction of involuntary movements. Neurologia 1989;4:282–287.
39. Jankovic J, Hunter C, Mejia N, Vuong K. Tetrabenazine: effective treatment for tardive dyskinesia. Mov Disord 2004;19(Suppl. 9): S73.
40. Cummings JL. What we can learn from open-label extensions of randomized clinical trials. Arch Neurol 2006;63:18–19.
41. Daniel CL, Moreland LW. Infliximab: additional safety data from an open label study. J Rheumatol 2002;29:647–649.
42. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1:113–119.
43. Jankovic J. Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. Ann Neurol 1982; 11:41–47.
44. Asher SW, Aminoff MJ. Tetrabenazine and movement disorders. Neurology 1981;31:1051–1054.
45. Swash M, Roberts AH, Zakko H, Heathfield KW. Treatment of involuntary movement disorders with tetrabenazine. J Neurol Neurosurg Psychiatry 1972;35:186–191.
46. McLellan DL, Chalmers RJ, Johnson RH. A double-blind trial of tetrabenazine, thiopropazate, and placebo in patients with chorea. Lancet 1974;1:104–107.