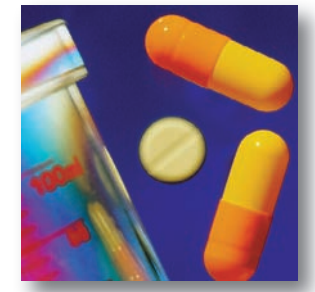

Tetrabenazine (Xenazine), An FDA-Approved Treatment Option For Huntington's Disease–Related Chorea

Tatiana Yero, PharmD, BS, and Jose A. Rey, PharmD, BCPP

Key words: tetrabenazine, Xenazine, Huntington's disease, chorea, Huntington's chorea

INTRODUCTION

Huntington's disease (HD) is a progressive autosomal-dominant neurodegenerative disorder caused by 36 or more trinucleotide (CAG) repeats on the short arm of chromosome 4.[1] The higher the number of repeats on the *huntingtin* gene, the more fully present the disorder. As a result of this abnormality, mutated *huntingtin* protein is formed and is a hallmark of HD.

HD occurs worldwide in all ethnic groups but predominantly in Caucasian populations.[1] The prevalence rate in Europe and the U.S. is 4 to 8 per 100,000 individuals.[2] In Japan, the prevalence is only 10% of this number.[2]

Symptoms generally appear between the ages of 35 and 40 but have been recorded as early as five years of age. These symptoms are devastating and disabling and involve movement disorders, incoordination, cognitive decline, personality and behavioral changes.[1,2] The most striking and characteristic symptom is chorea, or involuntary dance-like movements that seem purposeless and abrupt. As the severity of symptoms progresses, patients are at a higher risk of dying because of complications, such as falls and aspiration. The typical period between diagnosis and death of the patient is 20 years.[3]

As of this writing, no treatment is available that can delay the progression of HD. Existing management strategies focus on improving symptoms and quality of life.[4] Neuroleptic agents, including dopamine receptor blockers and presynaptic dopamine-depleting agents, have been used to control choreic movements.[2]

Until now, no medication had been approved in the U.S. for the treatment of chorea or any other symptom associated with HD. In August 2008, the FDA approved tetrabenazine (Xenazine) for this indication. In September 2008, Ovation Pharmaceuticals acquired the exclusive license in the U. S. to market this orphan drug from Prestwick Pharmaceuticals.

Tetrabenazine has been used for decades in several countries to treat chorea and other hyperkinetic movement disorders, such as dystonias and tics.[5] This article provides a concise review of the pharmacology, pharmacokinetics, safety, and efficacy of this much needed treatment option to ameliorate some of the disabling symptoms of HD.

Dr. Yero is a Psychiatric Pharmacy Practice Resident and Dr. Rey is Associate Professor, both at Nova Southeastern University College of Pharmacy in the Pharmaceutical Sciences Department in Fort Lauderdale, Florida. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

CHEMICAL AND PHYSICAL PROPERTIES

Tetrabenazine, an oral monoamine depleter, is a hexahydro-dimethoxy-benzoquinolizine derivative. A white to light yellow crystalline powder, it is sparingly soluble in water and soluble in ethanol. Scheduled to be launched by the end of 2008, it will be available as a cylindrical biplanar tablet with beveled edges in strengths of 12.5 mg (white) and 25 mg (yellow). The tablets should be stored at temperatures between 15˚ and 30˚C.[6]

MECHANISM OF ACTION

The production of neurotransmitters occurs in neurons. These neurotransmitters are then stored in vesicles for later release.[7] This results in higher levels of neurotransmitters inside the neuron and lower levels in the synaptic cleft, ensuring a gradual, regulated release across the plasma membrane.[7,8] The process also serves to protect the neurotransmitters from leakage or degradation by intraneuronal metabolism; in addition, the neuron is protected from the potential toxic effects of critically high levels of neurotransmitters.[7,8] The vesicular monoamine transporter-2 (VMAT-2) is found mainly in the central nervous system (CNS) and in histaminergic cells of the adrenal medulla, blood cells, and stomach.[7] The VMAT-2 transports serotonin, dopamine, norepinephrine, and histamine into vesicles for storage.

Tetrabenazine acts primarily as a reversible high-affinity inhibitor of monoamine uptake into granular vesicles of presynaptic neurons by binding selectively to VMAT-2.[9] As a result of this inhibition, monoamine degradation in the neuron is augmented, leading to depletion of the monoamines, particularly dopamine.[9] Studies have shown that tetrabenazine also blocks dopamine D_2 receptors, but this affinity is 1,000-fold lower than its affinity for VMAT-2.[10,11] It is unlikely that this mechanism is responsible for the therapeutic effects of this agent, but it might be involved with rarely reported acute dystonic reactions.[12]

The agent that is most similar to tetrabenazine and available in the U.S. is reserpine, which is also a monoamine depleter. Reserpine works by irreversibly inhibiting VMAT-1, in addition to VMAT-2, in the periphery.[5] This activity explains the higher frequency of drug-induced side effects such as hypotension and gastrointestinal pain and diarrhea. Tetrabenazine has a shorter half-life and a more rapid onset of action than reserpine, perhaps making it more beneficial in the clinical setting, because efficacy can be evaluated more quickly.[5]

Disclosure: The authors have no financial or commercial relationships to disclose in regard to this article.

PHARMACOKINETICS

Absorption and Distribution

The pharmacokinetic properties of tetrabenazine are summarized in Table 1.[6,9,13] Oral absorption of tetrabenazine is at least 75%. In trials, administration of food following a single dose had no effect on mean peak plasma levels (C_{max}) or on the area-under-the-curve (AUC) concentration; therefore, tetrabenazine may be given without regard to food intake.[6]

Tetrabenazine displays a relatively low bioavailability of 0.049 ± 0.032.[13] It is rapidly metabolized hepatically into two compounds: alpha- and beta-dihydrotetrabenazine (HTBZ). The alpha-HTBZ metabolite is active, whereas the beta-HTBZ metabolite is chemically inert.

Because of the drug's rapid metabolism, plasma concentrations of tetrabenazine are generally below the limit of detection. The C_{max} of both alpha-HTBZ and beta-HTBZ is reached within 1.5 hours after dosing.[6] Both forms of HTBZ are then further metabolized into another major metabolite, *O*-dealkylated-HTBZ. The C_{max} for this compound is reached in two hours after the dose is given.[6] In contrast to the parent compound, both forms of HTBZ have a high bioavailability and are less protein-bound (44% to 59%) than tetrabenazine (83% to 88%).[13] Plasma levels of HTBZ are higher than those of tetrabenazine.[13,14] Both compounds follow linear kinetics in the dosage range that was studied, which was 37.5 mg to 112.5 mg/day.[15]

Results of positron emission tomography (PET) scans, as indicated by the manufacturer, report that radioactivity was rapidly distributed to the brain following an intravenous (IV) injection of radiolabeled tetrabenazine, with the most binding occurring in the striatum and the least binding in the cortex.[6]

Metabolism and Elimination

Tetrabenazine displays a variable half-life among individual patients.[13] The half-life of the parent compound is 10 hours.[13,14] The alpha-HTBZ metabolite has a half-life of four to eight hours, and the beta-HTBZ's half-life is two to four hours.[6] Given these short half-lives, the drug should be taken two to three times daily. In addition, efficacy may be accurately evaluated within days.[9]

The alpha-HTBZ and beta-HTBZ metabolites are formed by carbonyl reductase, which occurs primarily in the liver. These compounds are then further metabolized, mainly by cytochrome P450 2D6, with some contribution by CYP 1A2.[6] Tetrabenazine and its metabolites are not likely to result in any significant inhibition or induction of CYP enzymes, and they are not likely to be substrates or inhibitors of P-glycoprotein.[6]

Elimination of tetrabenazine and its metabolites is primarily renal. In six healthy volunteers, approximately 75% of the tetrabenazine dose was excreted in the urine; fecal elimination accounted for approximately 7% to 16% of the dose.[6] No unchanged tetrabenazine has been isolated in human urine. The urinary excretion of alpha-HTBZ and beta-HTBZ accounted for less than 10% of the given dose.[6] The remainder of the dose found in the urine consists of other circulating metabolites and products of oxidative metabolism.[6]

Table 1 **Pharmacokinetic Properties of Tetrabenazine (Xenazine)**

	Tetrabenazine	HTBZ
Absorption and distribution		
Oral bioavailability	0.049 ± 0.032	—
Protein binding	83%–88%	44%–59%
Metabolism and elimination		
Mean half-life	10 hours	alpha-HTBZ, 4–8 hours beta-HTBZ, 2–4 hours
Primary metabolic pathway	CYP 2D6	CYP 2D6
Secondary metabolic pathway	Carbonyl reductase	CYP 1A2 (minimal)
Excretion	Renal, 75%	—
	Fecal, 7%–16%	—

CYP = cytochrome; HTBZ = dihydrotetrabenazine.

Data from Xenazine (tetrabenazine), product information;[6] Kenney C, et al. *Exp Rev Neurother* 2006;6(1):7–17;[9] and Roberts MS, et al. *Eur J Clin Pharmacol* 1986;29:703–708.[13]

DOSAGE

Adults. The dose of tetrabenazine should be individualized, and a medication guide should be included with the prescription for each patient.[6] The starting dose should be 12.5 mg/day once in the morning. After one week, the dose should be increased to 12.5 mg twice daily; it should then be titrated up slowly by 12.5 mg at weekly intervals to identify the lowest and best tolerated effective dose. If a dose of 37.5 to 50 mg/day is needed, it should be given in three divided doses. Each dose should not exceed 25 mg. *Patients who seem to require doses greater than 50 mg/day should undergo genotyping for CYP 2D6.* Doses above 100 mg/day are not recommended for any patient.[6]

Tapering of the tetrabenazine dose is not needed when the drug is being discontinued. Chorea may become evident within 12 to 18 hours after the last dose.[6] After a treatment interruption of more than five days, dosing should be retitrated. However, if treatment is interrupted for less than five days, the previous maintenance dose can be resumed with no titration.[6]

Extensive or intermediate metabolizers of CYP 2D6. At doses above 50 mg/day, tetrabenazine should still be titrated up slowly by 12.5 mg at weekly intervals. The higher doses should be divided into three daily doses. The maximum recommended daily dose is 100 mg, and the maximum single dose in this group is 37.5 mg.[6]

Poor metabolizers of CYP 2D6. The dosing of tetrabenazine is similar to that for patients who are extensive metabolizers. For poor metabolizers, however, the maximum single dose is 25 mg and the maximum recommended daily dosage is 50 mg.[6]

Elderly patients. No controlled studies have been performed in elderly adults.

Hepatically impaired patients. The manufacturer reports a study in which the effects of tetrabenazine in hepatic impairment were compared with its effects on healthy patients. Twelve patients with mild-to-moderate chronic liver im-

pairment (Child–Pugh scores of 5 to 9) and 12 patients with normal hepatic function were given a single 25-mg dose of tetrabenazine.[6] Plasma concentrations of tetrabenazine in patients with hepatic impairment were similar to or higher than the concentrations of alpha-HTBZ, indicating a decreased metabolism of the parent compound into the active metabolite.

The mean tetrabenazine C_{max} was approximately seven-fold to 190-fold higher in hepatically impaired patients than in healthy patients.[6] The elimination half-life of tetrabenazine was increased to 17.5 hours in this group, as were the half-lives of alpha-HTBZ (10 hours) and beta-HTBZ (eight hours). Exposure to alpha-HTBZ and beta-HTBZ was approximately 30% to 39% greater in patients with hepatic impairment, compared with the healthy group.[6] Because the safety and efficacy of this increase in exposure is unknown, it is not possible to adjust the dosage to ensure safe use of the drug. Therefore, tetrabenazine is contraindicated in hepatically impaired patients.[6]

Renally impaired patients. The effects of renal impairment on the elimination of tetrabenazine have not been evaluated in controlled studies.

Pregnant and lactating women. Tetrabenazine does cross the placenta, even though teratogenicity has not been reported.[13] No adequate, well-controlled studies have been performed in pregnant women, and tetrabenazine is therefore currently classified as a Pregnancy Category C drug. The medication is also excreted in breast milk; therefore, women taking tetrabenazine should avoid breastfeeding.[13]

Pediatric populations. No controlled studies with tetrabenazine for HD have been performed in these patients.

INDICATION

Tetrabenazine is indicated for the treatment of chorea associated with HD.

CONTRAINDICATIONS AND PRECAUTIONS

Tetrabenazine should not be prescribed for patients who are actively suicidal, for patients with untreated or inadequately treated depression, or for patients with hepatic impairment. It should not be used in conjunction with monoamine oxidase inhibitors or reserpine. If a patient is switching from reserpine to tetrabenazine, at least 20 days should lapse between the discontinuation of reserpine and the start of tetrabenazine.[6]

Proper dosing involves careful titration of therapy to determine the optimal dose for each patient. Before patients are given a daily dose exceeding 50 mg, they should be tested for CYP 2D6 gene polymorphisms to determine their type of metabolism so that the dose can be adjusted accordingly.[6] Because tetrabenazine reduces dopamine transmission, there is a potential for the development of neuroleptic malignant syndrome (NMS). Clinicians should be alert to any possible symptoms related to this syndrome. Tetrabenazine should not be taken with alcohol, because the drug increases sedation and affects liver function.[6]

Tetrabenazine causes a small increase of approximately 8 milliseconds in the corrected QT (QTc) interval. Caution should therefore be used when this agent is combined with others that also increase the QTc interval.[6]

ADVERSE DRUG EFFECTS

Known risks with tetrabenazine include suicidality, depression, and NMS. Tetrabenazine carries a black-box warning because of an increase in depression and suicidality, and clinicians must carefully weigh the risks along with the need for choreiform movement control.[6] In a controlled trial in HD, 19% of 54 patients receiving tetrabenazine experienced depression compared with none of the patients in the placebo group. In addition, one patient committed suicide and one patient had suicidal ideation, with no incidence of these effects in the placebo group.[6,16]

Other risks include akathisia and parkinsonism. Tardive dyskinesia is also a theoretical risk because of the presynaptic depletion of dopamine, although no cases have been reported with tetrabenazine or reserpine.[6]

Adverse events leading to discontinuation of titration or reduction in the dose of study drug consisted of sedation (28%), akathisia (13%), parkinsonism (7%), depression (5.5%), anxiety (4%), fatigue (2%), and diarrhea (2%).[6] The most commonly reported adverse effects include sedation and somnolence, insomnia, depression, anxiety, akathisia, nausea, and fatigue.[6,16]

DRUG INTERACTIONS

The CYP 2D6 isoenzyme is the major enzyme involved in the metabolism of tetrabenazine. Prescribers must use caution when giving any strong CYP 2D6 inhibitor, such as fluoxetine (Prozac, Eli Lilly), paroxetine (Paxil, GlaxoSmithKline), or quinidine, to patients receiving a stable dose of tetrabenazine. If this is the case, the dosage of tetrabenazine should be decreased by half. The effect of moderate or weak CYP 2D6 inhibitors has not been evaluated.[6]

Reserpine is an irreversible inhibitor of VMAT-2 and has a long duration of action. When switching a patient from reserpine to tetrabenazine, the physician should wait until chorea re-emerges before commencing treatment with tetrabenazine to avoid overdosage or major depletion of serotonin and norepinephrine. There should be an interval of at least 20 days between stopping reserpine and initiating tetrabenazine.[6]

CLINICAL EFFICACY

Kenney et al.[17]

Kenney and colleagues observed the short-term effects of tetrabenazine on chorea in patients with HD. Ten patients, with ages ranging from 35 to 71, were included in the study. They met clinical criteria for HD and were disabled enough by chorea to justify an intervention with medication. Patients also displayed 40 or more CAG repeats in the *huntingtin* gene. Stable tetrabenazine dosing was also a requirement for inclusion in the study.

Patients took their last dose of tetrabenazine the evening before participating in the study. At least 12 hours had to elapse between the last dose and the baseline assessment. One rater completed all evaluations, which consisted of the motor portion of the Unified Huntington's Disease Rating Scale (UHDRS) and the Beck Depression Inventory (BDI). All patients then took their regularly scheduled morning dose and underwent an assessment of UHDRS motor scores every 90 to 150 minutes. At least four assessments were completed before re-emergence of the baseline chorea indicated that the benefit of tetrabenazine was wearing off. This duration of effect was established as being the time needed for the chorea score on the UHDRS to reach the baseline value.

UHDRS chorea scores decreased by 42.4% ± 17.8% with a tendency to improve but then worsened over several hours. The mean duration of effect lasted for 5.4 ± 1.3 hours. This study supported the efficacy of tetrabenazine in the treatment of chorea and the findings of inter-individual variation in effects. It also demonstrated the rapid onset of action of tetrabenazine, because the rater was able to visualize improvement within 90 minutes in each patient.

Huntington Study Group[18]

The Huntington Study Group conducted the first multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, dosing, tolerability, and safety of tetrabenazine in two parallel groups of HD subjects with clinically manifested chorea. The study enrolled 84 subjects with HD (range, 25 to 77 years of age).

The diagnosis of HD was confirmed by presence of a characteristic movement disorder (e.g., chorea), a family history, and an expanded CAG repeat of 37 or more. The inclusion criteria consisted of being independently ambulatory, having a screening Total Functional Capacity (TFC) Scale score of greater than 5, and a total maximal chorea score of 10 or higher based upon motor subscales of the UHDRS. Patients were not permitted to enroll in the study if they had disabling depression, dysphagia, or dysarthria.

Each patient was randomly assigned to receive either a 12.5-mg tetrabenazine tablet or placebo for 12 weeks. During the first seven weeks of the study, patients received one tablet on the first day; the dosage was then increased to twice daily for the rest of the first week. The number of tablets was increased by one tablet each week until a dose of eight tablets (100 mg) per day was reached in three divided doses, the desired antichoreic effect was achieved, or intolerable adverse effects occurred. During the last five weeks, the dose remained unchanged (in the maintenance phase) unless intolerable adverse effects occurred. At the end of the 12 weeks, the study drugs were stopped and the subjects returned one week later for follow-up.

At each visit, the investigator rated the UHDRS total maximal chorea score to assess changes in severity of chorea. A full UHDRS assessment, which included motor, cognitive, behavioral, and functional components, was performed at baseline, at the end of the titration phase, and at the end of the maintenance phase. The investigators piloted a new instrument—the Functional Impact Scale (FIS)—to assess the degree of difficulty involved in certain activities of daily living, namely, bathing, dressing, feeding, social isolation, and toileting. The information was obtained from the accompanying caregivers. Each item was scored on a scale of 0 (zero) to 3, with a maximum score of 15, indicating complete dependence on others for daily activities.

The impact of tetrabenazine treatment on chorea severity (–5.0 ± 0.7 UHDRS units; $P < 0.0001$) was greater than the effect of placebo, but there was a mild reduction from baseline in that group as well. The adjusted effect size of –3.5 UHDRS units represents a 23.5% average reduction in chorea severity attributed to tetrabenazine. Whereas only 20% of subjects in the placebo group had a reduction of at least three UHDRS units in chorea, 69% of subjects in the tetrabenazine group had at least that much reduction in chorea ($P < 0.0001$).

Tetrabenazine was also superior to placebo, according to the Clinical Global Impressions (CGI) Improvement Scale. Twenty-four percent of the placebo subjects achieved a score of 3 or lower (corresponding to at least minimal improvement), compared with 69% of the tetrabenazine subjects ($P = 0.0001$). Only two participants receiving placebo had more than minimal improvement compared with 23 subjects receiving tetrabenazine ($P = 0.0004$).

No differences were found between tetrabenazine and placebo at the end of the washout phase compared with baseline values in motor, cognitive, behavioral, or global measures of illness severity. After discontinuation of treatment, chorea worsened further in those subjects who had received tetrabenazine compared with those who had received placebo ($P < 0.0001$).

Tetrabenazine was fairly well tolerated, but it was associated with a significant increase in reports of drowsiness and insomnia. Other adverse events that limited dosing included depressed mood in two patients, parkinsonism in two, and akathisia in four. These effects resolved with a dosage reduction.

No significant differences were observed in the number of adverse events reported between the tetrabenazine and placebo groups. Investigators also noted no adverse impact on Barnes Akathisia Scale scores or on measures of parkinsonism, dysphagia, or dysarthria. According to Hamilton Depression Scale (HAM-D) results, no evidence of tetrabenazine-related depression was found, although subjects receiving placebo had better scores in this scale. One subject in the tetrabenazine group committed suicide during this trial, although HAM-D scores had been in the normal range during previous assessments.

Overall, tetrabenazine demonstrated statistically significant reductions in chorea and improvement on the CGI scale in ambulatory patients in doses of up to 100 mg/day. However, it did not offer improvement in other functional outcome measures, suggesting that chorea is only one aspect of the disability seen in HD.

Frank et al.[19]

Frank and colleagues performed a randomized, double-blind study to confirm the efficacy of tetrabenazine by showing that chorea re-emerged when the drug was withdrawn from chronically treated patients. They also sought to determine the safety of withdrawal from short-term tetrabenazine treatment.

Thirty subjects with HD, ranging in age from 39 to 75 years, participated in this five-day study. HD was confirmed by clinical diagnosis and an expanded CAG repeat of 37 or more. Subjects also had to have been taking a stable dose of tetrabenazine for at least two months, and they had to have chorea that was determined to be responsive to the medication.

Eligible subjects were randomly assigned to a withdrawal group, a partial-withdrawal group (on the third day), or a no-withdrawal group. Withdrawal from tetrabenazine was performed in a double-blind manner, with the medication replaced by placebo tablets. The primary analysis compared the mean change from the baseline visit to the evaluation of UHDRS chorea scores on day three between the withdrawal group and the other two groups. The secondary outcome measure was the change in TFC

Scale scores. Investigators also explored changes in CGI scores and in cognitive, functional, and behavioral assessments.

The adjusted mean chorea scores for the withdrawal group increased by 5.3 units from days one to three; for the other two groups, it increased by 3.0 units ($P = 0.0773$). When the investigators performed a *post hoc* analysis of change in chorea scores adjusted for baseline motor scores (because of a significant imbalance at baseline), the results were similar ($P = 0.1202$). A *post hoc* analysis of the linear trend was positive for re-emergent chorea ($P = 0.0486$).

No statistically significant differences were found in the secondary efficacy or exploratory endpoints. Adverse reactions to sudden treatment withdrawal were generally mild and were considered unlikely to be related to the study procedures.

Overall, the Frank study demonstrated a significant trend in the re-emergence of chorea after sudden withdrawal of tetrabenazine, indicating the agent's efficacy in reducing chorea. Even so, there was no statistically significant difference between the three groups between days one and three. This study also indicated that a sudden discontinuation of tetrabenazine after chronic use, up to a dose of 150 mg/day, seemed safe.

COST

Pricing information is not yet available from the manufacturer or from wholesalers.

CONCLUSION

Although tetrabenazine has been available in other countries for many years, this is the first FDA-approved medication for the treatment of chorea secondary to HD. Antipsychotic agents have also been used to manage this movement disorder, but tetrabenazine may provide therapeutic benefit with a different side-effect profile and represents an appropriate treatment alternative to help manage this debilitating and progressive disease.

REFERENCES

1. Walker FO. Huntington's disease. *Lancet* 2007;369:218–228.
2. Fahn S. Huntington disease. *In:* Rowland LP, ed. *Merritt's Neurology,* 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:803–807.
3. Folstein S. *Huntington's Disease: A Disorder of Families*. Baltimore: The Johns Hopkins University Press, 1989.
4. Bonelli RM, Hofmann P. A systematic review of the treatment studies in Huntington's disease since 1990. *Exp Opin Pharmacother* 2006;7(17):1–13.
5. Paleacu D. Tetrabenazine in the treatment of Huntington's disease. *Neuropsychiatr Dis Treat* 2007;3(5):545–551.
6. Product information. Xenazine (tetrabenazine). Deerfield, IL: Ovation Pharmaceuticals; Inc., 2008.
7. Masson J, Sagne C, Hamon M, Mestikawy SE. Neurotransmitter transporters in the central nervous system. *Pharmacol Rev* 1999;51(3):439–463.
8. Schuldiner S. A molecular glimpse of vesicular monoamine transporters. *J Neurochem* 1994;62(6):2067–2078.
9. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. *Exp Rev Neurother* 2006;6(1):7–17.
10. Reches A, Burke RE, Kuhn CM, et al. Tetrabenazine, an amine-depleting drug, also blocks dopamine receptors in rat brain. *J Pharmacol Exp Ther* 1983;225:515–521.
11. Login IS, Cronin MJ, MacLeod RM. Tetrabenazine has properties of a dopamine receptor antagonist. *Ann Neurol* 1982;12:257–262.
12. Burke RE, Reches A, Traub MM, et al. Tetrabenazine induces acute dystonic reactions. *Ann Neurol* 1985;17:200–202.
13. Roberts MS, McLean S, Millingen KS, Galloway HM. The pharmacokinetics of tetrabenazine and its hydroxy metabolite in patients treated for involuntary movement disorders. *Eur J Clin Pharmacol* 1986;29:703–708.
14. Roberts MS, Watson HM, McLean S, Millingen KS. Determination of therapeutic plasma concentrations of tetrabenazine and an active metabolite by high-performance liquid chromatography. *J Chromatogr* 1981;226:175–182.
15. Mehvar R, Jamali F, Watson MW, Skelton D. Pharmacokinetics of tetrabenazine and its major metabolite in man and rat: Bioavailability and dose dependency studies. *Drug Metab Dispos* 1987;15: 250–255.
16. Food and Drug Administration, Center for Drug Evaluation and Research. Application No. 21-894: Tetrabenazine. Medical Review (Online). Available at: www.fda.gov. Accessed October 20, 2008.
17. Kenney C, Hunter C, Davidson A, Jankovic J. Short-term effects of tetrabenazine on chorea associated with Huntington's disease. *Mov Disord* 2007;22(1):10–13.
18. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: A randomized controlled trial. *Neurology* 2006;66(3):366–372.
19. Frank S, Ondo W, Fahn S, et al. A study of chorea after tetrabenazine withdrawal in patients with Huntington disease. *Clin Neuropharmacol* 2008;31:127–133. ■