R E V I E W

Management of Huntington's disease: role of tetrabenazine

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Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive involuntary movements, neuropsychiatric disturbances, and cognitive impairment. The use of tetrabenazine (TBZ), a specific inhibitor of vesicular monoamine transporter, is approved for chorea in HD patients. We aimed to review the medical literature concerning the efficacy and tolerability of TBZ in the treatment of HD patients and to report our personal experience about TBZ use in a cohort of HD patients. We searched PubMed (1960 to July 2010) using the following keywords: "tetrabenazine" + "huntington's disease + chorea". We included randomized controlled trials, open-label trials, and retrospective studies. We excluded case reports and studies conducted on fewer than 20 patients. In addition, we retrospectively evaluated 2 years' follow-up of TBZ treatment on motor and cognitive performances and functional abilities in 28 HD patients, compared with 10 patients treated by other neuroleptics (clotiapine). Only four papers fulfilled the requested criteria. In the first study, which included 84 randomized outpatients, TBZ showed a significant improvement of chorea compared with placebo. In the open-label study extension, TBZ confirmed its efficacy on chorea, with a frequent occurrence of withdrawals due to side effects. In a retrospective study of long-term efficacy, 63 patients under TBZ therapy for an average period of 34 months showed a stable effect on chorea, despite a slight reduction of effect over time. In a telephone survey conducted on a total of 118 patients affected by different movement disorders, TBZ showed the most favorable effect for the 28 included HD patients. Our HD patients showed a slight deterioration of motor performances over time that was nonsignificant compared with TBZ or clotiapine treatments. Despite the fact that the global effect of TBZ seems positive in HD, more attention on evaluating symptomatic treatments for cognitive and psychiatric deterioration as well as motor deterioration would alleviate this devastating disorder until a neuroprotective treatment becomes available.

Keywords: Huntington's disease, symptomatic treatment, tetrabenazine

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by midlife onset and a triad of symptoms, including progressive involuntary movements, neuropsychiatric disturbances, and cognitive impairment.[1] HD is caused by an enlarged CAG repeat expansion in the huntingtin protein gene on the short arm of chromosome 4, which results in a diffuse neuronal degeneration preferentially involving striatum and cortex.[2] As the disease progresses, motor disability develops, especially stereotypic involuntary movements (Huntington's chorea). There is no provided treatment for delaying the development of the disease or to stop the progression of HD. The current management of HD is focused on symptom reduction,

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because there is no treatment able to avoid the progressive global deterioration and death occurring within 10–20 years of disease onset. The goals of managing HD are to reduce the impact of the disease on individuals' abilities, primarily improving motor function, in order to obtain a favorable impact on their quality of life.

Movement disorders in HD consist of involuntary movements (chorea and dystonia) and impairment of voluntary movements (eg, gait, speech, swallowing, fine motor tasks). Both chorea and impairment of voluntary movements progress in the middle stages of HD, whereas in the progression of the disease, chorea often decline as patients become rigid and unable to initiate voluntary movements. Some medications that are effective on chorea may worsen voluntary movement, compromising gait or swallowing, and may induce depression, sedation, and tardive dyskinesia. Many pharmacological interventions have been reported in HD for their efficacy in the treatment of movement disorders such as hyperkinesias, dystonia, myoclonus, and tics. Among them, neuroleptics have demonstrated effectiveness in the treatment of chorea but may induce side effects on motor performance.[3,4]

Tetrabenazine (TBZ; Ro 1-9569) was first synthesized in 1956, and in 1958 was approved for the treatment of neuroses and psychoses/schizophrenia in Finland, the Netherlands, Switzerland, and the UK. Since the 1980s, TBZ has been used in the treatment of different dyskinesias. In May 2008, it was approved by the US Food and Drug Administration for the treatment of chorea in HD. To date, TBZ is marketed with the same indication in many other countries.[5] TBZ exerts its antichoreic effects by reducing the amount of dopamine in the brain in two ways.[6] The first and more widely recognized way is by preventing dopamine release from vesicles, inhibiting the uptake of monoamines. Special proteins called vesicular monoamine transporters (VMATs) are responsible for neurotransmitter transport into the vesicles. TBZ binds to the VMATs, preventing them from performing this function. As such, neurotransmitters like dopamine are not stored in vesicles and cannot be released into the synapse. 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.[7,8]

In addition, TBZ reduces dopamine by blocking dopamine receptors, as has been shown in in vitro studies.[9,10] TBZ binds to receptors on the surface of the receiving nerve cell, blocking dopamine from passing on its message. The mechanism of inhibiting dopamine receptors, however, is thought to be less significant at the TBZ dosages used in HD patients, although it may possibly be responsible for acute dystonic reactions, which are rarely reported with TBZ.[11]

Table 1 Main data across the selected studies about TBZ in HD patients

Study	Year	Study design	No. of HD patients under TBZ	No. of HD patients on placebo	No. of follow-up	Maximum time of observation
Paleacu et al[18]	2004	Open-label long-term follow-up	28 (HD plus other types of chorea) among a total of 150 patients with different movement disorders			88 weeks
Huntington Study Group[15]	2006	Multicenter, prospective, double-blind, placebo-controlled, dose-finding	54	30	1	12 weeks
Fasano et al[17]	2008	Long-term retrospective	68	0	2	137.6 + 100 weeks
Frank[16]	2009	Open-label extension study	45	0	3	80 weeks

Our aim was to review the medical literature concerning the efficacy and tolerability of TBZ in the treatment of chorea in HD patients. In addition, we aimed to report our personal experience about TBZ use in a cohort of HD patients.

Materials and methods

We searched PubMed (1960 to July 2010) using the following keywords: ''tetrabenazine'' + ''huntington's disease + chorea''. We included randomized controlled trials, open-label trials, and retrospective studies. We excluded case reports and studies conducted on fewer than 20 patients.

In addition, we retrospectively evaluated 2 years' follow-up of TBZ treatment on motor and cognitive performances and functional abilities in 28 HD patients, compared with 10 patients treated with other neuroleptics (clotiapine).[12]

The clinical outcome of 44 genetically confirmed HD patients, seen for the first time at the Center for Huntington's Disease of the Neurological and Psychiatric Sciences Department of Bari Aldo Moro University, Bari, Italy, and assigned to TBZ or clotiapine treatment, was checked after 24–30 months' (mean 25.5 ± 2.3 months) observation. Subjects were titrated to the more efficacious and well-tolerated individual dose for both treatments, with a maximum of 200 mg/day for TBZ and 100 mg for clotiapine. All subjects had been assessed according to the motor section of Unified Huntington's Disease Rating Scale (UHDRS)[13] and the Total Functional Capacity Scale[14] at the first access and after 24–30 months of treatment. The statistical analysis included two-way analysis of variance (ANOVA) with clinical scores as variables and time of observation and treatments as factors. In addition, in order to assess the efficacy of TBZ and clotiapine according to severity of motor disability, we evaluated the correlation between the total maximal chorea score in basal condition and the change occurring after treatment, employing Spearman's correlation test.

Results

Among the reviewed papers, only three fulfilled all the requested criteria, and one reported results from 28 patients affected by chorea, including an undefined number of HD sufferers.

The Huntington Study Group demonstrated the efficacy of TBZ in the first multicenter, prospective, double-blind, placebo-controlled, dose-finding study of TBZ for the treatment of chorea in HD.[15] Eighty-four ambulatory patients were randomized (in a 2:1 ratio) to receive either placebo or TBZ 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. Primary outcome measure was the reduction of 5.0 units from baseline in the chorea score of the UHDRS in TBZ-treated patients, compared with a reduction of 1.5 units on placebo treatment (Table 1).[15]

Mean TBZ dosage	Short-term change of TMC	Long-term change of TMC	Clinical global impression of change	Adverse effects	Serious adverse accidents or causes of withdrawal
Up to 150 mg/die (76.2 ± 38.4 mg, range 25–175)			32.14% marked improvement (among the total chorea patients)	Not defined in HD patients	Worsening (3), lack of benefit (7 patients with chorea including HD)
Up to 100 mg/die (range 25–100)	−5 ± 0.5 (M ± SE) (P = 0.0001 vs placebo)		40% much improved (P = 0.0007 vs placebo)	Sedation (13), akatisia (4), parkinsonism, (2), depression (5)	Suicide (1), intracerebral hemorrhage consequent to a fall (1), breast cancer (1)
57.5 ± 14.7 mg (range 6.25–150)	−21% (0–20) (P = 0.00001 vs baseline)	−9% (1–22) (n.s. vs baseline)		Drowsiness (17), depression (11), disturbances of gut function (8), worsening of parkinsonism (4), xerostomia (2), hypotension (1)	Worsening of psychiatric disturbance (1), disabling asthenia (1)
Up to 200 mg/die (range 12.5–175 mg)	−5.8 ± 5 (M + SD) (P < 0.05 vs baseline)	−4.6 ± 5.5 (M + SD) (P < 0.05 vs baseline)		Sedation (18), depressed mood (17), anxiety (13), insomnia (10), fatigue (7), agitation (5), fall (4), dysphagia (3), dystonia (3)	Vocal tics, depression, delusions (3); methastatic breast cancer (1); elevated bilirubine level, akatisia (1); elevated liver enzyme (1)

Abbreviations: HD, Huntington's disease; TBZ, tetrabenazine; TMC, Total Maximal Chorea score.

The same group of study participants was given the opportunity to participate in an open-label extension study. Subjects who completed the 13-week, double-blind protocol were invited to participate in this open-label extension study for up to 80 weeks.[16] Of the 75 participants, 45 subjects completed 80 additional weeks of treatment with TBZ. Subjects were titrated to the best individual dose or a maximum of 200 mg/day. Chorea were assessed using the Total Maximal Chorea (TMC) score from the Unified Huntington Disease Rating Scale.[13] At week 80, chorea had significantly improved
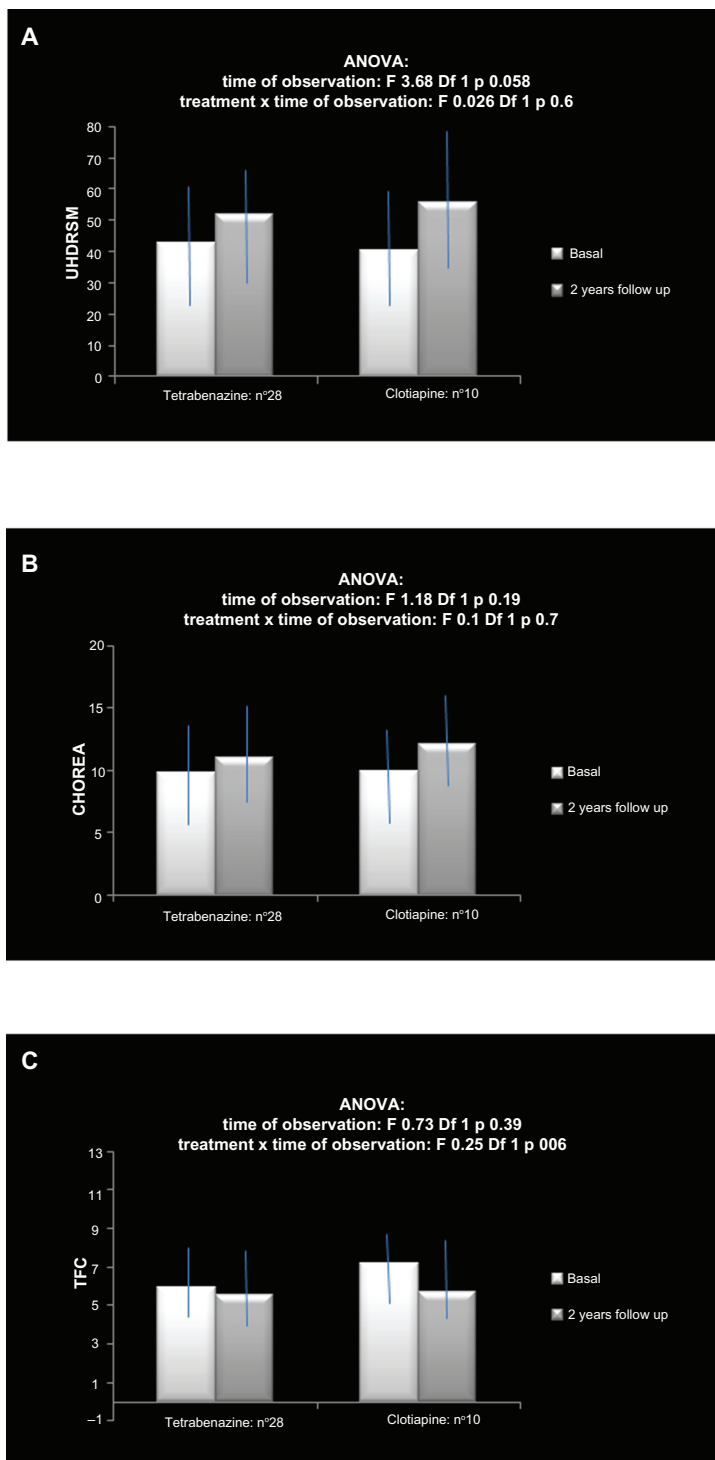
Figure 1 Mean values and standard deviations of **A**) the global motor score of the Unified Huntington's Disease Rating Scale (UHDRSM), **B**) the chorea score, and **C**) the Total Functional Capacity (TFC) Scale in a cohort of Huntington's disease patients before and after 2 years of treatment. The results of two-way analysis of variance (ANOVA) are reported.

Table 2 Mean values and standard deviations of the principal clinical features in our HD patients

	Tetrabenazine N = 28			Clotiapine N = 10		
	Basal	I year	2 years	Basal	I year	2 years
TFC	5.9 ± 3.9	5.8 ± 2.3	5.5 ± 3.9	7.13 ± 5.4	6.9 ± 4.5	5.7 ± 4.3
UHDRSM	43.77 ± 22	44.5 ± 20	50.21 ± 27	40.26 ± 28	44.3 ± 19.8	55.88 ± 22.3
Chorea	10 ± 5.96	9.6 ± 4.66	10.7 ± 4.29	9.8 ± 5.4	9.9 ± 6.3	12.12 ± 4.2

Abbreviations: HD, Huntingdon's disease; TFC, Total Functional Capacity Scale; UHDRSM, Motor Section of the Unified Huntington's Disease Rating Scale.

from baseline with a mean reduction in the TMC score of 4.6 (standard deviation 5.5) units. The mean dose at week 80 was 63.4 mg (range 12.5–175 mg). Three participants terminated due to adverse events. The other 26 subjects chose not to continue study extension for various reasons (Table 1).

Fasano et al[17] performed a retrospective study to evaluate the long-term efficacy and safety of TBZ in managing chorea. In the study, 68 HD patients were analyzed. Patients were treated with TBZ for a mean period of 34.4 ± 25.2 months. At the first follow-up, 9.7 ± 7.8 months after the prescription of TBZ (mean dose 35.3 ± 14.7 mg), mean score of chorea was 8.2 ± 4.1 (−21% compared with baseline), whereas at the latest follow-up visit (mean dose 57.5 ± 14.7 mg), it was 9.5 ± 5.0 (9%). During the follow-up, the clinical benefit persisted, but the magnitude was reduced despite a progressive increase of the doses (up to 60%). Five patients (7%) did not gain any improvement, and TBZ was discontinued. There were two withdrawals because of side effects; 34 patients reported at least one side effect (Table 1).

The authors reported that TBZ was well tolerated and produced long-term improvement of motor symptoms in HD patients, although a slight reduction of benefit occurred during the course of treatment.[17]

Paleacu et al[18] studied a total of 118 patients with hyperkinetic movement disorders, including a group of 28 subjects with chorea, with an unpredictable number of HD sufferers. Patients were assessed in the follow-up visit or by direct and telephone interview using the Clinical Global Impression of Change (CGIC), and the overall efficacy of treatment was shown via a composite score made up from the patient's and the caregiver's score.[18] Significant improvement of hyperkinesias was seen in 61% of patients, with a subgroup of subjects with chorea (nine, including an undefined number of HD patients) and facial dyskinesias responding most favorably (Table 1).[18]

Our experience
Among 44 patients, 32 had been assigned to TBZ and 12 to clotiapine treatment. Four patients in the TBZ group and two in the clotiapine group were lost to the 2-year follow-up (two

patients were hospitalized, two changed address, and two further patients discontinued TBZ after 2 months' therapy because of the sedation side effect). The remainder of the patients took the assigned treatment during the observation period, though in 10 patients in the TBZ group and five in the clotiapine group the minimum efficacious dosage was further reduced because of the occurrence of side effects (sedation, depression, and confusion in both groups), which were relatively resolved at the 2-year follow-up (two patients in the TBZ group and one in the clotiapine group reported sedation; two patients on TBZ reported fatigue). As a consequence, the TBZ dose was, on average, 75 ± 15 mg and the clotiapine dose was 30 ± 5.5 mg. The motor performances worsend in a nonsignificant way in both groups, without significant differences between the two treatments (Table 1; Figure 1A). In particular, in the TBZ group, the progression of chorea seemed slightly reduced compared with the clotiapine group (Table 1; Figure 1B). In fact, the mean change of chorea score over time was +0.85 ± 2.5 in the TBZ group and +2.3 ± 4.5 in the clotiapine group (t-test: nonsignificant). The functional capacities remained stable at follow-up in the TBZ group, with a slight deterioration in the clotiapine group (Table 1; Figure 1C).

The change of chorea score correlated in a negative way with the basal values in the TBZ group (Spearman's correlation test in the TBZ group: 0.521, $P = 0.002$; in the clotiapine group: 0.564, nonsignificant), suggesting more effect in patients with severe hyperkinesias.

Conclusion
Few studies have evaluated the efficacy of TBZ in large samples of HD patients, though it is the only approved drug for HD. In general, the symptomatic treatment of HD has not been evaluated in large cohorts of patients, and there are many aspects of the disease, such as other abnormal involuntary movements, cognition, affective disorders, and behavioral disturbances, for which the best therapeutic strategies are not determined.[19,20] Only one study[15] reported results of a short-term, double-blind, placebo-randomized design, and only one prospective[16] and one retrospective[17] study on the long-term effect of TBZ are available. A study

by Paleacu et al[18] did not explain the exact number of HD patients studied. In addition, the comparison between TBZ and other classical neuroleptics has not been extensively studied in any study. Brusa et al[21] compared the effects of TBZ with those obtained by aripiprazole in six HD patients, finding a slightly prevalent effect of TBZ on chorea but a greater tolerability of aripiprazolo concerning sedation and depression. The overall evaluation of the results obtained from the few TBZ studies on HD seems to partly support its efficacy on choreatic movements. The potential adverse effects of TBZ need a careful evaluation and dosage adjustment.[22] In fact, TBZ causes several adverse events, which in many cases has determined its reduction or even withdrawal. The dosage seems to vary conspicuously across studies and in the same patient group, in an attempt to balance efficacy and tolerability. In addition, the efficacy of TBZ is contrasted with the natural progression of the disease and the loss of efficacy.[17] Our observation confirms that in long-term studies the balance between efficacy and tolerability reduces the potential effect on motor symptoms of both TBZ and the considered atypical neuroleptic drug. In fact, compared with cases reported in previous studies, in our patients, TBZ exhibited a global reduction of efficacy concurring with a minor representation of adverse effects at the 2-year follow-up. Moreover, the worsening of chorea was not significant in both groups and appeared to be further reduced in TBZ-treated patients. The stability of functional capacities across time suggests that the medium–low drug dosages may partly reduce the progression of chorea without compromising other abilities or the occurrence of strong depression, sedation, or confusion. Animal studies have pointed to an important role of the dopaminergic pathway in HD and have suggested that the dopamine signaling pathway constitutes a potential therapeutic target for HD treatment.[23,24] Recently, long-term feeding with TBZ (combined with levodopa) alleviated the motor deficits and reduced the striatal neuronal loss in the mouse model of HD, thus suggesting a neuroprotective effect.[25] However, our retrospective observation does not exclude a lack of effect of both treatments on illness progression, for the absence of a placebo group, and may contribute to confirming the hypothesis suggested by Fasano et al with regard to a long-term loss of efficacy.[17] Nevertheless, we observed a major effect in patients presenting with more severe chorea, indicating an efficacy of TBZ in the progression of motor deterioration. The hypothesis that TBZ may act as a neuroprotective rather than a symptomatic drug should be tested in more

prolonged study designs.[25] The overall impression being derived from the available data and our personal experience is that the problems linked with the symptomatic treatments need further study in HD, especially when the long-term outcome has to be considered, also taking into consideration comparison with the efficacy and tolerability of typical and atypical neuroleptics frequently used in HD patients. Despite the global effect of TBZ seeming positive in HD, more attention on evaluating symptomatic treatments for cognitive and psychiatric deterioration as well as motor deterioration would contribute to alleviating this devastating disorder until a protective treatment against progressive neurodegeneration becomes available.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bates G, Harper P, Jones L. *Huntington's Disease*, 3rd ed. Oxford: Oxford University Press; 2002.
2. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72(6):971–983.
3. Leonard DP, Kidson MA, Brown JG, et al. A double blind trial of lithium carbonate and haloperidol in Huntington's chorea. *Aust N Z J Psychiatry*. 1975;9(2):115–118.
4. Barr AN, Fischer JH, Koller WC, et al. Serum haloperidol concentration and choreiform movements in Huntington's disease. *Neurology*. 1988; 38(1):84–88.
5. Frank S. Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease. *Neuropsychiatr Dis Treat*. 2010;6:657–665.
6. Scherman D, Jaudon P, Henry JP. Characterization of the monoamine carrier of chromaffin granule membrane by binding of [2-3H]dihydrotetrabenazine. *Proc Natl Acad Sci U S A*. 1983;80:584–588.
7. Mehvar R, Jamali F. Concentration-effect relationships of tetrabenazine and dihydrotetrabenazine in the rat. *J Pharm Sci*. 1987;76: 461–465.
8. Thibaut F, Faucheux BA, Marquez J, et al. Regional distribution of monoamine vesicular uptake sites in the mesencephalon of control subjects and patients with Parkinson's disease: a postmortem study using tritated tetrabenazine. *Brain Res*. 1995;692:233–243.
9. Login IS, Cronin MJ, MacLeod RM. Tetrabenazine has properties of a dopamine receptor antagonist. *Ann Neurol*. 1982;12:257–262.
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. Burke RE, Reches A, Traub MM, et al. Tetrabenazine induces acute dystonic reactions. *Ann Neurol*. 1985;17:200–202.
12. Gauch R, Lehner H. The metabolism of 2-chloro-11-(4-methyl-1-piperazinyl) dibenzo-(b,f)(1,4)-thiazepine (clotiapine). 3. The metabolism and excretion in the human. *Farmaco Prat*. 1969;24(2):100–109.
13. Huntington Study Group. Unified Huntington's disease rating scale: reliability and consistency. *Mov Disord*. 1996;11:136–142.
14. Shoulson I. Huntington's disease: functional capacities in patients treated with neuroleptic and antidepressant drugs. *Neurology*. 1981;31: 1333–1335.
15. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology*. 2006; 66(3):366–372.

16. Frank S. Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation study. Huntington Study Group/TETRA-HD Investigators. *BMC Neurol*. 2009;9:62.

17. Fasano A, Cadeddu F, Guidubaldi A, et al. The long-term effect of tetrabenazine in the management of Huntington disease. *Clin Neuropharmacol*. 2008;31(6):313–318.

18. Paleacu D, Giladi N, Moore O, et al. Tetrabenazine treatment in movement disorders. *Clin Neuropharmacol.* 2004;27:230–233.

19. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2011;10(1):83–98.

20. Poon LH, Kang GA, Lee AJ. Role of tetrabenazine for Huntington's disease-associated chorea. *Ann Pharmacother*. 2010;44(6):1080–1089.

21. Brusa L, Orlacchio A, Moschella V, et al. Treatment of the symptoms of Huntington's disease: preliminary results comparing aripiprazole and tetrabenazine. *Mov Disord*. 2009;24(1):126–129.

22. Guay DR. Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. *Am J Geriatr Pharmacother*. 2010;8(4):331–373.

23. Tang TS, Chen X, Liu J, Bezprozvanny I. Dopaminergic signaling and striatal neurodegeneration in Huntington's disease. *J Neurosci*. 2007;27: 7899–7910.

24. Paoletti P, Vila I, Rife M, et al. Dopaminergic and glutamatergic signaling crosstalk in Huntington's disease neurodegeneration: the role of p25/cyclin-dependent kinase 5. *J Neurosci*. 2008;28:10090–10101.

25. Wang H, Chen X, Li Y, et al. Tetrabenazine is neuroprotective in Huntington's disease mice. *Mol Neurodegener*. 2010;5:18–33.