Tetrabenazine in treatment of hyperkinetic movement disorders: an observational study

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Abstract

Background: Tetrabenazine (TBZ) is commonly used in hyperkinetic movement disorders. In this retrospective study, we aimed to assess the TBZ effectiveness and adverse events (AEs) in Huntington disease (HD), vascular chorea, tics, dystonia, tardive oromandibular (OM) dyskinesia and other tardive syndromes (TS).

Methods: Qualitative analysis of clinical response was used to estimate TBZ effectiveness. TBZ-associated AE frequency and subsequent discontinuation rate were used to estimate tolerability; the tolerability profile was measured through the TBZ minimal dose and exposure time required to elicit AEs.

Results: Of 108 included patients, 87% had a clinically meaningful improvement sustained over a period of 40 months. TBZ-responder rate ranged from 100% in HD to 62.5% and 77.1% in tic disorders and OM dyskinesia, respectively ($p < 0.001$). TBZ-associated AE frequency ranged from 40.9% in other TS and 41.7% in vascular chorea and HD, to 60% in OM dyskinesia ($p < 0.001$). The most common AEs were Parkinsonism (51.8%) and psychiatric disorders (25%). The 'other AEs' category (mainly somnolence) presented the shortest minimal exposure time (3 months). AE-eliciting dose differed from 18.8 mg and 25 mg in tics and tardive disorders, to 75 mg in HD ($p = 0.003$). Patients with AEs were tendentiously older at TBZ initiation ($p = 0.022$).

Conclusions: TBZ proved an effective and relatively well tolerated treatment in hyperkinetic disorders, with excellent results in HD. AEs were more common in OM dyskinesia, which may be related to higher age at TBZ initiation. TBZ-associated somnolence and Parkinsonism were more frequent during the titration and maintenance periods, respectively.

Keywords: dystonia, Huntington disease, oromandibular dyskinesia, tardive syndrome, tetrabenazine, tics

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Introduction

Tetrabenazine (TBZ), a benzoquinoline derivative, is an oral monoamine-depleting agent with selectivity for dopamine. It preferentially prevents the presynaptic monoamine storage by inhibiting the vesicular monoamine transporter type-2, a presynaptic transporter found mainly in the central nervous system [Pettibone *et al.* 1984]. Despite also blocking postsynaptic D_2 dopamine receptors, TBZ had rarely caused tardive dyskinesia at the doses commonly used [Jankovic and Clarence-Smith, 2011; LeWitt, 2013], making it a significant advantage over other dopamine receptor antagonists (such as neuroleptics) for treatment of hyperkinetic movement disorders. TBZ has been approved for treating chorea in Huntington disease (HD), and it has been often used off-label for treating a wide variety of other hyperkinetic movement diseases, including tardive syndromes (TS), dystonia and tic disorders, based on the concept that all these diseases are associated with central dopaminergic hyperactivity. Despite the confirmed antichorea efficacy in HD [Huntington Study Group, 2006; Fasano *et al.* 2008; Frank, 2009; Jimenez-Shahed and Jankovic, 2013], the TBZ clinical efficacy, tolerability and the optimal dosage regimens in other hyperkinetic conditions have not been widely documented by large and long-term

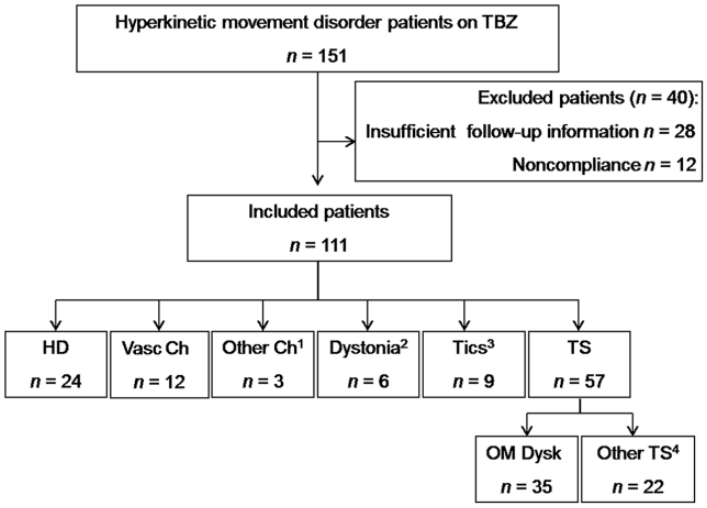

Figure 1. Patient selection.
(1) Including: neurolupus ($n = 1$), striatum cavernous angioma ($n = 1$), and hyperthyroidism ($n = 1$).
(2) Including: generalized hereditary dystonia (SCA3, $n = 1$), generalized acquired dystonia (iatrogenic, $n = 1$, viral encephalitis, $n = 1$, perinatal encephalopathy, $n = 1$), and segmental idiopathic sporadic ($n = 2$).
(3) Including: Gilles de la Tourette syndrome ($n = 3$, with simple motor and vocal tics) and chronic tic disorder ($n = 6$, with simple motor tics, and combined simple and complex motor tics).
(4) Including: dystonia ($n = 9$), chorea ($n = 4$), akathisia ($n = 1$), tics ($n = 1$) and OM plus (+ chorea, tics or dystonia, $n = 7$).
TBZ, tetrabenazine; HD, Huntington disease; Vasc, vascular; Ch, chorea; TS, tardive syndrome; OM Dysk, oromandibular dyskinesia; SCA3, Spinocerebellar ataxia type 3.

studies [Jankovic and Beach, 1997; Paleacu *et al.* 2004; Kenney *et al.* 2007; Porta *et al.* 2008; Shen *et al.* 2013]. Thus, the prevalence and impact of TBZ-associated side effects remain to be established.

The purpose of the current study is to expand the knowledge on the long-term effectiveness and tolerability of TBZ in clinical practice, in both HD and other hyperkinetic movement disorders. The safety issues were addressed more specifically with a focus on adverse event (AE)-eliciting conditions (TBZ minimal dose and exposure time required to elicit AEs) in each diagnostic category. These data can provide a valuable insight for the purpose of designing optimal dosage regimens, in order to find the safest and most effective treatment for each hyperkinetic disorder.

Methods

Patients

A retrospective observational study was conducted including all consecutive patients with hyperkinetic movement disorders who were under TBZ treatment, observed between 1 January 2006 and 31 December 2015, in Egas Moniz Hospital Outpatient Clinic (a tertiary referral center in the Lisbon area). All patients were observed by a movement disorders neurologist and etiological diagnoses were made according to accepted criteria.

Data sources included clinical evaluations and hospital pharmacy records. The exclusion criteria included: (i) insufficient follow up or (ii) insufficient compliance information. The study was approved by the ethics committee and conducted in accordance with the Declaration of Helsinki.

Procedures

A review of clinical records was performed. Clinical and demographic data, as well as data on TBZ effectiveness and AEs, were extracted into case-report forms using a qualitative approach. Patients were grouped into one of the major diagnostic categories of hyperkinetic movement disorders (Figure 1).

Clinical response was classified into one of three scores, comparing the baseline visit (immediately pre-TBZ onset) with follow-up visits: (i) improved and asymptomatic; (ii) improved but symptomatic; and (iii) poor or no clinical response.

Responder rate [(i + ii) / (i+ii+iii) × 100] was used to estimate TBZ effectiveness.

AEs were any unfavorable sign, symptom or disease temporally associated with the use of the drug. Based on the known profile of AEs in TBZ clinical trials, AEs were grouped as: (i) Parkinsonism, (ii) other movement disorders, (iii) psychiatric disorders and (iv) other AEs. For each AE, we registered: (i) the TBZ dose at onset (threshold dose of AE) and (ii) the time of TBZ exposure (threshold exposure time for AE). For those patients that presented two or more AEs, we considered the lowest dose or the shortest exposure time. TBZ-associated AE frequency and subsequent discontinuation rate were used to estimate TBZ tolerability.

After an AE, the physician could suspend TBZ or reduce the dose. The clinical response to TBZ withdrawal or dose reduction was classified into: (i) complete or (ii) partial clinical recovery.

Other concomitant medications used to treat hyperkinetic movement disorders were recorded, including neuroleptics, anticholinergics, botulinum toxin, benzodiazepines and baclofen.

Statistical analysis

Descriptive statistics were used to quantify our effectiveness and tolerability measures. In our primary analysis, effectiveness and tolerability measures were compared between different diagnostic categories. We additionally performed a specific analysis of AEs comparing the threshold dose for AEs, the threshold time for AEs and discontinuation rates and differences between patients with and without AEs.

We used the Pearson's chi-squared test (χ^2) for categorical variables and ANOVA, followed by the Bonferroni *post hoc* analysis, or Kruskall–Wallis test, (more than two groups), depending on data distribution, for continuous variables. Normality of distribution of the continuous variables was confirmed by the Kolmogorov–Smirnov test and homogeneity by the Levene test.

Results were analyzed by Statistical Package for Social Sciences (version 17.0). A p value $\leqslant 0.01$ was considered as a predetermined criterion for statistical significance in order to reduce the type I error that could be associated with a retrospective, clinical chart evaluation design.

Results

From 151 eligible patients, 111 (73.5%) were included in the study (Figure 1), grouped into seven diagnostic categories: HD ($n = 24$), vascular chorea ($n = 12$), other choreas ($n = 3$), dystonia ($n = 6$), tic disorders ($n = 9$) and TS, which were subdivided into tardive oromandibular (OM) dyskinesia ($n = 35$) and other TS ($n = 22$, including dystonia, chorea, akathisia and tic manifestations). The patients in the 'other choreas' category were excluded from subsequent analysis because they represented a restricted and heterogeneous group.

Demographic and clinical features

Demographic and clinical features are presented in Table 1. Males represented 45.4%. The duration of motor symptoms prior to TBZ treatment onset ranged from 0 to 516 months and treatment duration from 1 to 239 months. The age at TBZ treatment onset ranged from 9 to 90 years. The median starting dose ranged from 6.25 to 50 mg and the maximum dose reached from 6.25 to 225 mg. The TBZ was titrated up to a dose that provided the best possible efficacy or led to onset of AEs. The titration time to reach maximum dose ranged from 0 to 132 months.

The diagnostic subgroups differed significantly in all demographic and clinical variables, except in gender distribution and initial TBZ dose. The duration of motor symptoms prior to TBZ onset was significantly higher in tic disorders compared with HD ($p = 0.001$), vascular chorea ($p < 0.001$) and TS ($p < 0.001$). The age at TBZ treatment onset was lower in both dystonia, compared with vascular chorea ($p < 0.001$) and TS ($p < 0.001$), and HD, compared with OM dyskinesia ($p < 0.001$). Tic disorders presented the shortest TBZ treatment duration (6 months), while dystonia and HD presented the longest TBZ durations (90 and 72 months), but no statistically significant differences were observed in *post hoc* analysis. The maximum dose was significantly higher in HD when compared with vascular chorea ($p = 0.003$), tic disorders ($p = 0.004$) and TS ($p < 0.001$). Vascular chorea and HD patients presented the shortest and longest titration time (2.8 and 35.5 months, respectively), but no statistically

Table 1. Demographic and clinical features at baseline and follow-up.

Diagnostic category		n total (males %)	Duration of motor symptoms before TBZ onset (months)	Age at TBZ onset (years)	Initial TBZ dose (mg)	Duration of TBZ treatment (months)	Maximum daily dose (mg)	Time spent (months) to reach maximum TBZ dose	Concomitant medication n (%)
All patients		108 (45.4%)	24 (50.9; 0–516)	64 (62.2; 9–90)	12.5 (16.8; 6.25–50)	40 (49.4; 1–239)	37.5 (56.1; 6.25–225)	9 (22.8; 0–132)	42 (38.9%)
HD		24 (58.3%)	48* (56.6; 6–144)	54$ (53.9; 29–73)	25 (21.6; 6.25–50)	72 (67.1; 9–132)	93.8§ (100; 25–225)	35.5 (41.4; 0–132)	15 (62.5%) (neuroleptics *n* = 14; CNZ *n* = 1)
Vascular chorea		12 (66.7%)	4.5* (8; 0–24)	65$ (67.1; 53–82)	12.5 (19.9; 6.25–50)	17.5 (38.8; 1–161)	31.3§ (44.8; 12.5–100)	2.8 (7.8; 0–46)	3 (27.3%) (CNZ *n* = 2; neuroleptics *n* = 1)
Dystonia		6 (33.3%)	132 (155.5; 10–348)	28$ (31.2; 9–67)	12.5 (13.8; 6.25–25)	90 (107.8; 18–239)	37.5 (75; 12.5–187.5)	7 (39.8; 1–132)	5 (83.3%) (baclofen *n* = 3; benzodizepines *n* = 3; anticholinergic *n* = 2)
Tics		9 (55.6%)	114* (195.5; 9–516	63 (50.2; 19–75)	12.5 (14.1; 6.25–25)	6 (20.1; 1–120)	50§ (40.3; 12.5–87.5)	6 (17.7; 0–108)	3 (33.3%) (neuroleptics *n* = 3; botulinum toxin *n* = 1)
TS	OM dysk.	35 (45.7%)	12* (18.6; 2–60)	75$ (73.1; 35–90)	12.5 (15.7; 6.25–50)	40 (44.3; 1–144)	37.5§ (35.6; 6.25–75)	5 (16.3; 0–88)	4 (11.4%) (anticholinergic *n* = 2; botulinum toxin *n* = 1)
	Other TS	22 (13.4%)	12* (24.3; 2–96)	64.5$ (62.5; 37–85)	12.5 (12.9; 6.25–25)	33 (43.1; 5–145)	37.5§ (46.3; 12.5–100)	11 (17.8; 0–52)	10 (47.6%) (benzodizepines *n* = 6; anticholinergic *n* = 3; botulinum toxin *n* = 2)

TBZ, tetrabenazine; HD, Huntington disease; TS, tardive syndromes; OM Dysk., oromandibular dyskinesia; CNZ, clonazepam.
Values are expressed in median (mean; range).
*It was higher in tic disorders when compared with: HD ($p = 0.001$), vascular chorea ($p < 0.001$) and tardive syndromes ($p = 0.000$).
$It was lower in dystonia, when compared with vascular chorea and tardive syndromes ($p < 0.001$), and HD, when compared with OM dyskinesia ($p < 0.001$).
§It was higher in HD when compared with vascular chorea ($p = 0.003$), tics ($p = 0.004$) and tardive syndromes ($p = 0.000$).

significant differences were observed in *post hoc* analysis (Supplementary material: Figure S1).

Effectiveness of tetrabenazine

The effectiveness results are summarized in Table 2 and Figure 2. Overall, 87% ($n = 94$) of patients were judged to have had a clinical improvement over a median period of 40 months and at a maximum dose of 37.5 mg: of these patients, 90.4% ($n = 85$) remain symptomatic despite clinical improvement and 9.6% ($n = 9$) became asymptomatic. The remaining 13% ($n = 14$) did not improve: in 78.6% the TBZ dose was not increased, or it was discontinued early due to AEs' emergence (completing a median period of treatment of 6 months); in the remaining 14.3% ($n = 2$) the TBZ did not seem to provide an effective benefit over a median period of 34.5 months and on a maximum TBZ dose of 62.5 mg. No one had reported worsening of movement disorders on TBZ treatment.

Overall, responder rate differed among the various diagnostic categories ($p < 0.001$). HD presented the best TBZ response (100% of responder patients), while tic disorders and OM dyskinesia registered the worst outcomes (66.7 and 77.1%, respectively). These two groups included the two patients who did not show an effective clinical benefit despite increasing the TBZ dose (one of these patients had an additional generalized anxiety disorder). In dystonia, vascular chorea, and other TS categories, the responder rates were 83.3%, 91.7% and 95.5%, respectively.

Safety of tetrabenazine

The AEs presumably caused by TBZ are presented in Table 2 and listed in Table 3. TBZ was associated with AEs in 48.1% ($n = 52$) of patients, at median eliciting doses of 25 mg and at median exposure period of 12.3 months. It was observed in only one type of AE in 86.5% ($n = 45$). A total of 56 occurrences were reported (Table 3): 51.8% of them were Parkinsonism, 25% psychiatric disorders (14 patients, six of whom were on antidepressive treatment before TBZ onset), 3.6% other movement disorders and 19.6% other AEs (11 patients, six of whom with TBZ-associated somnolence). The psychiatric side effects were depression (37.5%), anxiety (25%) and worsening of pre-existing psychiatric disorder (37.5%). No patients experienced tardive dyskinesia. Analyzing the patients who developed nonpsychiatric side effects or who did not develop any side effects, 31.2% were on chronic antidepressive treatment. When comparing this group without psychiatric side effects with that with TBZ-induced psychiatric side effects, there were no significant differences regarding the proportion of patients on antidepressive treatment.

When analyzing the diagnostic categories (Table 2), the TBZ-associated AE rates differed among the different groups ($p < 0.001$), ranging from 40.9% and 41.7% in other TS, vascular chorea and HD, to 60% in OM dyskinesia. Tic disorders and dystonia groups registered 44.4% and 50%, respectively. No significant differences in AE types were observed among the diagnostic categories. Regarding the AE-eliciting conditions: the threshold exposure time was comparable among the diagnostic subgroups ($p > 0.01$; ranging from 7 and 7.5 months in tics and vascular chorea, respectively, to 31.5 and 48 months in dystonia and HD, respectively), but the threshold eliciting doses varied significantly ($p = 0.003$): HD required the highest eliciting dose for AE occurrence and differed significantly from tics ($p = 0.006$) and OM dyskinesia ($p = 0.001$) (Supplementary material: Figure S2).

When analyzing the different AEs (Table 3), no significant differences were observed among the four AE types regarding the threshold eliciting doses ($p = 0.029$) and exposure time differed among the four types ($p = 0.018$), despite the 'other AE' category presenting the shortest exposure time (3 months) and lowest eliciting dose (18.8 mg). The remaining TBZ-associated AE registered the following outcomes: Parkinsonism developed at 28 months and 37.5 mg, psychiatric disorders at 24 months and 26.3 mg and other movement disorders at 48 months and 50 mg (Supplementary material: Table S3).

The AE occurrence led to a reduction (56%, $n = 28$) or discontinuation (30%, $n = 15$) of TBZ. This resulted in total clinical remission of AE in 71.9% of cases ($n = 23$) and partial remission in 28.1% ($n = 9$, 1 with discontinuation and 8 with TBZ reduction dose). Also, 14% ($n = 7$) of patients (corresponding to 4 HD, 1 TS and 1 tic patients) maintained the same TBZ dose, since AEs were considered preferable to the expected motor status deterioration. In the HD group, the AE onset did not lead to TBZ withdrawal in any patient, while in the remaining groups, the discontinuation rate

Table 2. Tetrabenazine effectiveness and safety results.

Diagnostic category		All patients	HD	Vascular chorea	Dystonia	Tics	OM dysk	Other TS
Efficacy outcome								
n		108	24	12	6	9	35	22
Responder *n* (%)	Responder (A+B)	94	24	11	5	6	27	21
	A: Asymptomatic	9 (9.6%)	0	2 (18.2%)	0	1 (16.7%)	3 (11.1%)	3 (14.3%)
	B: Improvement but symptomatic	85 (90.4%)	24 (100%)	9 (81.8%)	5 (100%)	5 (83.3%)	24 (88.9%)	18 (85.7%)
Nonresponder *n* (%)	Nonresponder (C+D+E)	14	0	1	1	3	8	1
	C: Increasing of dose without effect	2 (14.2%)	0	0	0	1 (33.3%)[1]	1 (12.5%)[1]	0
	D: Without dose increasing by AE	6 (42.9%)	0	1 (100%)	1 (100%)	0	3 (37.5%)	1 (100%)
	E: Early interruption by AE	6 (42.9%)	0	0	0	2 (66.7%)	4 (50%)	0
Responder rate: (*n* responder patients/total *n*) × 100[2]		87%	100%	91.7%	83.3%	66.7%	77.1%	95.5%
Safety outcome								
n (%) patients with AEs[3]		52 (48.1%)	10 (41.7%)	5 (41.7%)	3 (50%)	4 (44.4%)	21 (60%)	9 (40.9%)
n total of side effect occurrences[4]		56	11	6	3	4	21	11
n/% of AE occurrences (% of affected patients *n* total of each one category)	Parkinsonism	29/ 51.8% (26.9%)	6 (25%)	1 (8.3%)	1 (16.7%)	0	14 (40%)	7 (31.8%)
	Psychiatric disorders	14/25% (13%)	4 (16.7%)	4 (33.3%)	1 (16.7%)	1 (11.1%)	3 (8.6%)	1 (4.5%)
	Other movement disorders	2/3.6% (1.9%)	0	0	0	0	1[5] (2.9%)	1[6] (4.5%)
	Other side effects	11/19.6% (10.2%)	1[7] (4.2%)	1[8] (8.3%)	1[7] (16.7%)	3[7,9,10] (33.3%)	3[7,11,12] (8.6%)	2[7] (9.1%)
TBZ dose/ duration at the time of AEs	Threshold dose for AE occurrence (mg)	25 (44.1; 6.25–162.5)	75[13] (85; 25–162.5)	27.5 (38; 25–75)	50 (50; 25–75)	18.8 (34.4; 12.5–87.5)	25 (28.6; 6.25–75)	25 (44.6; 12.5–100)
	Threshold exposure time of AE occurrence (months)	12 (29.7; 1–132)	48 (60; 3–132)	7 (7; 3–11)	31.5 (31.5; 1–62)	7.5 (10; 1–24)	10.8 (26.8; 1–90)	11 (13.3; 5–28)
Discontinuation rate: (*n* of patients with AEs that interrupted TBZ/total *n* of patients with AEs) × 100		30%	0	40%	33.3%	50%	42.9%	33.3%

HD, Huntington disease; TS, tardive syndromes; OM Dysk, oromandibular dyskinesia; AEs, adverse events; TBZ, tetrabenazine; values are expressed in *n* (%) and median (mean; range).
(1) In these patients, the TBZ dose was increased until maximum of 50 and 75 mg and TBZ treatment sustained over a 3 and 66 months, respectively.
(2) Responder rate differed among the diagnostic groups ($p < 0.001$).
(3) TBZ-associated AE rates differed among the different diagnostic groups ($p < 0.001$).
(4) 86.5% ($n = 45$) patients registered only one AE type, while 13.5% ($n = 7$) registered two or more.
(5) Akathisia.
(6) Dystonia, akathisia and postural tremor.
(7) Somnolence.
(8) Dizziness.
(9) Nausea/vomiting.
(10) Elevated transaminases levels.
(11) Rash.
(12) Mental confusion.
(13) HD required a higher eliciting dose for AE occurrence compared with tics ($p = 0.006$) and OM dyskinesia ($p = 0.001$).

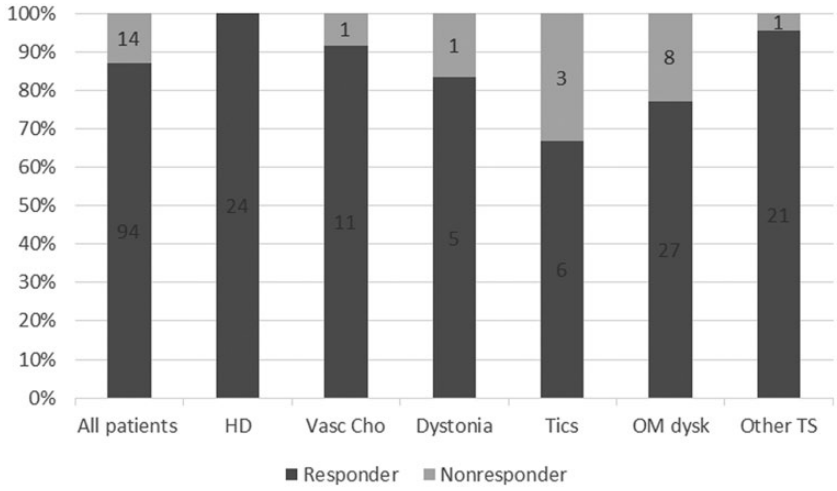

Figure 2. Tetrabenazine effectiveness results.

ranged from 33% in other TS to 50% in tic disorders.

Considering those nine patients with partial remission, three had HD and TBZ-associated Parkinsonism but maintained the treatment with neuroleptics after the TBZ reduction or withdrawal. The other six patients had TS and TBZ-induce Parkinsonism: two had an intermittent rest tremor prior to TBZ onset; one patient had asymmetrically reduced striatal uptake demonstrated by ^{123}ioflupane DaT scan; one other developed a progressive frontal cognitive dysfunction after TBZ withdrawal and the remaining two patients maintained a minimal TBZ dose, as the AE was considered preferable to the hyperkinetic movement re-emergence.

Predictive factors of adverse event occurrence

When comparing patients with and without AEs, the subgroup with AEs shows a tendency to have higher age at TBZ onset ($p = 0.022$). No statically significant differences were observed for diagnostic category, gender distribution, symptom duration prior to TBZ onset, duration of TBZ, initial and maximum daily dose, and titration time. Considering each diagnostic category separately, patients with and without AEs were similar with regard to all these variables.

Concurrent medications

Overall, 38.9% ($n = 42$) of patients received at least one concomitant medication targeting the hyperkinetic movement disorders treatment during the TBZ treatment period (Table 1). There were no significant differences between patients with or without concomitant medications with regard to TBZ effectiveness and tolerability.

Discussion

The results from this retrospective study are in accordance with previous works that had reported the TBZ effectiveness, alone or combined with other drugs, in the management of hyperkinetic movement disorders [Huntington Study Group, 2006; Jankovic and Beach, 1997; Paleacu *et al.* 2004; Kenney *et al.* 2007; Porta *et al.* 2008; Jankovic, 1982; Jankovic and Orman, 1988; Ondo *et al.* 1999].

About 87% of patients had a clinically meaningful improvement that was sustained over a median period of 40 months of TBZ treatment on maximum doses that ranged from 12.5 to 225 mg. Effectiveness results differed among the diagnostic categories. The best clinical outcomes were observed in the HD group (with 100% of TBZ-responder rate), which could be related to an earlier age of TBZ onset and to a more favorable tolerability profile (with a higher threshold dose required for eliciting AEs), thus allowing a gradual increase to more effective dosages. In other long-term studies, 75–96.5% of HD patients improved, at least minimally, on optimal TBZ doses [Fasano *et al.* 2008; Jankovic and Beach, 1997; Kenney *et al.* 2007; Shen *et al.* 2013]; although TBZ efficacy had been measured differently, the better outcomes observed in our study

Table 3. Side effects of tetrabenazine, threshold dose and exposure time.

Adverse events	*n* (%) total AEs	Subtypes	Threshold TBZ dose/ exposure time at the time of AE	
			Threshold dose (mg)	Threshold time (months)
All AEs	56 (100%)		25 (43.1; 6.25–162.5)	12 (29.7; 1–132)
Parkinsonism	29 (51.8%)		37.5 (51.5; 6.25–162.5)	28 (35.6; 3–132)
Psychiatric disorders	14 (25%)	Depression (*n* = 6) Anxiety (*n* = 4) Worsening of pre-existing psychiatric disorder (=6)	26.3 (45.7; 12.5–150)	24 (30.5; 3–94)
Other movement disorders	2 (3.6%)	Akathisia (*n* = 2) Dystonia (*n* = 1) Postural tremor (*n* = 1)	50 (50; 50)	48 (48; 12–84)
Other AEs	11 (19.6%)	Somnolence (*n* = 6) Mental confusion (*n* = 1) Nausea/vomiting (*n* = 1) Headache (*n* = 1) Rash (*n* = 1) Dizziness (*n* = 1) Elevated transaminase levels (*n* = 1)	18.8 (26.1; 11–75)	3 (12.4; 1–87.5)

AEs, adverse events; TBZ, tetrabenazine.

may be related to the fact that patients had a lower symptom duration and were in an earlier and more choreic phase of HD at initial TBZ treatment. In the present study, the lowest responder rate was observed in those with tic disorder (62.5%), which could be related to a shorter minimal exposure time and to a lower minimal dose required for AE emergence, thus not allowing adequate dose titration or leading to early withdrawal. Previous studies had reported an improvement, at least mild to moderate, in 50–77% of tic disorder patients [Jankovic and Beach, 1997; Paleacu *et al.* 2004; Kenney *et al.* 2007; Porta *et al.* 2008], which is in line with our outcomes. Positron emission tomography studies have demonstrated an increased striatal dihydrotetrabenazine binding (a dopamine terminal marker) in tics, which suggests that striatal dopaminergic hyperinnervation may underlie and be a plausible therapeutic target in this disorder [Albin *et al.* 2003].

Other authors have also admitted that TBZ may be more effective as antichorea treatment in HD [Jankovic and Beach, 1997; Paleacu *et al.* 2004; Chen *et al.* 2012]. Although TBZ clinical efficacy has been more extensively studied in HD than in the remaining movement disorders, the apparent better outcomes in that subgroup may reflect the different contribution of dopaminergic modulation to the clinical expression of these disorders. More specifically, selective degeneration of striatal GABA-ergic neurons projecting to the external segment of the globus pallidus, occurring early in the HD course, produces hyperactivity of the dopaminergic pathway which may precipitate a functional reserve against Parkinsonian signs' emergence in patients on TBZ treatment.

With regards the TBZ tolerability profile, AE onset was reported by 48.1% of all patients, at minimal eliciting doses of 25 mg and at minimal exposure time of 12.3 months, and was associated with a moderate discontinuation rate (30% of patients with TBZ-associated AEs). AEs were more common in OM dyskinesias despite a lower dose of TBZ and shorter therapy duration, which may be related to higher age at initial dose of TBZ. Based on present and previous studies, there is no evidence that long-term TBZ administration significantly increases the tardive dyskinesia risk, which differs from other dopamine receptor-blocking agents, including atypical neuroleptics, and confers relevant benefit in treatment of TS.

Parkinsonism was the most commonly reported AE (representing 51.8% of the events, predominantly akinetic–rigid syndrome), followed by psychiatric disorders (representing 25% of occurrences). In previous long-term studies, TBZ-induced AE frequency has ranged significantly from 16.1 to 86% [Frank, 2009; Jankovic and Beach, 1997; Paleacu *et al.* 2004; Kenney *et al.* 2007; Shen *et al.* 2013; Mikkelson, 1983], but direct comparisons are difficult to establish due to differences in TBZ dosage and frequent omission of maximum dose, titration time and minimal doses or exposure times required for eliciting AEs. Somnolence, Parkinsonism and depression have also been the TBZ-related AE more frequently reported. In our study, the 'other AEs' category registered the shortest minimal exposure time required for eliciting AEs (just 3 months), suggesting that somnolence and other systemic effects may occur even in the drug introduction period, while Parkinsonism, psychiatric and other movement complications tended to occur during the TBZ maintenance period (at 28.5, 24 and 48 months, respectively). In previous studies, TBZ-related somnolence frequency has ranged from 25 to 36.5% [Jankovic and Beach, 1997, Kenney *et al.* 2007]; the lower frequency in our study may be due to slower titration or lower doses at the beginning of treatment.

After TBZ reduction or withdrawal, the AE remission was complete in 71.9% of patients; the remaining 28.1%, all with iatrogenic Parkinsonism, had a partial recovery. With regard these patients, four had slightly asymmetric Parkinsonian signs before TBZ onset or developed progressive frontal cognitive dysfunction after TBZ withdrawal; this suggests that TBZ may unmask a concurrent neurodegenerative Parkinsonism where physiopathology is regained after drug interruption.

As observed previously [Kenney *et al.* 2007], age was the only predictive factor for AE occurrence, showing a tendency to be higher in the subgroup with AE, which may reflect, at least partially, the normal nigrostriatal pathway degeneration with increasing age, since the Parkinsonism was the most common TBZ-associated AE. Other authors have also suggested that patients with a depression history have a higher risk of developing depressive symptomatology during a TBZ course [Kenney *et al.* 2006]. In our cohort, 42.9% of the patients who developed psychiatric disorders during the TBZ course were on antidepressant drugs before initial TBZ treatment, suggesting a concomitant primary psychiatric disorder that is exacerbated by TBZ use. Thus, a directed clinical assessment with focus on mood disorders may be performed before TBZ and during the early stages. Moreover, 31.2% of patients who developed nonpsychiatric side effects or without TBZ-induced side effects were on chronic antidepressive treatment, suggesting that the use of antidepressants may prevent the onset of depression in some patients.

To summarize, we have found evidence to suggest that TBZ, alone or combined with other antidyskinetic drugs, showed effectiveness and was relatively well tolerated in the management of a in a wide spectrum of hyperkinetic movement disorders, with excellent results in the HD subgroup, which seems to reflect a better tolerability profile. The common TBZ-associated AEs included somnolence during the titration period, and Parkinsonism and psychiatric disorders during the maintenance period, although the latter may reflect underlying primary psychiatric disorders.

This study presents limitations, namely the lack of a control arm and the retrospective design, based on qualitative review of clinical records. Additionally, patients with different etiologies and anatomic distributions producing variable disability were grouped in the same diagnostic category, such as dystonia and tic disorders. Despite that, the large number of consecutively selected patients, and the long-term evaluation performed in the vast majority of patients make these outcomes relevant in terms of clinical practice and add valuable information on TBZ use in a wide spectrum of movement disorders.

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