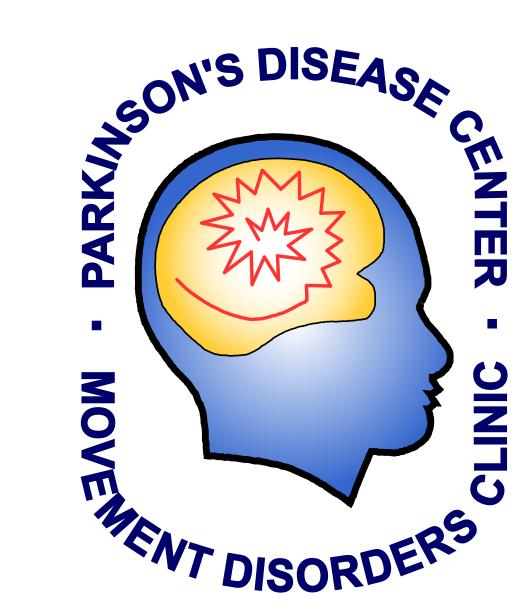


Tetrabenazine for the Treatment of Huntington's Disease and Other Choreas



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ABSTRACT

OBJECTIVE: To describe long-term experience with tetrabenazine (TBZ) in the treatment of Huntington's disease and other choreas.

BACKGROUND: Dopamine receptor blocking drugs (neuroleptics), commonly used in the treatment of involuntary movements, may cause potentially serious adverse effects, including tardive dyskinesia (TD). This side effect, however, has not been reported with TBZ, a synthetic benzoquinolizine that acts as a monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2). TBZ has been reported to have an ameliorating effect in a variety of hyperkinetic movement disorders, including TD, Huntington disease (HD), Tourette syndrome, and other involuntary movement disorders, but the drug has not yet been approved for the treatment of these disorders in the US. Marked improvement in chorea was reported in 83% of the first 90 patients, treated between 1980 and 1995 (Jankovic and Beach, Neurology 48:358-362,1997).

DESIGN/METHODS: A retrospective chart review was performed on subjects treated with TBZ between 12/1996 and 01/2004 at the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine. Response to treatment was assessed by a previously published response scale (1 = marked improvement; 4 = no response; 5 = worsening) (Jankovic and Beach, 1997).

RESULTS: Of the 165 (67 males) patients with chorea treated with TBZ, 98 had evaluable visits, 68 with HD and 30 with other choreas. Of these 98 patients, 88% and 74% with HD and with other choreas, respective, reported a marked or moderate improvement in chorea with improvement in overall function (rating of 1 or 2). The most frequent adverse effects included drowsiness, fatigue, depression, and akathisia. No patient experienced orthostatic hypotension or tardive dyskinesia.

CONCLUSION: TBZ is a safe and effective drug for chronic treatment of chorea associated with HD or other choreas.

INTRODUCTION

Patients suffering from chorea have been receiving tetrabenazine (TBZ) at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) at Baylor College of Medicine since the early 1980s. The first study conducted at this center was a double-blind, placebo-controlled, cross-over study conducted in patients with a variety of abnormal involuntary movements (including chorea). This study showed that the efficacy of TBZ was superior to that of placebo, and that the drug was well tolerated (Jankovic, 1982).

Following this double-blind study, patients with chorea continue to be treated with TBZ at the PDCMDC. Patients are offered treatment with tetrabenazine, providing chorea is troublesome and/or interferes with day-to-day activities. Response is rated on a scale from 1 to 5 (1 = marked improvement; 4 = no response; 5 = worsening), and patients are followed-up every three to six months. In some cases, follow-up occurs at greater time intervals, depending on the difficulties encountered by the patient in traveling back to Baylor. Most patients are videotaped prior to taking tetrabenazine and at one follow-up visit (often the first visit), allowing for a review of the videotapes by an independent neurologist.

To date, approximately 165 chorea patients have been treated at the PDCMDC. Results obtained in the first 90 patients (treated between 1980 and 1995) have been review-ed by Jankovic and Beach (1997). Response rate was high, with 83% of patients having marked improvement of chorea. Tolerability and safety were judged to be good.

The following analysis includes all chorea patients who were treated at the PDCMDC between January 1997 and January 2004. During this period a total of 95 patients received TBZ for the treatment of chorea. For the purpose of this analysis, patient data was first transcribed from the hospital records onto Case Report Forms (CRFs), then from the CRFs onto a database. The objective of the study was to analyze efficacy and safety.

Table 1. Patient Demographics

	Total□	HD	Chorea □	р
Patients, N□	98	68 (27 M) □	30 (14 M) □	ns
Age at sympt	om onset (yr)			
 Mean □ SE □ Range □	45.7	48.7□ □ 1.4□ □ 15.6 - □77.8□	39.1 □ □ 5.3 0.0 − □ 78.4	< 0.03
Duration of S	ymptoms (yr)			
 Mean □ SE □ Range □	7.0	7.2□ □ □ 0.6□ □ □ 0.0 − □23.5□	6.7□ □ 1.7 0.1 −□37.2	ns
Age at initial	TBZ treatment (yr)		
 Mean □ SE □ Range □	52.6 □ □ □ 1.9 □ □ □ 3.0 − □80.2 □	55.6□ □ 1.4□ □ 31.7 —□78.7□	45.8 □ □ 5.3 3.0 − □80.2	< 0.02
Duration of T	BZ treatment (m	10)		
 Mean □ SE □ Range □	24.7	27.8	17.6 □ □ 5.6 0.7 −132.6	ns

Table 2. Disease Severity by Indication

			Baseline Severity (Prior to TBZ Treatment)		
Indication □	N	Mild	Moderate□	Severe	Disabling
HD□ Chorea□	68□ 30□	0 □ 0 □	25 □ 15 □	33□ 13□	10 2

Table 3. Patient Disposition

		Total Number of Patients		
☐ ☐ ☐ N☐		Still Treated ☐ (as of 01-04) ☐	Withdrawn	
HD	68□	42 \Box	18□	8
Chorea □	30□	20□	7 🗆	3

KEY REFERENCES

- □ Toglia JU, McGlamery M, Sambandham RR. Tetrabenazine in the treatment of Huntington's chorea and other hyperkinetic movement disorders. J Clin Psychiatry 1978;39:81-87.
- 2.□ Asher SW, Aminoff MJ. Tetrabenazine and movement disorders. Neurology 1981;31:1051-1054.
- □ Jankovic J. Treatment of hyperkinetic movement disorders with tetrabenazine: A double-blind crossover study. Ann Neurol 1982;11:41-47.
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FINDINGS

- Differences by disease category were found among some demographic characteristics and illness severity. [Tables 1 and 2] An analysis of baseline severity of chorea shows that no patient suffered from mild chorea, and most patients presented with moderate to severe abnormal movements.
- □ Patient disposition was categorized as either "still treated", "withdrawn", or□ "no post-drug follow-up". [Table 3]
- Response rate did not vary over time. [Figure 1] The percentage of patients presenting with an efficacy rating of "1" or "2" is virtually identical at the first and at last visit. [Table 4] For some patients, last visit occurred many years after treatment initiation.
- The response rates obtained in this group of patients approximates 82% and is similar to the response rate previously published by Jankovic and Beach (1997), and more generally to the response rates reported in the literature.
- •□ In most cases, patients were treated with 50–75 mg of TBZ per day. Less than 20% of patients required doses greater than 75 mg per day. [Table 5]
- •□ In many patients tetrabenazine therapy was temporarily suspended to determine whether the patient's underlying chorea had spontaneously improved. In most cases the patient's symptoms deteriorated upon treatment interruption, only to improve again when TBZ was reinstated.
- Adverse events (AEs) were recorded at each follow-up visit. For each AE,
 the investigator determined relationship to tetrabenazine (probable, possible, unlikely). In addition, AEs were categorized as "not severe" or "severe". The most frequently reported AEs were drowsiness and depression, followed by akathisia. [Table 6]
- Various reasons for treatment discontinuation were reported by disease category.
 [Table 7]

Figure 1. Efficacy Response at Initial and Last Visit

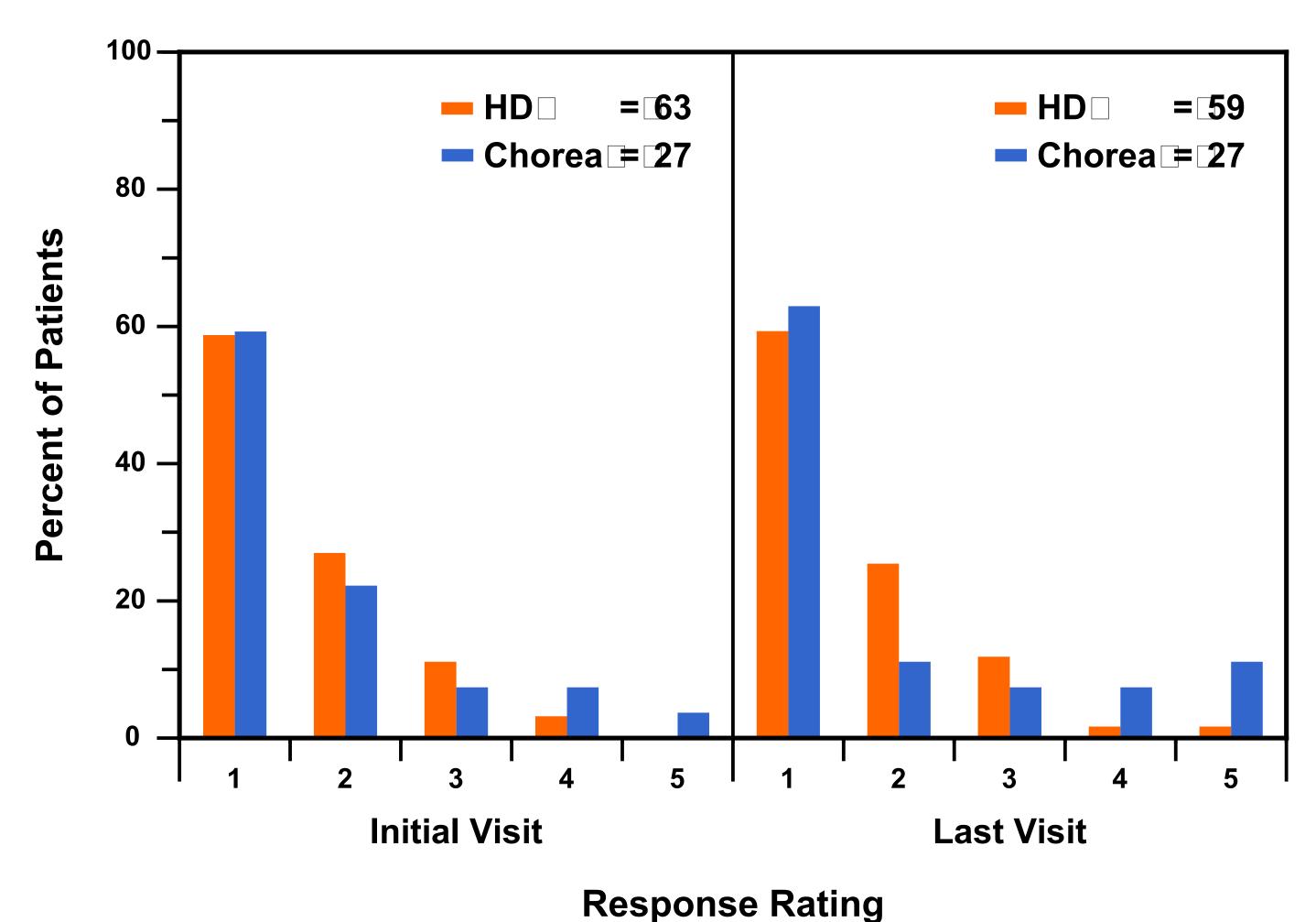


Table 4. Comparison of Efficacy Response at Initial and Last Visit

		Initial Visit□		Last Visit		
□ □ Indication □	N	Percent Patients ☐ with Response ☐ Rating of 1* or 2* ☐	N	Percent Patients with Response Rating of 1* or 2*		
HD□ Chorea□	63 □ 27 □	86%□	59 □ 27 □	88% 74%		

^{*1 =} marked reduction in abnormal movements, excellent improvement in function

Table 5. TBZ Stable Dosing

	Initial Stable Dose□		Last Stable Dose	
Indication □	Mean (SD)□	Range	Mean (SD)□	Range
HD□ Chorea□	50.4□(32.1)□ 1 51.0□(22.1)□ 1		70.0 □(41.7) □ 2 50.9 □(27.3) □ 2	

Table 6. Adverse Event (Number Reported)

Adverse Event□	HD	Chorea
Drowsiness/fatigue □	13□	14
Depression	6□	2
Nausea/vomiting	3□	1
Insomnia	3□	3
Akathisia□	5□	1
Nervousness/anxiety □	3□	2
Parkinsonism <a>□	3□	6
Salivation	3□	2
Dizziness	3□	0
Orthostasis □	0	0
Other AEs	10□	8

Table 7. Reasons for Treatment Discontinuation

Reason for Discontinuation	HD	Chorea
Lack of Efficacy □	1 🗆	2
Spontaneous Improvement ☐	1 🗆	0
Adverse Event□	7 🗆	6
Death□	0	0
Administrative *	8	0
Better Results with BTX	0	0
Other	4	1
Total Discontinued □	21 □	9

^{*} Includes travel/financial reasons. For many patients, traveling back to Baylor is difficult. In addition, some patients cannot afford the cost of TBZ.

CONCLUSION

The analysis of a cohort of patients with moderate to severe chorea treated at Baylor College with tetrabenazine (25 to 200 mg per day) between January 1997 and January 2004 shows that the drug is efficacious and appears to be safe. Response rate is high, and approximates 82%. This high response rate is sustained over the duration of treatment, which for some patients was several years.

^{*2 =} moderate reduction in abnormal movements, very good improvement in function