Tetrabenazine: Does prior history of depression preclude this drug as a treatment option?

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Abstract

OBJECTIVE: To provide data on a possible relationship between pre-existing depression and subsequent use of tetrabenazine (TBZ). **BACKGROUND:** TBZ has been reported to have an ameliorating effect in a variety of hyperkinetic movement disorders. Depression has been reported in about 15% of patients treated with TBZ (Jankovic and Beach, 1997). TBZ acts primarily as a monoamine depleting agent by binding to and inhibiting the human vesicular monoamine transporter isoform 2 (VMAT2). Noradrenaline depletion has been postulated to be a likely mechanism of TBZ induced depression. **METHODS:** Charts were reviewed and response was assessed by a previously published response scale (Jankovic and Beach, 1997). Adverse events (AEs) were captured and coded according to their relationship to the drug, as well as an existing relationship to any pre-existing concomitant conditions such as depression. **RESULTS:** 518 (217 males or 41.9%) patients treated with TBZ at Baylor College of Medicine between 1997 and 2004 were included. Age ranged from 3-87.6 years (mean 50.1 years). The indications for treatment included HD and other choreas (31.3%), TD (30.1%), dystonia (27.4%), TS (18.3%), and myoclonus (3.7%). The majority of the patients experienced robust improvement in their involuntary movements. The most frequent AEs, all of which were dose related and none were permanent, included drowsiness or fatigue 142 (27.4 %), parkinsonism 61 (11.8%), depression 49 (9.5%), and akathisia 46 (8.9%). No symptomatic orthostatic hypotension or tardive dyskinesia was reported. 272 subjects (52.5%) had a prior documented history of depression and/or prior treatment with antidepressant therapy before initiation of TBZ treatment. During TBZ treatment (mean duration 29.7 months, mean dosage 62 mg/day), 50 (18.4%) had an exacerbation of their depression or required a change in antidepressant (15.4%) and 28 (11.4%) experienced a new onset of depression. Total of 16 (3.1%) discontinued treatment because of depression. There was no statistical difference in the discontinuation rate of those with prior history (3.3%) versus those with new onset depression (2.8%). **CONCLUSION:** Although depression is a potentially serious AE of TBZ, our data indicate that the drug is a safe and effective treatment of hyperkinetic movement disorders even in a setting of preexisting depression.

Background / Methods

☐ Tetrabenazine (TBZ) is a synthetic benzoquinolizine that acts as a monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2) [Figure 1 and Table 1]. Human VMAT2 is a product of a gene on chromosome 10q25, whereas VMAT1 gene is localized on chromosome 8p21.3. In contrast to VMAT1, which is predominantly expressed in the periphery, VMAT2 is expressed in the brain. The high selectivity of TBZ for VMAT2 (by a factor of 104 over VMAT1) may explain the CNS-specific effects of the drug.

☐ Over a thousand patients suffering from hyperkinetic movement disorders have been treated with TBZ at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine since we received Notice of Claimed Investigational Exemption for a New Drug (IND) in March of 1979. Patients were included if they met the following criteria: the presence of troublesome or disabling involuntary movements; willing and able to give informed consent for the TBZ trial and videotape protocol, and have adequate follow-up every three to six months per protocol.

☐ Response to treatment was assessed using a previously reported scale (Jankovic J, Beach J. Neurology 1997), based on a 1 to 5 response rating (1 = marked reduction in abnormal movements, excellent improvement in function; 2 = moderate reduction in abnormal movements, very good improvement in function; 3 = moderate improvement in abnormal movements, only mild or no improvement in function; 4 = poor or no response; 5 = worsening). Past medical history was obtained including history ☐ of depression and/or prior or concomitant treatment of depression. AEs, including responses to specific questions related to level of alertness, mood and motor function were captured and one of the investigators (JJ) rated their causal relationship to TBZ as either "probable", "possible", or "unlikely".

Table 1: Demographic and Treatment Information Among Patients Receiving TBZ Treatment (N = 517)

☐ ☐	n☐	Mean☐	SD☐	Min☐	Max
Age at symptom onset☐	496☐	42.7☐	23.8☐	0.0☐	82.9
Initial treatment					
☐ Age at TBZ treatment☐	501☐	50.1☐	22.0☐	3.0☐	87.6
☐ Symptom duration (yr)☐	496☐	7.4☐	8.8☐	0.0☐	64.0
☐ Disease severity☐	498☐	2.7☐	0.7☐	1.0☐	4.0
☐ TBZ daily dose (mg)☐	492☐	53.0☐	30.7☐	12.5☐	225.0
☐ Response rating☐	449☐	1.9☐	1.2☐	1.0☐	5.0
Last visit					
☐ Disease severity☐	441☐	2.4☐	0.8☐	1.0☐	4.0
☐ TBZ daily dose (mg)☐	449☐	61.6☐	38.7☐	0.0☐	300.0
☐ Response rating☐	423☐	2.0☐	1.3☐	1.0☐	5.0
Duration of TBZ treatment (mo)☐	461☐	29.7☐	40.7☐	>0.0☐	258.6

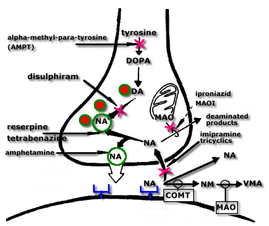

Figure 1

Table 2: Indications for TBZ Treatment (N = 517)

☐ ☐	n☐	%
Chorea☐	162☐	31.3
Dyskinesia☐	156☐	30.2
Dystonia☐	142☐	27.5
Tics☐	95☐	18.4
Myoclonus☐	19☐	3.7
Other☐	14☐	2.7

*Table 3: Comparison Among Patients Receiving TBZ Treatment by History of Depression **

☐ ☐ ☐ ☐ ☐ ☐	Negative History☐ of Depression☐ (N = 244)☐			Positive History of Depression (N = 273)		
☐ ☐	n☐	Mean☐	SD☐	n☐	Mean☐	SD
Age at onset☐	226☐	41.6☐	24.6☐	270☐	43.6☐	23.0
Initial treatment						
☐ Age at TBZ treatment☐	228☐	48.7☐	23.7☐	273☐	51.3☐	20.4
☐ Symptom duration (yr)☐	226☐	7.1☐	8.9☐	270☐	7.7☐	8.7
☐ Disease severity☐	226☐	2.7☐	0.7☐	272☐	2.6☐	0.7
☐ TBZ daily dose (mg)☐	222☐	52.2☐	32.4☐	270☐	53.6☐	29.3
☐ Response rating ^☐	202☐	2.1☐	1.2☐	247☐	1.8☐	1.1
Last visit						
☐ Disease severity☐	194☐	2.4☐	0.8☐	247☐	2.4☐	0.8
☐ TBZ daily dose (mg)☐	198☐	62.6☐	41.6☐	251☐	60.7☐	36.2
☐ Response rating☐	186☐	2.1☐	1.3☐	237☐	1.9☐	1.2
Duration of TBZ treatment (mo)☐	208☐	26.7☐	42.0☐	253☐	32.1☐	39.5

* Unless otherwise specified, all comparisons were not statistically significant, $p > 0.05$.
^ $z = -2.9$, $p < 0.003$.

Results

☐ A subset of 517 patients (41.8% male), treated during the period of 1997 and 2004, out of the total of 1113 patients treated with TBZ at Baylor's Parkinson's Disease Center and Movement Disorders Clinic were included in this study [Table 1]. Chorea, tardive dyskinesia and dystonia were the most frequent indications [Table 2]. A total of 273 (52.8%) patients have a history of depression sometime during the course of their illness, but there was no difference in various demographic data between patients with or without prior depression, except those with depression responded significantly better to TBZ than those without prior depression [Table 3]. After somnolence and parkinsonism, depression represented the most frequent AE [Table 4], but only 2.9% without and 3.3.% of those with prior history of depression discontinued TBZ (NS).

Discussion

☐ Alterations in brain catecholamines have been long hypothesized to play a critical role in abnormal mood and depression (Shelton RC, 2004; Delgado PL, 2004). Drugs such as TBZ have been used to study the effects of increasing and decreasing neurotransmitter levels on behavior in animal models.

☐ Our study showed that during TBZ treatment (mean duration 29.7 months, mean dosage 62 mg/day), 50 (18.4%) of patients had an exacerbation of their depression, (15.4%) required a change in antidepressant, and 28 (11.4%) experienced a new onset of depression. The overall AE rate of depression with causality related to TBZ treatment in this cohort was 9.5% which is actually considerably lower than previously reported prevalence estimate of major depression in general population of about 17% (Blazer DG, 1994; Kessler RC, 2003). A total of 16 (3.1%) discontinued treatment because of an AE of depression. There was no statistical difference in the discontinuation rate of those with prior history (3.3%) versus those with new onset depression (2.8%). Although depression is a potentially serious AE of TBZ, our data indicate that the drug is a safe and effective treatment of hyperkinetic movement disorders even in a setting of preexisting depression.

*Table 4: Most Common Adverse Effects Reported by Patients Receiving TBZ Treatment **

☐ ☐	Patients☐		Incidents of AE	
☐ ☐	n☐	%☐	n☐	%
Somnolence☐	142☐	27.5☐	155☐	24.8
Parkinsonism☐	61☐	11.8☐	62☐	9.9
Depression☐	49☐	9.5☐	52☐	8.3
Akathisia☐	46☐	8.9☐	49☐	7.8
Nervousness/anxiety☐	37☐	7.2☐	41☐	6.5
Insomnia☐	37☐	7.2☐	39☐	6.2
Nausea/vomiting☐	30☐	5.8☐	34☐	5.4
None reported☐	105☐	20.3☐	-☐	-

* Listed by higher prevalence

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