Clinical Characteristics of Tetrabenazine-Induced Parkinsonism

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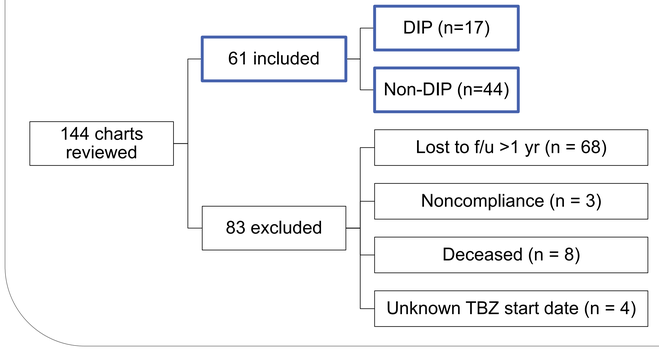
BACKGROUND

- Tetrabenazine (TBZ) is dopamine depleting drug used for treatment of Huntington's disease (HD) chorea and off-label for other hyperkinetic disorders including non-HD chorea, tardive dyskinesia (TD), hemiballisumus, dystonia, tic disorders and Tourette's syndrome (TS).
- Most commonly reported adverse effects (HSG 2006) include depression, parkinsonism, akathisia, drowsiness and insomnia.
- Most of these occur during titration period
- In long term use, commonly reported side effects include drowsiness (25.0%), Parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%), and all were dose-dependent (Kenney 2007).
- Unlike other dopamine receptor blocking drugs, tardive dyskinesia is not an adverse effect of TBZ.
- Kenney and colleagues (2007) noted that age was a significant predictor of Parksinonsim as a side effect and suggested that there may be an underlying age-related dopamine deficiency that manifests with tetrabenazine use.
- Currently, little is known about the clinical manifestations of TBZ-induced parkinsonism, how risk varies with indication for use and whether presentation is early in the course of treatment or during the maintenance phase.
- Objective: To describe the clinical characteristics of patients with tetrabenazine-induced parkinsonism.

METHODS

- Retrospective chart review of cross-sectional population of tertiary Movement Disorders center
- Inclusion criteria:
  - ✓ Treated with TBZ over 1 month with follow up within past year
  - ✓ Development of parkinsonism (tremor, rigidity, bradkinesia or postural instability) attributable to TBZ use
- Exclusion criteria:
  - ✓ Medication noncompliance
  - ✓ Lost to follow up for over a year or deceased
  - ✓ Unknown TBZ start date
- By chart review, we collected indication for TBA, total duration of TBZ treatment, presence of DIP and date of diagnosis, latency to onset of DIP, TBZ dose at time of diagnosis and at last follow-up, symptoms of DIP, treatment of DIP and response, and any DaTscan results.
- Information was extracted to a database for analysis. Statistical methods included 2-tailed Fisher's exact test to compare incidence of DIP across disease states, ANOVA to compare mean duration of therapy and dosage at time of diagnosis of DIP, and two tailed t tests to compared characteristics of TBZ treatment in patients with and without DIP.

Fig1: Subjects included in analysis



RESULTS

Fig2: Indication for TBZ use

Other: myoclonus, non-HD chorea, hemiballismus

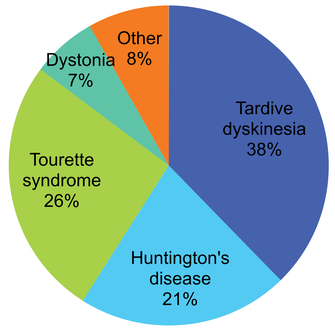


Fig3: DIP by disease state

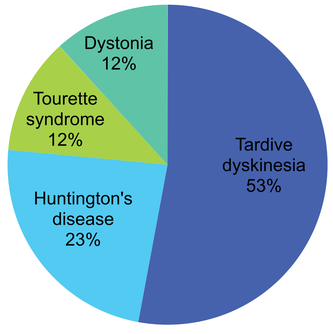


Fig. 4. Features of DIP

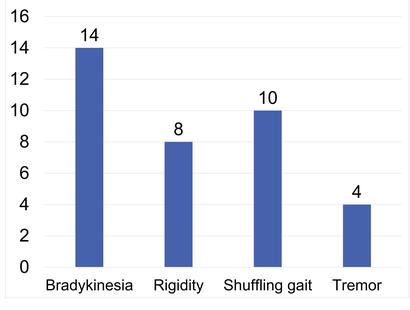


Table 3: Management Strategies for DIP

Levodopa (n=7)
Dopamine agonist (n=1)
Amantadine (n=3)
Trihexyphenidyl (n=1)
Lower dose of TBZ (n=3)

Table 1: DIP vs. non-DIP

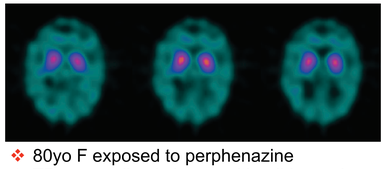
	DIP (at time of DIP diagnosis)	Non-DIP (at last follow up)	P value (two tailed t test)
Age	58.12 ± 19.5	47.23 ± 24. 3	0.1036
Mean age at onset of TBZ therapy (yrs)	53.4 ± 19.5	43.8 ± 24.6	0.152
Mean total dose of TBZ (mg)*	61.4 ± 27.1	69.3 ± 37.0	0.427
Mean duration of therapy (mos)	50 ± 52.1	46.6 ± 35.7	0.775

*n=5 were taking concomitant dopamine receptor blocking agents

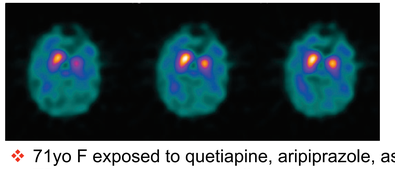
Table 2: Onset of DIP by indication for TBZ

Disease	N	Mean dose of TBZ (mg)	Latency to onset (mos) [SD, range]	Mean full duration of therapy, all patients (mos)
TD	9	58.3 ± 28.6	50.2 ± 67.3* [1 to 216]	76.0 ± 68.2
TS	2	65.6 ± 48.6	39.5 ±30.4 [18, 60]	51.1 ± 35.0
HD	4	71.9 ± 15.7	50.5 ± 40.8 [10 to 90]	61.0 ± 39.1
Dystonia	2	50 ± 35.3	58.5 ± 28.1 [38, 79]	41.3 ± 48.7
Total	17	61.4 ± 27.1	50 ± 52.1 [1 to 216]	59.1 ± 52.1
	p = 0.249[a]	p = 0.73[b]	p = 0.97[b]	P = 0.42[b]

[a]Fisher's exact test; [b]ANOVA, *4 occurred within first 10 months of therapy



- 80yo F exposed to perphenazine
- TD: generalized chorea with milder orobuccal movements
- TBZ: 12.5mg bid
- Parkinsonism: after increase TBZ to 12.5mg tid; 3+ BK, 3+ rigidity, shuffling, freezing, falls
- TBZ reduced to 12.5/6.25mg and levodopa added



- 71yo F exposed to quetiapine, aripiprazole, asenapine with prior DIP
- TD: severe orobuccal and lingual stereotypies, respiratory dyskinesia
- TBZ: 12.5mg bid
- Parkinsonism: worse after increase TBZ to 12.5mg tid; tremor, BK, gait changes
- PD treated with ropinirole, TBZ dose unchanged

CONCLUSIONS

- In this cohort, TBZ was used to treat a variety of hyperkinetic movement disorders
- DIP occurred in 27.9% of the group (n=17) – though this is not a true prevalence estimate based on the study methods
  - ➢ We intended to include only patients whose active treatment status was known rather than assuming lack of onset of DIP since last known follow-up, or assuming TBZ dose.
- TBZ-induced parkinsonism was most common in patients with tardive dyskinesia, though this was not statistically significant (p=0.249, Fisher's exact test).
  - ➢ Likely due to small sample size
- Age at onset of DIP or onset of TBZ therapy did not differentiate those with DIP from those without DIP.
- Mean dosage of TBZ and duration of therapy at the onset of DIP also was not significantly different in DIP vs. non-DIP groups.
- Latency to onset of DIP ranged from 1-216 months of TBZ therapy, but on average occurred 50 months after TBZ therapy was begun
  - ➢ DIP may occur earlier in the course of TBZ therapy in the TD group (3 of 9 cases had onset within first 6 months of therapy, whereas onset was 10mos or later in other diseases).
- Based on factors analyzed in this study, predictors of TBZ are unclear; individual factors (such as pharmacogenomics) may therefore also be relevant
  - ➢ Clinicians should maintain a high index of suspicion of DIP in individuals treated with TBZ, regardless of disease state, throughout therapy, and throughout the dosing range
- Bradykinesia and gait changes are the most common initial manifestations of DIP, followed by rigidity and tremor.
  - ➢ DaTscans can be useful in differentiating DIP from those who have co-existing idiopathic PD or other neurodegenerative parkinsonisms.
- In this cohort, levodopa was most commonly used for management of DIP, and less commonly amantadine and dopamine agonists. Three responded to decrease in TBZ dose alone.
  - ➢ Patients responded well to all management options fairly equally with improvement and/or stability in parkinsonian symptoms, with most described as having "mild" symptoms by clinician.
- Limitations of this study include:
  - ➢ Retrospective analysis
  - ➢ Non-uniform description parkinsonism features
  - ➢ Difficulty ascertaining whether parkinsonism in an HD patient is related to disease manifestations or DIP
  - ➢ Small sample size
  - ➢ CYP2D6 metabolizer status unavailable on all subjects
- Prospective, long-term data regarding parkinsonism in patients treated with TBZ are needed.

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