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CONCOMITANT USE OF ANTIDEPRESSANTS AND NEUROLEPTICS WITH TETRABENAZINE DURING TREATMENT OF HUNTINGTON'S DISEASE

Kathleen Clarence-Smith[1], Vivienne Shen[2], Christine Hunter[3], Joseph Jankovic[3]

[1]KM Pharmaceutical Consulting LLC, Washington, DC; [2]Lundbeck LLC, Deerfield, IL; [3]Baylor College of Medicine, Houston, TX

ABSTRACT (UPDATED)

Objective: To assess antidepressant (ATD)/neuroleptic (NL) use by Huntington's disease (HD) patients receiving tetrabenazine (TBZ).

Background: The potential interaction between TBZ and ATDs/NLs has not been well studied.

Methods: Patients with hyperkinetic movement disorders were evaluated at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine. Patients were initially hospitalized and TBZ was started at 12.5 mg/day. Dosage was increased every 3 days, until a dosage-limiting adverse event (AE) occurred. TBZ was then down-titrated to greatest tolerated dosage. Responses were rated on a 1–5 scale (1 = marked chorea reduction, excellent improvement in function; 2 = moderate chorea reduction, very good improvement in function; 3 = fair chorea improvement, only mild improvement in function; 4 = poor/no response for chorea/function; 5 = worsening chorea/some functional deterioration).[1]

Results: By 2004, 98 HD-chorea patients had participated in this trial. At baseline, 31 were on ATDs (tricyclics or SSRIs). Later, 25 additional patients received an ATD. The percentage of patients ever reporting marked/moderate response was 73% for those receiving an ATD vs. 82% for those not receiving an ATD. The 5 most common AEs for the ATD and no ATD groups were somnolence (30%, 37%), insomnia (20%, 4%), depression (20%, 7%), akathisia (14%, 4%), and nervousness (13%, 4%). Twelve patients received NLs before TBZ initiation, and most discontinued them after initiation. Later, 25 had a NL added. The percentage of patients ever reporting marked/moderate response was 65% for those on NLs (at any time) vs. 88% for those not on NLs. The 5 most common AEs with NL and no NL were somnolence (36%, 27%), insomnia (15%, 16%), depression (17%, 16%), akathisia (8%, 16%), and nervousness (15%, 4%).

Conclusions: Most TBZ-treated patients received a concomitant ATD, NL, or both. TBZ response and TBZ-related AEs did not differ substantially between patients with or without these concomitant medications.

BACKGROUND

- Prior to approval of TBZ for the treatment of chorea associated with Huntington's disease (HD) in the United States, some US patients were able to obtain the drug from abroad, while others received TBZ under physician Investigational New Drug Applications (INDs)
- The Parkinson's Disease Center and Movement Disorder Clinic (PDCMDC) at Baylor College of Medicine administered TBZ under Dr. Jankovic's IND, issued in 1979[2,3]
- Patients were enrolled and treated at the PDCMDC under Protocol H-721, "Compassionate Use of TBZ in the Treatment of Hyperkinesias," a single-center, open-label, individualized-dosage study[2,3]
- From January 1979 through February 2004, 165 patients received TBZ for chorea
- During this 25-year period, 98 patients with chorea associated with HD were treated and had complete records available for analysis[4]
- Data from these patients were analyzed for various treatment effects

OBJECTIVE

- To determine the rate of concomitant use of antidepressants and neuroleptics in HD patients and their possible impact on the efficacy and safety of TBZ treatment of chorea

METHODS

Patients

- Patients with hyperkinetic movement disorders evaluated at the PDCMDC underwent a detailed neurologic examination and a video recording designed to capture the phenomenology and severity of the disorder
- Male and female patients with HD-associated chorea were eligible for treatment with TBZ if their chorea was functionally significant (i.e., chorea had to interfere with activities of daily living, occupational activities, and/or academic activities)
- Patients were also required to have failed available conventional treatments or not derived satisfactory relief from these treatments

Treatment

- Treatment with TBZ was started at 12.5 mg/day and dosage was adjusted upward by 12.5-mg/day increments every 3–7 days until satisfactory improvement of the chorea was achieved or a troublesome adverse event (AE) occurred. If a troublesome AE occurred, the dosage was down-titrated to the optimal dosage, defined as the dosage judged by the investigator to provide the greatest efficacy with minimal or tolerable AEs.[4]

Assessments

- Outpatient visits were scheduled 6 weeks after treatment initiation and every 3 months thereafter
- Dosage, efficacy, and AEs were collected at each clinic visit and entered on a Case Report Form (CRF)
- Response to treatment was rated on a scale of 1–5[1]
  - 1 = marked chorea reduction, excellent improvement in function
  - 2 = moderate chorea reduction, very good improvement in function
  - 3 = fair chorea improvement, only mild improvement in function
  - 4 = poor or no response for chorea and function
  - 5 = worsening chorea and some functional deterioration

Data Extraction

- Data were extracted from the Baylor CRFs into a database
- The data transfer was audited and the data analyzed
- Of the 165 patients listed in the Clinic Log as having received TBZ after being diagnosed with chorea, 98 patients had chorea associated with HD and were used for this analysis

Statistical Analysis

- Descriptive statistics were employed to summarize demographic and illness characteristics, response to treatment, and AEs

RESULTS

Treatment Duration and Patient Disposition

- Throughout the study, only 10 of 98 patients (10%) did not receive either a concomitant antidepressant or a neuroleptic with their TBZ treatment
- For most patients, concomitant treatment with an antidepressant or a neuroleptic did not last for the entire length of the study
- Neither concomitant antidepressants nor neuroleptics appear to have affected the duration of TBZ treatment or reasons for TBZ discontinuation (Table 1)

Table 1. Treatment Duration and Reasons for TBZ Discontinuation

End of study disposition	Antidepressant[a] (N=71)	No antidepressant (N=27)	Neuroleptic[b] (N=53)	No neuroleptic (N=45)
Length of study participation, mean (range), years	3.5 (<1–9)	2.1 (<1–11)	3.4 (<1–11)	2.7 (<1–8)
Cumulative TBZ treatment duration >2 years, n (%)	43 (61)	10 (37)	30 (57)	23 (51)
Treatment status, n (%)				
Continuing treatment	14 (20)	5 (19)	10 (19)	9 (20)
Withdrawn from treatment	57 (80)	22 (81)	43 (81)	36 (80)
Death	6 (8)	0	6 (11)	0
Adverse events	12 (17)	5 (19)	11 (21)	6 (13)
Lack of efficacy	3 (4)	1 (4)	4 (8)	0
Disorder resolved spontaneously	0	1 (4)	0	1 (2)
Travel/financial reasons	5 (7)	2 (7)	3 (6)	4 (9)
Other	31 (44)	13 (48)	19 (36)	25 (56)

TBZ=tetrabenazine.
Concomitant treatment may have occurred at any time during the study.
[a]At baseline, 31 patients were on an antidepressant, 52 were not. Start date was missing for 15 patients, who could therefore have been on an antidepressant at baseline.
[b]At baseline, 12 patients were on a neuroleptic, and 73 were not. Neuroleptic start date was unknown for 13 patients. Many patients taking a neuroleptic at baseline were titrated off the neuroleptic before TBZ was started.

Demographics and Baseline Characteristics

- Demographics, baseline characteristics, and time since first symptom onset did not appear to be different for patients who had received concomitant antidepressants and neuroleptics compared with those who had not (Table 2)
- At some point during the study, 71 of 98 patients (72%) were treated with an antidepressant
- Neuroleptics were received by 55% of patients
- Concomitant use of an antidepressant and a neuroleptic with TBZ occurred in 34 patients (concomitant use of both types of medications did not always overlap)

Table 2. Demographics and Time Since Symptom Onset as a Function of Concomitant Antidepressant or Neuroleptic Treatment at Any Time During the Study

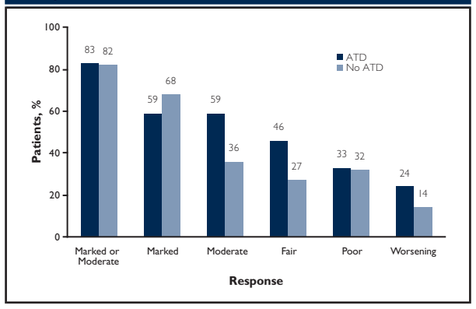
Demographic	Concomitant Use	No Concomitant Use
Concomitant ATD use at any time	**N=71**	**N=27**
Female, n (%)	44 (62)	14 (52)
Age (range), years	53 (31–73)	60 (34–79)
Time since symptom onset (range), years	8.6 (<1–35)	6.7 (<1–18)
Concomitant NL use at any time	**N=53**	**N=45**
Female, n (%)	29 (55)	29 (64)
Age (range), years	54 (31–78)	55 (31–79)
Time since symptom onset (range), years	8.8 (<1–35)	7.2 (<1–24)

ATD=antidepressant; NL=neuroleptic.

Efficacy

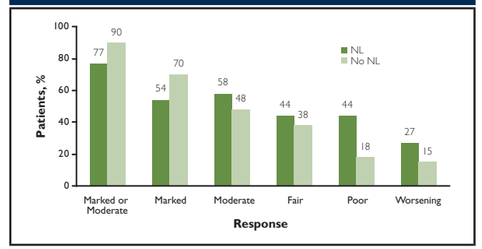
- Of the 98 patients included in this analysis, 92 had a valid efficacy response rating
- Across all patients, at any dosage, and at any time during the study, 83% of patients were judged to have a "marked or moderate" response to treatment
- Maximal response to TBZ did not seem to be affected by either concomitant antidepressant or concomitant neuroleptic use at any time during the study (Figures 1 and 2)

Figure 1. TBZ Efficacy Ratings in Patients With or Without Antidepressant Treatment



ATD=antidepressant; TBZ=tetrabenazine.
Patients either received an antidepressant at any time during the study or never received an antidepressant during the study; patients could be counted more than once.

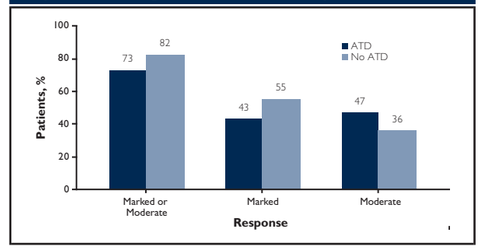
Figure 2. TBZ Efficacy Ratings in Patients With or Without Neuroleptic Treatment



NL=neuroleptic; TBZ=tetrabenazine.
Patients either received a neuroleptic at any time during the study or never received a neuroleptic during the study; patients could be counted more than once.

- At optimal TBZ dosage (i.e., dosage that provided the greatest efficacy with tolerable AEs) and across all patient groups, 75% of patients were reported to have a "marked or moderate" response
- Concomitant treatment with an antidepressant at any time did not significantly affect response to treatment at optimal dosage (Figure 3)

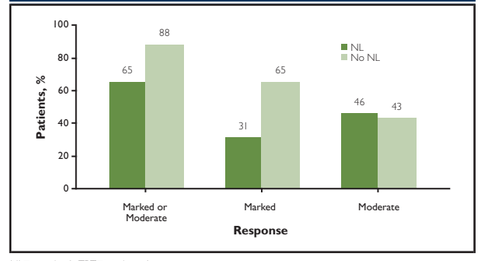
Figure 3. Patients With "Marked" and/or "Moderate" Efficacy Rating at Optimal TBZ Dosage With or Without Antidepressant Treatment



ATD=antidepressant; TBZ=tetrabenazine.
Patients either received an antidepressant at any time during the study or never received an antidepressant during the study; patients could be counted more than once.

- By contrast, "marked or moderate" and "marked" response tended to be greater at optimal dosage for patients who did not receive a neuroleptic during the study (Figure 4)

Figure 4. Patients With "Marked" and/or "Moderate" Efficacy Rating at Optimal TBZ Dosage With or Without Neuroleptic Treatment



NL=neuroleptic; TBZ=tetrabenazine.
Patients either received a neuroleptic at any time during the study or never received a neuroleptic during the study; patients could be counted more than once.

Safety

- The incidence of certain AEs (insomnia, depression, akathisia) appeared to be greater for the group of patients who received an antidepressant at any time during the study than for those who did not (Table 3)
- Certain AEs (somnolence, nervousness, asthenia) appeared to be more frequent for patients who had received a neuroleptic at any time during the study than for those who had not
- Surprisingly, akathisia appeared to be more frequent in those patients who had not receive a neuroleptic

Table 3. Incidence of AEs as a Function of Concomitant TBZ and Antidepressant or Neuroleptic Treatment

AE[a], n (%)	Antidepressant[b] (N=71)	No antidepressant (N=27)	Neuroleptic[b] (N=53)	No neuroleptic (N=45)
Somnolence	21 (30)	10 (37)	19 (36)	12 (27)
Insomnia	14 (20)	1 (4)	8 (15)	7 (16)
Depression	14 (20)	2 (7)	9 (17)	7 (16)
Akathisia	10 (14)	1 (4)	4 (8)	7 (16)
Nervousness	9 (13)	1 (4)	8 (15)	2 (4)
Parkinsonism	8 (11)	1 (4)	6 (11)	3 (7)
Nausea	5 (7)	2 (7)	5 (9)	2 (4)
Asthenia	6 (8)	0	6 (11)	0

AE=adverse event; TBZ=tetrabenazine.
[a]AEs were possibly or probably related to TBZ.
[b]Concomitant antidepressants or neuroleptic treatment could have occurred at anytime during the study.

Limitations

- Limitations of this *post-hoc* analysis include:
  - Unknown baseline depression status
  - Unknown reasons for neuroleptic use
  - Neither antidepressants nor neuroleptics were used concomitantly with TBZ for the entire length of the trial, thus efficacy ratings could have been made on or off concomitant medication

CONCLUSIONS

- Overall response to TBZ did not appear to be different for patients who did vs. those who did not receive concomitant antidepressant or neuroleptic treatment at any point during the study
- Incidence of AEs may be influenced by concomitant medications
  - Insomnia, depression, akathisia, nervousness, and parkinsonism appeared to have occurred more frequently in patients who received an antidepressant during the study
  - Nervousness, asthenia, and parkinsonism were more frequent in patients who received a neuroleptic
  - Interpretation of these results is complex (e.g., greater incidence of depression in those who received an antidepressant may simply reflect the reason why antidepressant treatment was initiated in these patients)

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