Comparison of Weight Gain in Treatments for Tourette's Syndrome: Tetrabenazine Versus Neuroleptics

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ABSTRACT

BACKGROUND: Tics are the most common pediatric movement disorder, and are traditionally treated with dopamine antagonists (neuroleptics). Weight gain is seen with most of these medications, and is particularly associated with greater histamine affinity. Tetrabenazine (TBZ) is a VMAT2 inhibitor that inhibits the release of dopamine, and other monoamines. It is used to treat a variety of hyperkinetic movement disorders, including tics. Weight gain with TBZ has never been systematically evaluated. **METHODS:** We compared weight gain over time (minimum 4 months) in a group of pediatric tic patients taking TBZ to an age matched group of tic patients taking neuroleptics. Patients presenting to us already on neuroleptic medications were excluded. Gross efficacy was measured on a -3 (markedly worse) to +3 (markedly improved) scale. **RESULTS:** In the TBZ group (N=36, 32 male), the age at initial therapy was 13.4 ± 3.3 and they were followed for 25.2 ± 12.3 months. The average dose of TBZ (all visits) was 54.4 ± 26.6 mg/day. In the neuroleptic group (N=41, 33 male), the age at therapy onset was 12.3 ± 4.0, and they were followed for 18.9 ± 14.8 months. The neuroleptic medications included fluphenazine (29), risperidone (10), aripiprazole (1), and haloperidol (1). Weight increase in the TBZ group was 0.8 lbs/month, compared to 1.9 lbs/month in the neuroleptic group, (p=0.006). Most patients who switch from a neuroleptic to TBZ subsequently lost weight. Although the study was not designed to compare efficacy, this tended to be greater with TBZ than neuroleptics. **CONCLUSION:** Weight gain with TBZ was half that of neuroleptics and was probably consistent with normal growth.

INTRODUCTION

Tics are the most common pediatric movement disorder. Tourette syndrome (TS) is variably defined, but the most widely accepted definition requires: multiple motor tics and at least a single phonic tic, change over time, a duration of at least one year, onset under the age of 21, and no other explanation for tics.[1] Co-morbid disorders including obsessive-compulsive disorder and attention deficit disorder are commonly found.[2]

Tics are traditionally treated with dopamine antagonists (neuroleptics). These drugs are reasonably effective but have a large number of adverse events. Weight gain is seen with most of these medications, although has been most reported with newer marketed "atypical' drugs both in general [3], and when used for tics.[4,5]. The pathogenesis of neuroleptic induced weight gain is not clear. Matsui-Sakata and colleagues calculated mean receptor occupancies of neurotransmitter receptors and found that Histamine1 (H1) and Muscarinic Acetylcholine (mACh) receptor occupancy correlated with antipsychotic-induced weight gain, while H1, mACh and Serotonergic (5-HT2c) receptors correlated with weight gain and new onset type-2 diabetes mellitus. Weight gain can be the major limiting factor when neuroleptics are used for tics.

Tetrabenazine (TBZ) is a VMAT2 specific inhibitor that reduces the release of dopamine, and other monoamines to a lesser extent. It is used to treat a variety of hyperkinetic movement disorders, including tics[6-8]; however, controlled efficacy trials for tics have not been done. The medication is available in many countries and is currently under review in the United States by the Food and Drug Administration as a treatment for Huntington's chorea. Weight gain with TBZ has never been systematically evaluated. Anecdotally we have not appreciated weight gain with TBZ and the little controlled data on TBZ has not demonstrated weight gain when used for Huntington's disease.[6,9] We here compare long term weight gain with TBZ compared to neuroleptic treatments in children with TS.

METHODS

The Baylor College of Medicine database was queried for TS. Inclusion criteria for entry were: diagnosis of idiopathic TS, age between 5 and 21 at initiation of the therapy in question, monotherapy treatment for tics with either a neuroleptic or TBZ for the queried period, follow-up with same scale weights for at least 4 months on the same drug (minimum of one visit and maximum of six visits). We excluded all patients who presented to us already taking a neuroleptics or TBZ, patients who took combination therapy with two or more agents for tics, patients with inadequate follow-up weight data or less than 4 months duration of recorded therapy.

Weight, along with demographic data (age at onset, sex, previous treatments prior to entry, was entered into a database. To partially control for other commonly used medications that could also effect weight in this population, we tabulated concurrent use of serotonin / norepinephrine re-uptake inhibitors (SNRI), associated with weight gain, and stimulant medications, associated with weight loss. These were scored as 1 if they used these throughout the entire period that weight was assessed, and 0.5 if used for part of the time that weight was assessed. Gross efficacy for tic suppression was measured on a -3 (markedly worse) to +3 (markedly improved) scale based on interpretation of chart information by an investigator not otherwise familiar with the patients. In three cases this could not be clearly determined.

All calculations were performed using Stata v.5.0. All tests were two-sided, and were considered statistically significant if $p \leq 0.05$. Weight change was calculated as mean gain (loss) per month by dividing weight change from baseline to final visit by the number of months over which the patient made clinic visits while receiving drug. Tests for differences in weight were done using unpaired Student's t-test with unequal variances; efficacy was also evaluated using the t-test, and was additionally evaluated by considering those patients whose scores (which ranged from -3 to +3) were either 2 or 3, and comparing them using Fisher's Exact method of the chi-square test.

RESULTS

We identified 77 subjects (41 neuroleptic, 36 TBZ) who met inclusion criteria. The age of tic onset was equivalent in each group (6.6 ± 2.2 years TBZ, 6.3 ± 2.4 years neuroleptic). [Table 1] In the TBZ group (N=36, 32 male), the age at initial therapy was 13.4 ± 3.3 and they were followed for 25.2 ± 12.3 months. The average dose of TBZ (all visits) was 54.4 ± 26.6 mg/day. In the neuroleptic group (N=41, 33 male), the age at therapy onset was 12.3 ± 4.0, and they were followed for 18.9 ± 14.8 months. The neuroleptic medications included fluphenazine (29), risperidone (10), aripiprazole (1), and haloperidol (1). Weight increase in the TBZ group was 0.79 ± 1.03 lbs/month, compared to 1.66 ± 1.51 lbs / month in the neuroleptic group, (p=0.006). The TBZ group had higher rates of SNRI use than the neuroleptic group (20 used the entire period and 8 part of the time vs. 11 the entire period and 13 part of the time), (p=0.019, entire period, p<0.001, all use). Stimulant use was not significantly different (TBZ: 8 entire time and 2 part of the time vs. neuroleptics: 8 entire time and 7 part of the time), NS. In patients who switched from a neuroleptic to TBZ, 10/15 lost weight at the subsequent visit despite being 6.4 ± 5.4 months older.

Although the study was not designed to compare efficacy, this tended to be greater with TBZ than neuroleptics [Table 1]. Adverse events thought to be related to TBZ included sleepiness/fatigue (9), depression (3), anxiety/akathisia (2), nausea (2), insomnia (1). Adverse events thought to be related to neuroleptics included sleepiness/fatigue (10), weight gain (5), acute dystonic reaction (1), anxiety (1), depression (1), reduced cognition (1).

RESULTS

Table 1: Demographics and Data - Tetrabenazine vs. Neuroleptics

	Tetrabenazine	Neuroleptic
Male/female	N=36 (32 male/4 female)	N=41 (33 male/8 female)
Tic onset age (year)	6.6 ± 2.2	6.3 ± 2.4
Age at this therapy (year)	12.5 ± 3.0	11.2 ± 3.6
Mean duration of follow-up (month)	34 ± 22	27 ± 23
Mean # visits	2.2	2.5
Average dose TBZ	53.2 ± 24.5 mg/day	--
Medication	TBZ (36)	Fluphenazine (29) Risperdone (10) Aripiprazole (1) Haloperidol (1)
Concurrent use of SNRI	Entire period (20)^ Partial period (8)^	Entire period (11)^ Partial period (13)^
Concurrent use of Stimulants	Entire period (8) Partial period (2)	Entire period (8) Partial period (7)
Mean Efficacy (+3 to -3)	1.62 ± .97	1.26 ± 0.99*
Efficacy (+2 or +3)	24/35** (68.6%)	17/39** (43.6%)
Weight gain per month	0.79 ± 1.03 lbs ^^ Range: -2.0 to 3.9	1.66 ± 1.51 lbs ^^ Range: -0.2 to 7.2
Comparison of # of visits with weight loss vs. visits with weight gain from previous visit	53 loss / 147 gain #	29 loss / 155 gain #

^ p=0.019-entire period; p<0.001 all use, Chi-square test, Fisher's exact method
* p=0.12, (NS) Students t-test, unequal variances
** p=0.04, Chi-square test, Fisher's exact method
^^ p=0.004, Students t-test, unequal variances
# p=0.013, Chi-square, Fisher's exact method

DISCUSSION

Chronic treatment of TS with TBZ was associated with less weight gain than therapy with neuroleptics, and was probably consistent with normal growth. This difference was significant despite a higher use of SNRI in the TBZ group, potentially causing relatively greater weight gain in that group. We do not feel this difference suggests greater depression or obsessive compulsive disorder caused by TBZ because it was powered by people already on a SNRI at the initiation of TBZ vs. the initiation of neuroleptics (20/36 vs. 11/41). Patients who switched directly from a neuroleptic to TBZ usually lost weight at their subsequent visit. TBZ also tended to be more efficacious and was well tolerated.

The majority of our neuroleptic subjects were on fluphenazine, which is not particularly associated with weight gain within the neuroleptic class. Formal data, however, is lacking. We did not obtain heights on patients so could not calculate body mass indexes. However there is no evidence to suggest that these drugs affect height differently so we doubt there is any intrinsic bias.

The efficacy and tolerability data must be interpreted with great caution. Patients were not randomly assigned to a treatment. In general, we reserve TBZ, which is not covered by insurance plans in the U.S., for more severe cases. Often they previously failed neuroleptics. Tolerability data only includes patients with adequate follow-up data, therefore excludes patients who discontinued treatment early do to any reason, including adverse events. Nevertheless, in light of the grave problems of childhood obesity, the advantageous weight profile of TBZ is a major benefit compared to traditional neuroleptic therapy. Controlled trials of TBZ for TS are beginning.

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