An Open-Label Study of the Treatment Efficacy of Olanzapine for Tourette's Disorder

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Background: An open-label trial was performed to explore efficacy and safety of olanzapine, an atypical neuroleptic with diverse receptor activity including both dopamine-2 and serotonin-2A and -2C antagonism, for treatment of Tourette's disorder.

Method: Ten adult patients aged 20 to 44 years with Tourette's disorder were treated using an open-label, flexible dosing schedule for 8 weeks. Three patients who continued olanzapine were reevaluated after 6 months. Three subjects were psychotropic medication naive, 5 patients experienced intolerable side effects with conventional neuroleptics, and 2 patients had remote (≥ 10 years) successful response to conventional neuroleptics. Tic severity was rated by the Yale Global Tic Severity Scale; weight, vital signs, and adverse effects were assessed weekly. Electrocardiogram, laboratory studies, and comorbid symptoms, assessed by the Yale-Brown Obsessive Compulsive Scale and ADHD Behavior Checklist for Adults, were measured at baseline and at week 8.

Results: Two of 10 patients prematurely discontinued olanzapine owing to excessive sedation. Of 8 patients who completed the 8-week trial, 4 (50%) demonstrated reduction of global tic severity scores by ≥ 20 points, and 6 (75%) demonstrated reductions by ≥ 10 points. No significant changes in comorbid symptoms were demonstrated. Sedation, weight gain, increased appetite, dry mouth, and transient asymptomatic hypoglycemia were the most common side effects. Tic improvements were maintained in 3 patients reassessed 6 months later. Final olanzapine dosages ranged from 2.5 mg to 20 mg daily (mean = 10.9 mg/day).

Conclusion: This open-label study suggests that olanzapine should be explored as a potential alternative to conventional neuroleptic medications for treatment of motor tics and Tourette's disorder.

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Conventional neuroleptic medications such as haloperidol, pimozide, and fluphenazine, which block dopamine-2 (D_2) receptors, have been used since the late 1960s for treatment of tic symptoms in Tourette's disorder.[1–4] Although several controlled clinical trials[5–8] have documented the efficacy of conventional neuroleptics for tic suppression, these medications are frequently accompanied by unacceptable side effects including acute dystonic reactions, parkinsonism, akathisia, school phobia, and dysphoria.[9,10] The risks of adverse reactions such as tardive dyskinesia or neuroleptic malignant syndrome associated with the conventional neuroleptics are also concerns for those patients with Tourette's disorder who require prolonged medication intervention.[11–13]

The development of atypical antipsychotic medications, which are characterized by lower rates of extrapyramidal symptoms, has been a major clinical advance for the treatment of schizophrenia. These atypical agents have a broad, multineurotransmitter spectrum of activity that may be related to their reduced rates of extrapyramidal side effects and potential benefits for treating a variety of disorders associated with dopaminergic dysfunction within diverse brain networks.[14]

We previously conducted an open-label study[15] of the efficacy and safety of the atypical neuroleptic risperidone, a benzisoxazole derivative with potent D_2 and serotonin-2 ($5\text{-}HT_2$) antagonism for treatment of Tourette's disorder which indicated that this agent may be a promising alternative to conventional tic medications and may also improve comorbid symptoms. Clinical trials using the thienobenzodiazepine analog olanzapine, an atypical antipsychotic that has high affinity for $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_6$, D_1, D_2, D_3, D_4, muscarinic M_1 through M_5, α-adrenergic, and histaminergic H_1 receptors, indicate that this agent is a safe and effective treat-

ment for schizophrenia with a low liability for tardive dyskinesia.[16–18] Bhadrinath[19] initially reported a single case of a 16-year-old girl with Tourette's disorder who experienced tic reduction following treatment with 10 mg/day of olanzapine over a 9-week period. Subsequently Stamenkovic et al.[20] reported that olanzapine was a safe and effective treatment during a 6-week open-label pilot study of 14 adults with Tourette's disorder. A second case report[21] described successful olanzapine treatment of an adolescent with Tourette's disorder. On the basis of our own clinical experience, we hypothesized that olanzapine can suppress tic symptoms, and we explored its potential efficacy and safety in an open-label 8-week pilot study in 10 adult patients with Tourette's disorder.

METHOD

Ten adult patients meeting DSM-IV diagnostic criteria for Tourette's disorder (2 women and 8 men) and ranging in age from 20 to 44 years (mean ± SD age = 28.4 ± 8.3 years) volunteered to participate in an open-label clinical trial of olanzapine. Average weight of subject was 200.9 lb (90.4 kg) at baseline (range, 138–350 lb [62.1–157.5 kg]).

Three patients had never received any medication for tics, 2 patients had been successfully treated with conventional neuroleptics in the past (≥ 10 years ago) but had no recent exposure to tic medications, and 5 patients had intolerable side effects with conventional neuroleptics either currently or in the past. Two of 10 patients had Tourette's disorder only; 4 of 10 had Tourette's disorder and met DSM-IV diagnostic criteria for comorbid attention-deficit/hyperactivity disorder (ADHD), residual; 1 of 10 had Tourette's disorder and met DSM-IV diagnostic criteria for comorbid obsessive-compulsive disorder (OCD); and 3 of 10 had Tourette's disorder and met DSM-IV diagnostic criteria for ADHD, residual, and OCD. Only 1 patient, with Tourette's disorder only, also received levothyroxine and nortriptyline for maintenance treatment of hypothyroidism and previous depression. Otherwise, no current psychotropic medication was permitted. Possible risks and benefits were explained to all patients, and informed consent was obtained.

Patients were evaluated at screening, after a 1-week washout period for the 2 patients who were receiving conventional neuroleptic medication at screening, and at weekly intervals for 8 weeks. Tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS)[22] at screening, 4 weeks, and 8 weeks. The YGTSS consists of the separate rating of severity for motor and phonic tics along 5 dimensions: (1) number, (2) frequency, (3) intensity, (4) complexity, and (5) interference. It also includes a checklist for specific types of motor and vocal tics. Although not formally measured, all patients described premonitory symptoms at baseline. An independent rating of impairment, which focuses on the impact of tics over the previous week, is added to the total tic score to obtain a final score.[22] A side effects inventory, measurements of vital signs, and weight were completed at all visits. Symptoms of ADHD and OCD were rated at screening, after washout, and at week 8 of olanzapine treatment using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[23,24] and the ADHD Behavior Checklist for Adults.[25] Complete blood profiles, comprehensive metabolic panels, urine analysis, and electrocardiograph (ECG) were performed at screening, after week 1 of olanzapine treatment, and at week 8.

Olanzapine was titrated by 2.5- to 5.0-mg increments as tolerated each week to a maximum dose of 20 mg daily given at bedtime. Five patients opted to continue taking olanzapine after completing the study; 3 of 5 were reevaluated after an additional 6 months. Two of 5 decided to discontinue olanzapine at week 12 and week 15 because of excessive weight gain.

Since this was a small pilot study, simple methods of statistical analysis were used to analyze the data. To simplify the data, only 3 timepoints over the 8-week treatment period were considered in the analysis: baseline, week 4, and week 8. Intermediate weeks were excluded. A set of paired t tests was used to compare mean total motor, total vocal, and total tic scores from baseline to 8 weeks. The nonparametric Wilcoxon signed rank test was also applied, with nearly identical results.

Mean medication dosage, changes in weight, vital signs, and changes in Y-BOCS and ADHD Behavior Checklist for Adults scores from baseline were calculated for all patients at week 8. Side effects and laboratory abnormalities were recorded if any abnormality was reported or found at any time during the 8 weeks of active treatment.

RESULTS

Two patients (20%) dropped out before completing the 8-week trial owing to intolerable sedation occurring at the lowest dose, 2.5 mg daily: 1 patient who was medication naive dropped out after 3 weeks of treatment and 1 patient who had previously been tapered off conventional neuroleptics dropped out after 5 weeks of treatment.

Eight patients completed the 8-week trial, and 5 patients opted to continue olanzapine after the 8-week trial was completed; of these, 2 of 5 discontinued olanzapine at week 12 and week 15, respectively, because of concerns about weight gain; 3 patients continued olanzapine at a stable dose and were reevaluated 6 months after study completion.

Dosage was gradually increased from a mean of 3.1 mg daily at week 1 to a mean of 9.7 mg daily at week 4. From weeks 5 to 8, mean ± SD daily dosage increased only fractionally and was 10.9 ± 6.0 mg daily at week 8, ranging from 2.5 mg to 20 mg daily.

Table 1. Primary Efficacy Variables[a]

	Week 0		Week 4		Week 8		
	Mean	SD	Mean	SD	Mean	SD	p Value[b]
YGTSS global severity score	65.5	6.5	57.9	9.1	44.9	14.5	.004
YGTSS total tic score	26.6	5.0	23.0	6.6	18.6	7.3	.004
YGTSS total motor tic score	17.0	1.7	13.8	3.2	10.9	4.9	.005
YGTSS total vocal tic score	9.6	5.5	9.3	5.5	7.8	4.3	NS

[a]Abbreviation: YGTSS = Yale Global Tic Severity Scale.
[b]Change from baseline at week 8.

The means for primary efficacy variables in this study are reported in Table 1. YGTSS total motor tic score decreased significantly from baseline to week 4, and even further by week 8. YGTSS total vocal tic score did not decrease significantly from baseline at either week 4 or week 8. YGTSS total tic score did not decrease significantly from baseline to week 4 but did decrease significantly by week 8. YGTSS global tic severity score decreased from baseline to week 4 and even more significantly by week 8. At week 8, 4 (50%) of 8 patients had a reduction of global tic severity scores by ≥ 20 points and 6 (75%) of 8 had a reduction by ≥ 10 points. At 8 weeks, 5 of 8 subjects described decreased premonitory symptoms; 3 of 8 reported no subjective change in premonitory symptoms.

Neither ADHD Behavior Checklist for Adults nor Y-BOCS scores changed significantly from baseline by week 8, and no statistically significant changes in ADHD Behavior Checklist for Adults or Y-BOCS scores occurred in the 3 subjects studied at 6-month follow-up.

During the 8 weeks of the study, patient vital signs exhibited no significant changes over time with the exception of weight. The mean ± SD weight gain of the 8 subjects at 8 weeks was 10 ± 7 lb (4.5 ± 3.2 kg), (range, 3.5–24 lb [1.6–10.8 kg]). Two of 3 subjects reassessed 6 months later had lost some or all of the initial weight they gained since starting olanzapine by increasing physical exercise and close dietary supervision; 1 subject lost 7 of 24 lb (3.2 of 10.8 kg) gained, the other subject lost 7 of 7 lb (3.2 of 3.2 kg) gained plus an additional 3 lb (1.4 kg) below baseline weight. The other subject gained an additional 4 lb (1.8 kg) over the 6-month follow-up time period.

Sedation (8/8), weight gain (8/8), increased appetite (6/8), and dry mouth (5/8) were the most commonly reported side effects. Other reported side effects in order of decreasing frequency included articulation impairment (4/8), constipation (3/8), headache (2/8), postural hypotension (2/8), dizziness (2/8), internal restlessness (2/8), transient amnesia (2/8), rhinitis (2/8), nervousness or agitation (1/8), rash (1/8), anxiety (1/8), tachycardia (1/8), and hostility (1/8).

To evaluate changes in laboratory studies with olanzapine, a patient was considered to be positive for a change if it occurred at any point during the 8-week period. Five patients had transient asymptomatic ECG changes including tachycardia, bradycardia, and premature ventricular beats. No changes in complete blood count or urine analysis occurred. Three subjects experienced transient minor elevations of liver function test results, and 7 patients experienced transient asymptomatic hypoglycemia.

No statistically significant correlation was found between the results of treatment and sex or age. There was also no statistically significant difference between the response to treatment and the dose of olanzapine or previous medication exposure. No significant statistical correlation was noted between the type or the severity of side effects and the age, initial severity of tics, or comorbid diagnoses or concomitant medication(s) of the patients.

CONCLUSION

This 8-week open-label, flexible dosing study of olanzapine suggests that it is safe and well-tolerated in adults with Tourette's disorder. Most common side effects included sedation, increased appetite, weight gain, and dry mouth. Additional reported side effects included articulation impairment, constipation, postural hypotension, headache, insomnia, nervousness or agitation, dizziness, internal restlessness, hostility, anxiety, and transient amnesia. Transient and reversible abnormalities on ECG, liver function test results, and serum glucose levels were observed.

Six-month follow-up data in 3 patients who elected to continue treatment show that improvement in tic symptoms was sustained and that weight gain associated with olanzapine was reversible with dietary restriction and exercise in some cases.

Of clinical and theoretical interest was the commonly reported experience by 5 of 8 subjects that premonitory urges were also significantly reduced with olanzapine treatment. Premonitory urges are experienced as nearly irresistible, compelling urges that are only relieved with the execution of a particular tic or set of tics. These symptoms, which are not directly assessed by the YGTSS, are hypothesized to reflect a heightened sensitivity to internal somatosensory cues and contribute to the overall morbidity associated with Tourette's disorder.[26–28] Subjective reports of decreased premonitory urges were accompanied by a subjective sense of having greater control over one's tics. If reduction of premonitory urges with olanzapine did indeed occur, it may account for the significant decrease in impairment scores observed in this pilot study. Further medication trials should formally assess premonitory urges and response of these symptoms to treatment.

The frequency of reported side effects was, while in most cases tolerable, still significant. Twenty percent of subjects (2/10) dropped out because of intolerable sedation. Concerns about excessive weight gain prompted 2 subjects who had experienced improvement in tic symp-

toms during the 8-week study to later discontinue olanzapine. Most conventional antipsychotic medications have been associated with substantial weight gain and drug-induced obesity, which are common causes of noncompliance and discontinuance of treatment. Drugs that block 5-HT_{2C}, H_1, and D_2 receptors are more likely to be associated with weight gain.[29–33] Substantial evidence now suggests that the novel antipsychotics, particularly clozapine and olanzapine, may be even more prone to cause weight gain, and this side effect can be a serious deterrent to their use. However, evidence from this small pilot study and other recent trials implies that olanzapine's weight gain effect may be reversible in some cases with dietary and other behavioral maneuvers.[34]

Although there have been some reports that olanzapine and other potent 5-HT_2 antagonists such as clozapine and risperidone can induce or worsen obsessive-compulsive symptoms,[35–38] we did not observe any statistical change, either improvement or worsening, of obsessive-compulsive symptoms with olanzapine during the 8-week study period or in the 3 patients who continued olanzapine and were reassessed 6 months later. Likewise, we found no evidence that preexisting symptoms of ADHD were either improved or worsened during the study period with olanzapine. However, this small, uncontrolled study did show a trend (not statistically significant) that patients with increasing comorbid disorders may not respond as well to olanzapine as those patients without multiple comorbidities; this observation requires replication by further studies.

Overall, the frequency of some extrapyramidal adverse events was lower than that typically encountered with conventional neuroleptics. The relatively lower D_2 blockade of olanzapine compared with risperidone or conventional neuroleptics likely accounts for the lower frequency of some extrapyramidal adverse events. Although treatment-emergent akathisia was not directly assessed, complaints of internal restlessness were reported at least once during the active medication period by 2 of 8 patients. Akathisia has been reported in 5% of patients with schizophrenia enrolled in the short-term clinical trials using olanzapine, but appears to occur at a significantly decreased rate compared with haloperidol-treated patients; fewer olanzapine-treated than haloperidol-treated patients discontinued treatment because of extrapyramidal symptoms.[17,39,40] Follow-up investigations must directly evaluate extrapyramidal symptoms, including akathisia, in patients with Tourette's disorder since such side effects pose a major obstacle for treatment.

In summary, this small, open-label trial suggests that olanzapine may be associated with tic suppression in Tourette's disorder. These results should be viewed as preliminary and must be followed up by a double-blind study comparing olanzapine with a conventional neuroleptic such as haloperidol or pimozide and/or placebo to ascertain efficacy.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), levothyroxine (Synthroid and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), pimozide (Orap), risperidone (Risperdal).

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