An Open Trial of Olanzapine in Anorexia Nervosa

Nicole C. Barbarich, B.S.; Claire W. McConaha, B.S.N.; Jill Gaskill, C.R.N.P.; Maria La Via, M.D.; Guido K. Frank, M.D.; Sarah Achenbach, B.S.; Katherine H. Plotnicov, Ph.D.; and Walter H. Kaye, M.D.

Background: Recent reports raise the possibility that olanzapine can assist weight gain and improve behavioral symptoms during refeeding in anorexia nervosa.

Method: Seventeen DSM-IV anorexia nervosa subjects hospitalized between May 1999 and October 2000 were enrolled in open-label treatment with olanzapine for up to 6 weeks. Baseline weight and symptoms were compared to patients' status at the end of treatment.

Results: Olanzapine administration was associated with a significant reduction in depression, anxiety, and core eating disorder symptoms, and a significant increase in weight. A comparison with our historical data suggests that subjects in this study had a significantly greater decrease in depression.

Conclusion: These data lend support to the possibility that olanzapine may be useful in treating anorexia nervosa. However, a controlled trial is necessary to demonstrate that olanzapine is efficacious.

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Corresponding author and reprints: Walter H. Kaye, M.D., Anorexia and Bulimia Nervosa Research Module, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, 600 Iroquois, Pittsburgh, PA 15213 (e-mail: kayewh@msx.upmc.edu).

Anorexia nervosa is a disorder of unknown etiology that predominantly occurs in women. This illness is characterized by restricted eating, the relentless pursuit of thinness, and obsessive fears of being fat. These symptoms result in profound weight loss and considerable psychological morbidity. Pharmacologic and psychological treatments for anorexia nervosa have been of limited efficacy.[1] Consequently, individuals with anorexia nervosa often have a chronic, relapsing illness[2] and the highest death rate of any psychiatric disorder.[3] Moreover, the hospital utilization rate for people with anorexia nervosa is higher than for any other psychiatric disorder, aside from schizophrenia and organic mental disorders.[4]

Uncontrolled studies[5–9] have raised the possibility that olanzapine may be helpful in increasing weight and improving mood in underweight anorexia nervosa patients. The rationale for treatment with atypical neuroleptics includes the fact that this class of medication is often associated with weight gain[10] and that these drugs may be useful in reducing severe agitation and mood lability. This open trial was designed to determine whether olanzapine was associated with positive effects on weight or behavioral symptoms.

METHOD

Olanzapine was administered in an open-label trial for 6 weeks to 17 patients with anorexia nervosa who were hospitalized in the eating disorders program at Western Psychiatric Institute and Clinic, Pittsburgh, Pa., between May 1999 and October 2000. All subjects provided written informed consent prior to the start of the study, and the study had the approval of the University of Pittsburgh's Institutional Review Board. According to DSM-IV criteria, 12 subjects had a history of restricting type anorexia nervosa, and 5 had a history of binge-eating/purging type anorexia nervosa, 1 of whom had a history of restricting and purging only. Subjects were required to stop taking other psychoactive or antidepressant medications before starting olanzapine. This included 1 subject who had taken risperidone for 5 days prior to admittance to the inpatient program (Table 1). Three subjects were treated with antidepressant medications following the start of the study (see Table 1).

Subjects enrolled in the study were started on a dose of 1.25 to 5.00 mg of olanzapine. Individual doses were titrated throughout the study to balance side effects such as sedation with beneficial effects (increased appetite, reduced negative affect or obsessionality). With the exception of 1 subject treated only with olanzapine, all subjects received concomitant treatment in the inpatient or outpatient program using both cognitive behavioral therapy and dialectical behavioral therapy. Subjects were weighed twice weekly and received a psychological evaluation at baseline and then every 2 weeks. This evaluation included the Spielberger State-Trait Anxiety Inventory (STAI),[11]

Table 1. Treatment History and Outcome of Patients With Anorexia Nervosa Treated With Open-Label Trial of Olanzapine

Subject	Diagnosis	Olanzapine Dose, mg	Weeks of Treatment				Weight, kg		Other Medication	Outcome
			Olanzapine	Inpatient	Outpatient	Other	Baseline	Exit		
1	RAN	2.50	6	6	0	0	22.7	29.5	Risperidone for 5 days pre-study	Discharged to outpatient
2	RAN	2.50	6	6	0	0	36.4	44.1		Discharged to outpatient
3	RAN	7.50	6	4.5	1.5	0	43.2	47.6		Discharged after outpatient
4	BAN	7.50	6	5	1	0	41.0	44.8	Started SSRI at week 2	Continued outpatient after study
5	RAN	3.75	6	2	4	0	46.2	53.1		Discharged from outpatient
6	RAN	2.50	5	3.5	0	1.5	30.8	39.6		Left against medical advice
7	BAN	5.00	6	3	0	2.5	40.1	50.6	Started SSRI at end of week 3	Discharged inpatient, no treatment
8	RAN	5.00	5	4	0	0.5	36.4	43.2		Left against medical advice
9	RAN	6.25	6	6	0	0	33.4	40.7		Continued inpatient and outpatient
10	RAN	6.25	6	6	0	0	35.9	43.4	Started SSRI at end of week 4	Discharged to home
11	RAN	5.00	6	4.5	1	0	39.7	48.2		Left outpatient program
12	RAN	3.75	6	3	3	0	43.0	48.5		Completed outpatient
13	BAN	3.75	4	0	0	0	50.9	51.8		No eating disorder treatment
14	RAN	5.00	4	1.5	0	1.5	44.4	51.0		Left against medical advice
15	BAN	3.75	6	1.5	4	0	44.1	53.6		Discharged from outpatient
16	RAN-P	5.00	3	3	0	0	52.6	57.7		Discharged from inpatient
17	RAN	5.00	6	2	2	2	42.3	47.7		Completed outpatient

Abbreviations: BAN = binge-eating/purging type anorexia nervosa, RAN = restricting type anorexia nervosa, RAN-P = restricting and purging type anorexia nervosa, SSRI = selective serotonin reuptake inhibitor.

Table 2. Comparison of Weight and Symptoms Before and After Treatment With Olanzapine in Patients With Anorexia Nervosa

Variable	Baseline (mean ± SD)	Endpoint (mean ± SD)	t Score	p Value
Proportion of ideal body weight, %	69 ± 10	81 ± 9	10.8	.000
Beck Depression Inventory score	23 ± 7	11 ± 6	5.3	.000
State-Trait Anxiety Inventory (state anxiety) score	58 ± 7	50 ± 13	3.0	.014
Yale-Brown Obsessive Compulsive Scale score	16 ± 15	12 ± 14	1.8	NS
Yale-Brown-Cornell Eating Disorders Scale score	22 ± 7	15 ± 9	4.4	.001

Abbreviation: NS = nonsignificant.

the Beck Depression Inventory (BDI),[12] the Yale-Brown Obsessive Compulsive Scale (YBOCS),[13] and the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS),[14] as described elsewhere.[15] An intent-to-treat analysis was used, whereby all patients who were evaluated at least once following drug initiation were included with the last assessment carried forward. Paired t tests were used to compare baseline and last assessment.

RESULTS

The mean ± SD age of subjects with anorexia nervosa was 20.5 ± 5.1 years, and the mean age at onset of illness was 16.2 ± 4.6 years. Twelve subjects completed the full 6 weeks of the study, 2 subjects completed only 5 weeks, 2 subjects completed only 4 weeks, and 1 subject completed only 3 weeks. All subjects except 1 started the study while in the inpatient unit; 7 subjects participated in some outpatient treatment during the study period (see Table 1). The mean daily dose of olanzapine administered at endpoint was 4.7 ± 1.6 mg with a range of 2.5 mg to 7.5 mg.

Subjects had a significant increase in weight and a significant decrease in score on the BDI, STAI, and YBC-EDS but no change on the YBOCS. There was no relationship between dose of olanzapine and the variables described in Table 2. There were no significant differences in outcome measures between the subjects who underwent additional treatment with an antidepressant compared to subjects treated solely with olanzapine.

When baseline and endpoint change was calculated, subjects taking olanzapine had a significantly larger decrease in BDI scores than that observed[16] in 22 unmedicated women with anorexia nervosa who were assessed when underweight and after short-term weight restoration (12 ± 7 vs. 4 ± 13, respectively; t = 2.11, p < .05). However, there were similar changes for the STAI score (8 ± 10 vs. 7 ± 11, t = 0.46, p = NS).[16] Subjects' intermittent physical complaints recorded during the medication trial included headache (N = 5), abdominal pain or bloat-

ing (N = 5), diarrhea (N = 2), ankle edema (N = 2), dizziness (N = 2), and nausea (N = 1).

DISCUSSION

This open-label study provides further support for the possibility that olanzapine may be useful for the treatment of behavioral symptoms and weight restoration in anorexia nervosa.[5–9] A comparison to subjects previously treated in our center[16] suggested that the effects of olanzapine may improve mood.

Because olanzapine interacts with dopaminergic, serotonergic, adrenergic, and muscarinic receptors,[17] the neuronal systems responsible for this drug's potential efficacy remain uncertain. Considerable animal and human studies implicate these systems in the modulation of feeding behavior, mood, and obsessionality. Several lines of evidence suggest that disturbances of serotonin and dopamine may contribute to the pathogenesis of anorexia nervosa,[18] which opens the possibility of understanding how olanzapine may be beneficial in the treatment of this illness.

The major limitation of this study is that it was an open trial with no control group. Moreover, the perceived effects of olanzapine may have been confounded by the cumulative effects of the multidisciplinary treatment program. Additionally, 4 of the study subjects either left treatment against medical advice (N = 3) or due to insurance limitations (N = 1), and 1 was discharged from the inpatient unit and had no further local treatment, but none discontinued as a result of the study medication. Thus, these findings must be considered with extreme caution. Still, it is well known that individuals with anorexia nervosa are often resistant to treatment and to taking medication. The fact that many subjects cooperated with this study and were compliant with olanzapine administration is noteworthy. Laboratory findings at follow-up showed no abnormal changes on routine blood screenings. Future studies should include mechanisms to be compliant with the Health Insurance Portability and Accountability Act (HIPAA) to allow for long-term follow-up. Currently, there are no other effective pharmacotherapies that significantly improve behavior in ill patients with anorexia nervosa, a population that represents both high morbidity/mortality and a substantial cost to health care. The findings from this study support the need for a controlled trial to determine whether or not olanzapine, or any drug of this class, is an effective clinical treatment for anorexia nervosa.

Drug names: olanzapine (Zyprexa), risperidone (Risperdal).

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