Olanzapine Treatment of Female Borderline Personality Disorder Patients: A Double-Blind, Placebo-Controlled Pilot Study

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Background: The intent of this study was to compare the efficacy and safety of olanzapine versus placebo in the treatment of women meeting criteria for borderline personality disorder (BPD).

Method: We conducted a double-blind, placebo-controlled study of olanzapine in 28 female subjects meeting Revised Diagnostic Interview for Borderlines and DSM-IV criteria for BPD. The subjects were randomly assigned to olanzapine or placebo in a 2:1 manner. Treatment duration was 6 months. Primary outcome measures were self-reported changes on anxiety, depression, paranoia, anger/hostility, and interpersonal sensitivity scales of the Symptom Checklist-90.

Results: Nineteen subjects were randomly assigned to olanzapine; 9, to placebo. When random effects regression modeling of panel data was used, controlling for baseline level of severity, olanzapine was associated with a significantly ($p < .05$) greater rate of improvement over time than placebo in all of the symptom areas studied except depression. Weight gain was modest in the olanzapine-treated group but was significantly higher than in those treated with placebo ($p < .02$). In addition, no serious movement disorders were noted.

Conclusion: Olanzapine appears to be a safe and effective agent in the treatment of women with criteria-defined BPD, significantly affecting all 4 core areas of borderline psychopathology (i.e., affect, cognition, impulsivity, and interpersonal relationships).

(J Clin Psychiatry 2001;62:849–854)

Received June 16, 2000; accepted April 18, 2001. From the Laboratory for the Study of Adult Development, McLean Hospital, Belmont, and the Department of Psychiatry, Harvard Medical School, Boston, Mass.

Supported, in part, by a grant from Eli Lilly.

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Borderline personality disorder (BPD) is a common and serious psychiatric disorder. It is estimated that 2% of the adult American population meet criteria for the disorder at some point in their lives.[1] BPD patients are also very impaired socially and vocationally and use high levels of mental health and other social service resources.[1–3]

There are 4 core areas of borderline psychopathology. These areas, which characterize and distinguish BPD patients from those with other types of personality disorders,[4] are intense dysphoric affects; disturbed cognitions, particularly dissociative experiences, nondelusional paranoia, and quasi-psychotic thought[5]; forms of impulsivity specific to BPD (i.e., physically self-damaging acts and help-seeking suicidal efforts); and interpersonal relationships marred by such problems as extreme dependence, masochism, devaluation, manipulation, demandingness, and entitlement.

Most controlled studies of standard antipsychotic agents in the treatment of BPD have shown that these agents have a broad spectrum of activity, significantly affecting several symptom areas of BPD. This result was found in 2 studies[6,7] that compared one standard neuroleptic with another. Similar results were found by Goldberg et al.[8] and Soloff et al.,[9] respectively, in placebo-controlled studies of thiothixene and haloperidol. In addition, Cowdry and Gardner,[10] who studied 16 female outpatients with severe BPD in a complex crossover design, found that trifluoperazine (if taken for more than 3 weeks) led to improvement across a range of symptoms, including physician-rated anxiety and patient-rated depression, anxiety, and sensitivity to rejection.

In a second study of the efficacy of haloperidol versus placebo, Soloff et al.[11] were unable to replicate their findings of a broad spectrum of efficacy for this agent. In a continuation study of this same sample, haloperidol was found to be significantly more effective than placebo only in reducing irritability.[12] The authors acknowledge that this finding might have been due to a type II error and speculate that the lack of efficacy found in their second study may be due to the second sample of BPD patients being less severely ill than those in the first study.

Interest in the use of antipsychotic agents in the treatment of BPD has increased with the advent of the atypical

or novel antipsychotic agents. These agents (clozapine, risperidone, olanzapine, and quetiapine) are more easily tolerated than the conventional antipsychotic agents because of diminished extrapyramidal side effects.

Our group examined the usefulness of clozapine in 15 patients with both BPD and ongoing psychotic symptoms (psychotic disorder not otherwise specified) and found decreased severity in their overall symptomatology and improvement in their psychosocial functioning.[13] These findings have been replicated by Benedetti et al.[14] in a sample of borderline patients without a comorbid psychotic condition and by Chengappa et al.[15] in a sample of borderline patients with a variety of psychotic-level diagnoses. Not surprisingly, the mean dose in our study[13] (253 mg/day) and that in the Chengappa et al. study[15] (421 mg/day) were substantially higher than in the study by Benedetti et al.[14] (44 mg/day).

However, the use of clozapine is limited in BPD patients because of the stringent requirements for weekly or biweekly blood work made necessary by the risk of agranulocytosis with this agent. As a result of this limited applicability, considerable clinical interest in the use of the other atypical antipsychotic agents in the treatment of BPD has developed. Yet, to date, there have been very limited efficacy and safety data available for these other atypical antipsychotic agents in the treatment of BPD. Schulz et al.[16] have conducted the only published study of a nonclozapine novel antipsychotic in the treatment of criteria-defined BPD patients. These investigators reported that olanzapine was safe and effective in an open-label study in 11 patients with BPD and dysthymia.

METHOD

Recruitment of women between the ages of 18 and 40 years who were disturbed by moodiness, distrustfulness, impulsivity, and painful and difficult relationships was accomplished primarily through advertisements in Boston-area newspapers. Subjects who answered the advertisement were screened by telephone to assess whether they met the DSM-IV criteria for BPD using the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders.[17] A general medical and psychiatric history was also taken at the time of first telephone contact. Potential subjects were excluded if they had been treated with olanzapine, were medically ill, had a seizure disorder, currently were being prescribed any psychotropic medication that they thought was helping to alleviate troublesome symptoms, were actively abusing alcohol or drugs, or were acutely suicidal (i.e., had a clear-cut and pressing intent to commit suicide in the near future). Subjects who were pregnant, breastfeeding, planning to become pregnant, or not using reliable forms of contraception were also excluded.

Subjects were next invited to participate in face-to-face interviews. At that time, written informed consent was obtained. Two semistructured diagnostic interviews were then administered to each subject: (1) the Structured Clinical Interview for DSM-IV Axis I Disorders[18] and (2) the Revised Diagnostic Interview for Borderlines (DIB-R).[19] Subjects were included if they met both DIB-R and DSM-IV criteria for BPD and did not meet current criteria for major depression. They were excluded if they met current or lifetime criteria for schizophrenia, schizoaffective disorder, or bipolar disorder. Subjects then underwent a physical examination and laboratory analyses, including hematologic indices, serum chemistry studies, and a pregnancy test.

Subjects also filled out a series of self-report measures. These measures were the Symptom Checklist-90 (SCL-90),[20] the Hamilton Depression Inventory (HDI),[21] and the Dissociative Experiences Scale (DES).[22] In addition, 2 observer-rated scales were administered: the Positive and Negative Syndrome Scale (PANSS)[23] and the Global Assessment of Functioning scale (GAF).[24]

Study duration was 6 months. Subjects were seen every week for the first month and then monthly for the next 5 months. All psychiatric rating scales were readministered to each subject at each subsequent visit. Subjects were weighed at every visit. In addition, the presence of extrapyramidal side effects and movement disorders was assessed at each follow-up visit using the following 3 scales: the Simpson-Angus scale,[25] the Barnes Akathisia Scale,[26] and the Abnormal Involuntary Movement Scale.[27] Patients were also asked at every postbaseline visit about other side effects using a structured questionnaire.

At the beginning of the study, subjects received one half tablet per day of study medication. Each tablet contained either 2.5 mg of olanzapine or matching inert placebo. Tablets were supplied in numbered bottles containing drug or placebo as determined by a random number sequence. This sequence was arranged so that twice as many subjects would be treated with active drug as with placebo. Dose was adjusted according to perceived response and side effects. Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken after the acquisition of all endpoint data for all subjects.

Data Analysis

Data were analyzed using SPSS and STATA software. Between-group baseline demographic data, clinical history variables, and baseline values for our 5 primary outcomes were analyzed using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Random effects regression analyses were used to assess between-group differences in outcome measures using all available panel data. Baseline value, treatment status, time, and interaction between treatment

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Table 1. Demographic Characteristics and Treatment Histories of Olanzapine and Placebo Groups

Characteristic	Olanzapine Group (N = 19)	Placebo Group (N = 9)	Wilcoxon Rank Sum	p Value
Age, y, mean (SD)	27.6 (7.7)	25.8 (4.5)	–0.123	.902
Education, y, mean (SD)	14.6 (1.3)	14.6 (1.7)	–0.076	.940
Socioeconomic class, mean (SD)[a]	4.2 (0.9)	4.3 (0.9)	0.400	.690
White, %	79.0	55.6	...	.371
Ever received individual psychotherapy, %	84.2	77.8	...	1.0
Ever been treated with other psychotropic medication, %	63.2	66.7	...	1.0
Ever hospitalized for psychiatric reasons, %	15.8	11.1	...	1.0

[a]As determined using the 5-point Hollingshead-Redlich scale (1 = highest socioeconomic class, 5 = lowest socioeconomic class).

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status and time were the independent variables in these modeling analyses.

In these models, the random effects were subjects, and the fixed effects were the baseline value for each symptom area, treatment status, time, and the interaction between treatment status and time. The residual or error is assumed to have zero mean, to be homoskedastic, to have no autocorrelation, and to be uncorrelated with both the explanatory factors and the subject random effect. The interaction term is the most important outcome in these models, representing the difference in rates of change between the olanzapine and placebo groups.

The primary outcome measures were changes on the SCL-90 scales measuring symptom areas that are particularly relevant to BPD (anxiety, depression, paranoia, anger/hostility, and interpersonal sensitivity). Secondary outcome measures were the summary scores of the HDI, DES, PANSS, and GAF. (Due to the small number of subjects, results pertaining to secondary outcome measures will not be reported. However, these results are available from the authors on request.)

RESULTS

Thirty subjects completed all aspects of prerandomization assessment. However, 2 of these subjects were excluded from further study because it was determined that they were responding well to a selective serotonin reuptake inhibitor. Twenty-eight subjects entered the trial and were randomly assigned to olanzapine (N = 19) or placebo (N = 9). All 28 subjects completed at least 2 postbaseline visits and were included in all subsequent analyses.

Table 1 describes the demographic characteristics and treatment histories of these 2 groups of subjects. As can be seen, no significant olanzapine versus placebo differences were found. Both groups of subjects were, on average, in their mid-20s, had about 2 years of college, and came from a lower-middle-class background as measured by the 5-point Hollingshead-Redlich scale (1 = highest, 5 = lowest).[28] The majority of both groups were white, although about 20% of the olanzapine-treated group (4/19) and about 40% of the placebo-treated group (4/9) were women of color. In terms of past treatment, about 80% (23/28) had been in psychotherapy, over 60% (18/28) had been treated with other psychotropic medications, and less than 20% (4/28) had ever been hospitalized for psychiatric reasons. It should also be noted that only 1 subject in the olanzapine-treated group and none in the placebo-treated group met DSM-IV criteria for schizotypal personality disorder.

Table 2. Baseline Values of Primary Outcome Measures for Olanzapine- and Placebo-Treated Groups[a]

	Olanzapine Group (N = 19)		Placebo Group (N = 9)		Wilcoxon Rank Sum	
SCL-90 Scale	Mean	SD	Mean	SD	z	p
Interpersonal sensitivity	2.57	0.64	2.24	0.75	–1.307	.191
Anxiety	2.26	0.82	1.76	0.41	–1.531	.126
Depression	2.58	1.03	2.42	0.37	–0.640	.522
Anger/hostility	2.16	0.71	1.89	0.85	–1.012	.311
Paranoia	2.39	0.78	1.93	0.92	–1.233	.218

[a]Abbreviation: SCL-90 = Symptom Checklist-90.

Table 2 shows the mean ± SD baseline values for both groups on the primary outcome measures. As can be seen, moderate symptom levels were reported by those in both study groups at the time of their entry into the study. As can also be seen, no significant between-group differences in baseline values were found.

Attrition was quite low throughout the first 5 months of the study for both groups of subjects. More specifically, 89.5% (17/19) and 88.9% (8/9) of the olanzapine-treated and placebo-treated subjects remained in the study through week 4, 63.2% (12/19) and 66.7% (6/9) remained for the first 12 weeks, and 42.1% (8/19) and 44.4% (4/9) remained through week 20. However, a substantially but not significantly higher percentage of olanzapine-treated subjects than placebo-treated subjects (42.1% [N = 8] vs. 11.1% [N = 1]) remained in the study all 24 weeks (Fisher exact test = 0.195). Reasons for discontinuation in the olanzapine group were the following: sedation (N = 1), increased anxiety or depression (N = 3), perceived weight gain (N = 2), and lost to follow-up (N = 5). Reasons for discontinuation in the placebo group were increased depression (N = 2) and lost to follow-up (N = 6).

Table 3. Effect of Olanzapine Treatment on Outcome Measures for 28 Subjects With Borderline Personality Disorder Treated With Olanzapine (N = 19) or Placebo (N = 9)[a]

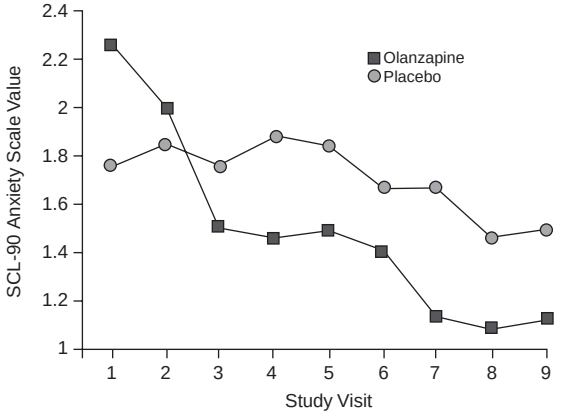
SCL-90 Scale	Coefficient	SE	z	p
Interpersonal sensitivity				
Baseline value	0.3916	0.1441	2.717	.007
Treatment status	0.5431	0.2027	2.680	.007
Time	0.0230	0.0055	4.213	.000
Treatment-by-time interaction[b]	0.2843	0.1182	2.405	.016
Anxiety				
Baseline value	0.4807	0.1081	4.445	.000
Treatment status	0.4661	0.1644	2.834	.005
Time	0.0202	0.0056	3.618	.000
Treatment-by-time interaction[b]	0.3837	0.1212	3.165	.002
Depression				
Baseline value	0.5303	0.1127	4.704	.000
Treatment status	0.2994	0.2075	1.443	.149
Time	0.0169	0.0057	2.981	.003
Treatment-by-time interaction[b]	0.1130	0.1226	0.922	.357
Anger/hostility				
Baseline value	0.4899	0.1216	4.030	.000
Treatment status	0.4053	0.1932	2.098	.036
Time	0.0126	0.0057	2.197	.028
Treatment-by-time interaction[b]	0.2358	0.1095	2.152	.031
Paranoia				
Baseline value	0.4980	0.1232	4.042	.000
Treatment status	0.4445	0.1878	2.367	.018
Time	0.0131	0.0056	2.519	.012
Treatment-by-time interaction[b]	0.3683	0.1225	3.006	.003

[a]Abbreviation: SCL-90 = Symptom Checklist-90.
[b]The treatment-by-time interaction represents the difference in rates of change between the olanzapine and placebo groups, estimated by random effects regression modeling, with control for baseline levels.

Table 3 summarizes olanzapine versus placebo rates of change over the course of the entire study for primary outcome measures. As can be seen, the olanzapine group experienced a significantly greater rate of change than placebo on all of the SCL-90 scales studied except depression. Figure 1, which is typical of the pattern that was found for the study's primary outcome measures, shows the change over time on the SCL-90 anxiety scale for the olanzapine and placebo groups. Olanzapine was associated with a rapid decline in self-reported anxiety in the first 4 weeks and a more gradual decline over the remaining 5 months of the study. In contrast, the placebo group, while showing a small placebo effect, experienced substantially less improvement on the SCL-90 anxiety measure. The olanzapine versus placebo slopes of Figure 1 differ significantly, as shown by the data in Table 3 (z = 3.165, p = .002).

As was expected, side effects were few. Minor sedation was reported by slightly but not significantly more of those in the olanzapine-treated group than the placebo-treated group (42.1% [8/19] vs. 33.3% [3/9]) (Fisher exact test = 0.704). There was also a trend for constipation to be more commonly reported by the olanzapine-treated subjects than the placebo-treated subjects (31.6% [6/19] vs. 0.0% [0/9]) (Fisher exact test = 0.072).

Figure 1. SCL-90 Anxiety Scores[a]



[a]Abbreviation: SCL-90 = Symptom Checklist-90.

Subjective reports of weight gain were significantly more common among the olanzapine-treated subjects than the placebo-treated subjects (47.4% [9/19] vs. 0.0% [0/9], Fisher exact test = 0.026). However, the average weight gain of the olanzapine-treated subjects was actually quite small (2.87 ± 5.69 lb [1.29 ± 2.56 kg]; range, –14 to +12 lb [–6.3 to +5.4 kg]). Their mean percentage weight change was also quite small (2.09 ± 3.76 lb [0.94 ± 1.69 kg]; range, –8.38 to +8.41 lb [–3.77 to 3.78 kg]). In contrast, the placebo-treated subjects lost an average of 0.78 ± 2.59 lb (0.35 ± 1.17 kg) (range, –7 to +2 lb [–3.2 to +0.9 kg]). Their mean percentage of weight change was also in the negative direction (–0.64 ± 2.11 lb [0.29 ± 0.95 kg]; range, –5.69 to +1.63 lb [2.56 ± 0.73 kg]). In terms of between-group comparisons, olanzapine-treated subjects had both a significantly larger weight gain (z = –2.509, p = .0121) and a significantly larger percentage of weight gain (z = –2.496, p = .0126) than subjects treated with placebo.

Importantly, no tardive dyskinesia or other serious movement disorders were observed. However, 1 olanzapine-treated subject developed mild rigidity, which was successfully treated with benztropine (0.5 mg/day). No other extrapyramidal side effects were noted among either placebo or olanzapine subjects. In addition, no subjects in either treatment group engaged in self-mutilative or suicidal acts during the study. Counts of other adverse effects did not differ significantly between the olanzapine and placebo subgroups (data not shown).

The mean daily dose at endpoint evaluation for olanzapine-treated subjects was 5.33 ± 3.43 mg. The mean number of tablets per day at endpoint evaluation for the olanzapine-treated and the placebo-treated subjects was 1.1 ± 0.68 and 1.2 ± 0.75, respectively.

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DISCUSSION

Olanzapine treatment, even after controlling for baseline level of severity, resulted in a significantly greater rate of change than placebo in all 4 core sectors of borderline psychopathology. More specifically, olanzapine showed greater efficacy than placebo in the affective area of anxiety but not depression, the cognitive area of paranoia, the impulsive area represented by the SCL-90 anger scale (which assesses angry acts more than angry affects), and the area of troubled relationships represented by the SCL-90 interpersonal sensitivity scale. The results of this trial are consistent with the findings of earlier studies that found that standard antipsychotic agents[6–10] as well as the atypical antipsychotic agent clozapine[13–15] led to improvement across a range of symptoms among borderline subjects. These results are also consistent with those that Schulz et al.[16] found in their open-label study on the efficacy of olanzapine in the treatment of BPD. However, the results of the current study extend these findings in that olanzapine was tested against placebo and over an extended period of time.

It should be noted that Schulz et al.[16] found that SCL-90 depression scores decreased significantly. As Table 3 shows, our subjects' depression scores also declined significantly, but the rate of change was similar for those BPD patients treated with olanzapine and those treated with placebo. While other studies have shown that olanzapine has mood-elevating properties in other patient groups,[29] our results may have been limited by the fact that our BPD subjects were not suffering from a concurrent mood disorder and thus had relatively little room for improvement.

Anecdotal evidence from subjects (who we later learned were treated with olanzapine) suggests that the medication calmed their affective symptoms (particularly anxiety and panic) and that this, in turn, led to less distrust of others, fewer angry outbursts, and ultimately more stable and satisfying relationships. These subjects also reported that this sequence of symptom reduction was self-reinforcing, growing easier to maintain over the course of their participation in the study.

In terms of dose and weight gain, we used a lower mean dose of olanzapine than Schulz and associates (5.33 ± 3.43 mg vs. 7.73 ± 2.61 mg). Our subjects also gained less weight than those in the Schulz et al. study. Our patients gained an average of 2.87 ± 5.69 lb (1.29 ± 2.56 kg), while those of Schulz et al. gained a mean of 8.89 ± 5.98 lb (4.00 ± 2.69 kg). This finding is particularly important when working with young women with BPD, since substantial medication-induced weight gain often leads to noncompliance and premature termination of a medication trial.

However, this finding on weight gain runs counter to the common finding that olanzapine treatment is associated with significant weight gain.[30] There may be several reasons for this difference. First, our subjects were leading active social and vocational lives. Many also exercised regularly and paid careful attention to their nutrition. This contrasts with the probably more sedentary lifestyles of the more chronic patients described in most earlier studies of olanzapine treatment. Second, we used a very low dose of olanzapine, while trials of other diagnostic groups have tended to use substantially higher doses. Third, our subjects were at normal weight at baseline and thus were particularly motivated to minimize their weight gain. The more chronic patients described in earlier studies may have already become habituated to gaining weight as a result of taking psychotropic medications and been more willing to tolerate this side effect due to the more disabling nature of their symptoms.

Taken together, the results of this double-blind, placebo-controlled trial suggest that low-dose olanzapine is effective in the treatment of the symptoms of BPD. These results concerning low-dose olanzapine are consistent with Benedetti and colleagues'[14] finding that low-dose clozapine is effective in the treatment of borderline subjects without a comorbid psychotic disorder.

Limitations and Directions for Further Research

This study has several methodological limitations. First, the sample size was small. Second, the sample consisted only of women with BPD. Whether these results would also apply to men meeting criteria for BPD is unknown. Third, the sample was composed of moderately ill outpatients who were not suffering from a concurrent major depressive episode, abusing substances, or taking concurrent medications. It is unknown if similar results would be obtained in a more severely impaired sample of BPD patients, particularly those who are inpatients at the time that their participation in a controlled trial of olanzapine begins. Fourth, our retention rates throughout much of the study were both good and comparable to those of earlier, much shorter studies of the pharmacotherapy of BPD.[9,11,12] However, only 1 subject in the placebo-treated group and 8 subjects in the olanzapine-treated group actually completed the entire 6-month trial. This result speaks to the difficulty in keeping BPD patients on medication for sustained periods of time. The differential dropout rates between the 2 study groups also suggest that subjects may have had strong suspicions as to what study group they had randomly been assigned. However, there is no evidence that they knew what compound they were taking, and thus, the blind was maintained throughout the study. Nonetheless, these differential dropout rates may have affected our results in some way that is difficult to determine. It is of note that Cornelius et al.[12] found a significantly greater dropout rate in their haloperidol group than in their placebo group in a 4-month continuation study. This contrasting finding underscores the greater

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tolerability of olanzapine compared with that of older, standard neuroleptics.

Additional research is needed to see if these results will be replicated. Studies that contain male BPD patients and BPD patients with more severe morbidity and/or co-occurring psychiatric disorders are also needed.

CONCLUSIONS

Olanzapine appears to be a safe and effective agent in the treatment of women with criteria-defined BPD, significantly affecting all 4 core areas of BPD psychopathology (i.e., affect, cognition, impulsivity, and interpersonal relationships).

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others).

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