Olanzapine Versus Placebo in the Treatment of Borderline Personality Disorder

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Background: Atypical antipsychotics are increasingly used in clinical practice in the management of borderline personality disorder (BPD), and a small but growing body of literature supports their efficacy. Here, we report the results of a double-blind, placebo-controlled study of olanzapine as a treatment for BPD.

Method: Forty BPD patients (25 female, 15 male) were randomly assigned in equal numbers to olanzapine and placebo. Diagnoses were made using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders and the Mini-International Neuropsychiatric Interview. Patients with schizophrenia, bipolar disorder, or current major depression were excluded. Olanzapine dosage was flexible, and the dose range was 2.5 to 20 mg/day, with most patients receiving 5 to 10 mg/day. No concomitant psychotropic medications were allowed. Patients were assessed at baseline and at 2, 4, 8, and 12 weeks. The primary outcome was change in the total score for the 9 BPD criteria on a 1-to-7 Likert scale, the Clinical Global Impressions scale modified for borderline personality disorder (CGI-BPD), using an analysis of covariance model including baseline score as covariate. Data were collected from July 2000 to April 2002.

Results: Olanzapine was found to be significantly ($p < .05$) superior to placebo on the CGI-BPD at endpoint, with separation occurring as early as 4 weeks. Similar results were found for the single-item Clinical Global Impressions scale. Weight gain was significantly ($p = .027$) greater in the olanzapine group.

Conclusions: This study supports the efficacy of olanzapine for symptoms of BPD in a mixed sample of women and men. Further studies with olanzapine and other atypical antipsychotics are needed.

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Borderline personality disorder (BPD) is common in general psychiatric practice and is one of the most challenging disorders to treat.[1] There is no U.S. Food and Drug Administration–approved pharmacologic treatment for BPD. However, clinical experience and limited data from controlled studies support the efficacy of typical and, more recently, atypical antipsychotics for signs and symptoms of BPD.[2]

Earlier studies showed mixed results of treatment of BPD with typical antipsychotics. Serban and Siegel[3] compared haloperidol and thiothixene (no placebo group) in 52 BPD patients. Overall, 84% of patients were moderately or markedly improved at 12-week follow-up, with greater improvement in the thiothixene group. Soloff et al.[4] initially reported that haloperidol was superior to placebo and to amitriptyline across a wide range of BPD symptoms. However, a later study[5] found that haloperidol-treated patients did no better than those receiving placebo. In the seminal Cowdry and Gardner[6] crossover study, patients completing 3 or more weeks of treatment with trifluoperazine (7/10 subjects) showed a trend for global improvement. The frequent severe side effects and high dropout rates found in these studies limit the value of typical antipsychotics in this population.

The newer atypical antipsychotics have shown considerable promise in the treatment of BPD. Three open-label studies found significant improvement in BPD patients treated with clozapine.[7–9] However, the risk of agranulocytosis and the need for frequent blood monitoring weigh strongly against the clinical use of clozapine for BPD. In another open-label study, Schulz et al.[10] reported significant improvement in patients with BPD and comorbid dysthymia treated with open-label olanzapine. In a double-blind, placebo-controlled study, Schulz et al.[11] reported no significant difference between risperidone and placebo for BPD. In a recently reported double-blind, placebo-controlled trial with 28 female BPD patients, olanzapine-treated patients showed significantly greater improvement than those treated with placebo across a broad range of BPD symptomatology, including interpersonal sensitivity, anxiety, anger, hostility, and paranoia, but not depression.[12] This study used scores on the self-report Symptom Checklist-90 (SCL-90) as the primary outcome measure, but also employed secondary measures including the Dissociative Experiences Scale, the Positive and Negative Syndrome Scale, the Global Assess-

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ment of Functioning (GAF), and the Hamilton Depression Inventory. Although this study lasted 24 weeks, only about a third of the patients completed the entire 24 weeks.

Clearly, there is a need for further studies of atypical antipsychotics for BPD. Limitations of the extant studies include small samples, underrepresentation of men, variable comorbid diagnoses, and use of outcome measures that may not measure change in the defining criteria of BPD. Here, we report the results of a 12-week double-blind trial of olanzapine versus placebo in 40 women and men with BPD.

METHOD

Patients

Forty patients with BPD were enrolled in the study, recruited from the community and from outpatient clinics at a university psychiatric hospital. Data were collected from July 2000 to April 2002. The study protocol was approved by the institutional review board, and after a complete description of the study, patients provided signed informed consent before completing any study-related procedure. Patients were medically stable women and men between the ages of 18 and 60 years. The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) was used to establish the diagnosis of BPD.[13] Prior to participation in the study, patients were required to be free of mood stabilizers, antipsychotics, benzodiazepines, and antidepressants for at least 2 weeks. Females of childbearing potential were required to employ effective contraception.

The Mini-International Neuropsychiatric Interview, Clinician Rated (version 4.4) (MINI) for Axis I diagnoses was used to screen for other psychiatric disorders.[14] The MINI is a relatively brief (approximately 15-minute) structured diagnostic interview. Extensive reliability and validity studies have shown it to have excellent interrater reliability, very good test-retest reliability, and good to very good concordance with the Structured Clinical Interview for DSM-III-R and the Composite International Diagnostic Interview, with a tendency to be somewhat more inclusive than these longer instruments.[14] Patients were excluded if they met criteria for schizophrenia, schizoaffective disorder, bipolar affective disorder, current major depressive episode, psychotic disorder due to a substance or a general medical condition, or substance dependence that was not in full or partial remission. Patients were excluded if they were actively suicidal, defined as any clinically significant suicide attempts in the past 6 months or any current suicidal intent or definite plan, not including self-injurious behavior with minimal potential for serious harm (e.g., superficial cutting or burning). Further exclusion criteria included pregnancy and significant neurologic impairment.

Intervention

Patients were randomly assigned in equal numbers to 12 weeks of double-blind treatment with olanzapine (dose range, 2.5–20 mg) or placebo. Olanzapine treatment was started at 2.5 mg/day. The dose was increased by 2.5- to 5-mg increments/week up to 10 mg/day, based on clinical efficacy. After 8 weeks of therapy, if additional dose increases were necessary, the dose could be increased further by 2.5- to 5-mg increments/week to a maximum dose of 20 mg/day. The dose could be decreased in 2.5- to 5-mg increments/week if intolerable side effects arose at any point in the study. No other medications were given as part of the study, and no other psychotropic medications could be taken during the study or in the 2 weeks prior to the study. Patients could continue to take medication for stable, chronic medical conditions such as hypertension. Patients were allowed to continue ongoing psychotherapy (if initiated more than 3 months prior to randomization) but could not begin new psychotherapy while in the study.

Measures

Assessments were performed prior to the initiation of treatment with olanzapine (0 weeks) and after 2, 4, 8, and 12 weeks of treatment with study medication. Baseline safety measures included medical history, physical examination, electrocardiogram, and laboratory tests including pregnancy test, Chem-7, liver function tests, complete blood count, prolactin, and hemoglobin A_{1c}. The primary outcome measure was the total score for the 9 DSM-IV BPD criteria, each scored on a 1-to-7 Likert scale analogous to the Clinical Global Impressions scale (CGI)[15] and hence called the Clinical Global Impressions scale modified for borderline personality disorder (CGI-BPD) (available from the authors on request). The standard CGI was included as a secondary global outcome measure. Measures of impulsive aggression were the Overt Aggression Scale-Modified (OAS-M) and the Anger, Irritability, and Assault Questionnaire (AIAQ).[16] The Hamilton Rating Scale for Depression (HAM-D)[17] and the Hamilton Rating Scale for Anxiety (HAM-A)[18] were used as measures of depression and anxiety, respectively. The SCL-90[19] was used as a secondary self-report measure covering multiple domains of psychopathology. The alcohol and drug portions of the Addiction Severity Index (ASI)[20] were completed monthly as a measure of alcohol and drug use. Movement disorders were assessed using the Abnormal Involuntary Movement Scale (AIMS),[21] Barnes Akathisia Scale,[22] and Simpson-Angus Scale.[23] Weight was recorded at each visit.

Statistical Analysis

Data were analyzed in SPSS (SPSS, Inc., Chicago, Ill.) and SAS (SAS Institute Inc., Cary, N.C.). Baseline demographic characteristics and baseline values of outcome measures were compared using t tests, Mann-Whitney U

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Figure 1. Borderline Personality Disorder Patients Remaining in Study at Each Timepoint

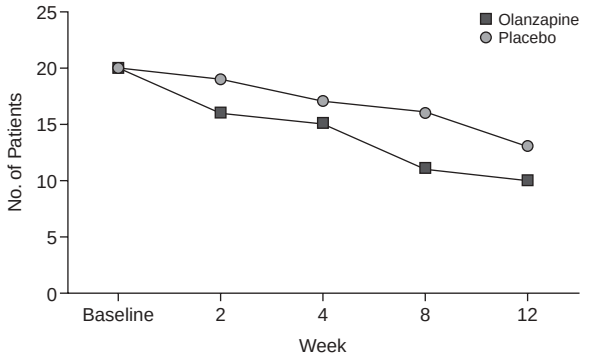
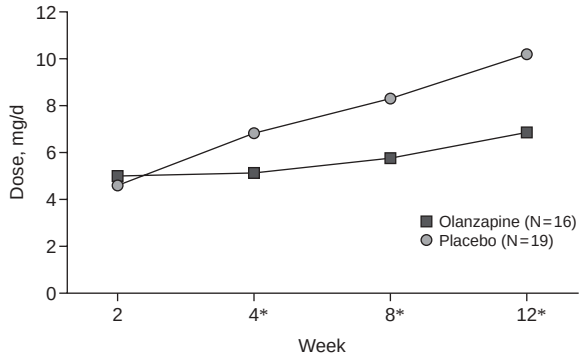


Figure 2. Medication Dosage in Borderline Personality Disorder Patients (N = 35, LOCF)



*p < .05.
Abbreviation: LOCF = last observation carried forward.

tests, or chi-square tests as appropriate. The a priori primary analysis was an analysis of covariance (ANCOVA) comparing endpoint CGI-BPD scores in the 2 groups with the baseline score as a covariate, using the last observation carried forward (LOCF) for all evaluable patients, with alpha set at .05. Additional ANCOVAs were run for each timepoint. Analogous secondary ANCOVA analyses were performed for the CGI, AIAQ, SCL-90 (global and subscale scores), GAF,[24] Barnes Akathisia Scale, and weight. Because of highly nonnormal distributions, the OAS-M, ASI, AIMS, and Simpson-Angus Scale scores were analyzed by comparing change from baseline using Mann-Whitney U tests (exact significance) at each timepoint. All tests were 2-tailed. Taking attrition into account, the study had power of approximately .82 to detect a large effect size of d = 1.0.

RESULTS

Twenty-five women and 15 men were enrolled in the study. The mean ± SD age was 32.6 ± 10.3 years (range, 18–54 years). Twenty-three patients (57.5%) were white (non-Hispanic), 10 (25.0%) were Hispanic, 3 (7.5%) were Asian/Pacific Islander, and 4 (10.0%) were other/unknown. Patients met criteria for a mean of 2.9 SCID-II personality disorders (including BPD) and a mean of 2.2 Axis I diagnoses from the MINI. Twenty-three patients (57.5%) had at least 1 suicide attempt, and 9 patients (22.5%) had a history of psychiatric hospitalization. Twenty-five patients (62.5%) had a history of nonsuicidal self-injurious behavior. Eighteen patients (45.0%) had a history of antidepressant treatment, but only 3 (7.5%) had been treated with an antipsychotic. Five patients (12.5%) were in counseling or therapy during the study (beginning at least 3 months prior to enrollment in the study), and 20 (50.0%) had some history of psychotherapy. Patients receiving active medication and those receiving placebo did not differ significantly on any of these measures.

Patients were moderately ill (mean baseline CGI score = 4.3 for both groups), with relatively mild or no substance use problems. There were no significant differences between olanzapine and placebo groups on baseline values of any of the outcome measures. Thirty-five patients completed at least 2 weeks of treatment and at least 1 postbaseline assessment and hence were included in the endpoint analysis. Twenty-three patients completed the full 12 weeks of the trial. There were no hospitalizations, suicide attempts, or other serious adverse events in either group. Dropouts by timepoint are summarized in Figure 1. Reasons for early termination were as follows: lost to follow-up, 2 (10%) in the olanzapine group and 5 (25%) in the placebo group; lack of efficacy, 2 (10%) in each group; weight gain, 2 (10%) in the olanzapine group; sedation, 2 (10%) in the olanzapine group; and patient violation of protocol, 2 (10%) in the olanzapine group.

Figure 2 shows mean dose of medication for each timepoint. Mean ± SD dose at endpoint was 6.9 ± 3.2 mg for patients receiving olanzapine versus a pseudo-dose of 10.2 ± 5.3 mg for patients receiving placebo (p = .029).

Psychometric Performance of the CGI-BPD

Details of the psychometric properties of the CGI-BPD will be reported elsewhere. Cronbach's alpha for the CGI-BPD ranged from .66 to .83 at the various timepoints. The scale was significantly correlated with the single-item CGI at all timepoints (r ranging from .353 to .909). It was significantly correlated with OAS-M, AIAQ, and SCL-90 total scores at randomization and at endpoint.

Efficacy

The ANCOVA model showed a significant effect of treatment condition (olanzapine vs. placebo) on endpoint CGI-BPD score (endpoint treatment effect F = 5.16, df = 1,32; p = .030). The effect size for the primary end-

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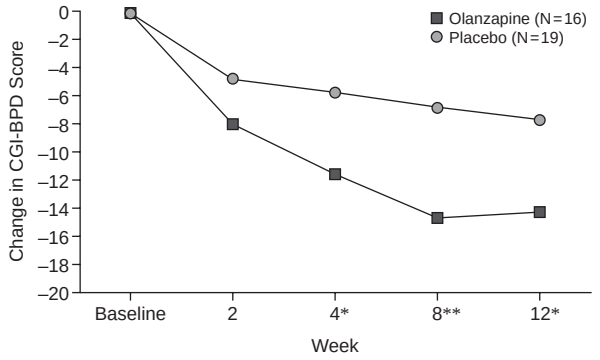
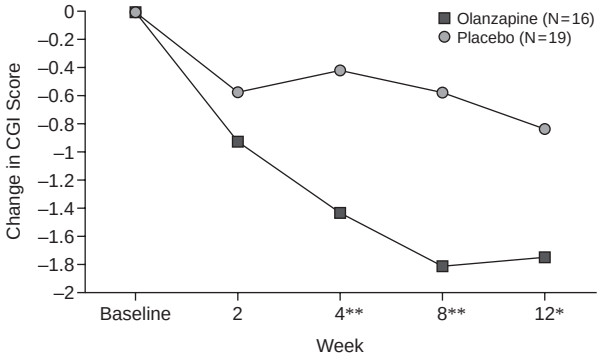
Figure 3. Change in Borderline Personality Disorder Symptomatology (CGI-BPD) (LOCF, N = 35)



*p < .05.
**p < .005.
Abbreviations: CGI-BPD = Clinical Global Impressions scale modified for borderline personality disorder, LOCF = last observation carried forward.

Figure 4. Change in Single-Item CGI Score in Borderline Personality Disorder Patients (N = 35, LOCF)



*p < .05.
**p < .005.
Abbreviations: CGI = Clinical Global Impressions scale, LOCF = last observation carried forward.

point analysis (including baseline score as a covariate) was d = 0.77. When gender was added to the model for the primary outcome (endpoint CGI-BPD score), there was no significant effect of gender or the interaction of gender and treatment condition on outcome.

Secondary analyses showed that the significant treatment effect started at 4 weeks. Figure 3 shows the mean change for each timepoint. Figure 4 shows that similar results were found for the global CGI (endpoint treatment effect F = 5.23, df = 1,32; p = .029). GAF scores were not significantly different at endpoint, but were significantly more improved in the olanzapine-treated group at weeks 4 (p = .048) and 8 (p = .036). AIAQ scores were not significantly different at endpoint, but were lower for olanzapine at week 8 (p = .036), with a trend at week 4 (p = .074). OAS-M scores did not differ significantly at any timepoint. Scores on the HAM-A and HAM-D were not significantly different at endpoint. At week 8, patients taking olanzapine improved significantly more on the HAM-D (p = .047), and there was a trend favoring olanzapine on the HAM-A (p = .062). There were no significant differences between groups on the SCL-90 total score or any of the SCL-90 subscales at any timepoint in the LOCF analysis. ASI alcohol and drug composite scores did not differ significantly at any timepoint.

Item-level changes in CGI-BPD scores (Table 1) were explored in the interest of learning whether particular signs of BPD might be more or less responsive to olanzapine. Because several of these variables had nonnormalizable distributions, means for the olanzapine- versus placebo-treated groups were compared using the Mann-Whitney U test. All but 1 of the items (item 5, suicidal ideation, which was very low in the group as a whole, with mean scores of 1.45 at baseline and 1.14 at endpoint) differed in the expected direction. Only 1 of the item-level comparisons was significant at the p = .05 level (item 8, inappropriate anger), not correcting for multiple comparisons.

Table 1. CGI-BPD Item-Level Outcomes (endpoint change) in Patients Receiving Olanzapine (N = 16) or Placebo (N = 19)

Item	Treatment	Mean Change	SD	Mean Rank	p Value
1. Frantic efforts to avoid abandonment	Olanzapine	–0.8125	1.16726	17.84	.93
	Placebo	–0.8421	1.83373	18.13	
2. Unstable interpersonal relationships	Olanzapine	–2.1250	1.74642	16.34	.37
	Placebo	–1.5263	2.14394	19.39	
3. Identity disturbance	Olanzapine	–1.3750	1.78419	16.84	.52
	Placebo	–1.1053	1.66315	18.97	
4. Impulsivity	Olanzapine	–1.5000	1.50555	17.19	.66
	Placebo	–0.9474	2.22295	18.68	
5. Recurrent suicidal ideation	Olanzapine	–0.1250	0.34157	19.50	.29
	Placebo	–0.5263	1.17229	16.74	
6. Affective instability	Olanzapine	–1.8750	2.06155	15.72	.21
	Placebo	–1.0526	1.89952	19.92	
7. Chronic feelings of emptiness	Olanzapine	–1.6875	2.12034	17.25	.67
	Placebo	–1.4211	1.60955	18.63	
8. Inappropriate anger	Olanzapine	–2.1875	1.68201	14.31	.047
	Placebo	–1.1053	1.55973	21.11	
9. Transient paranoia or dissociation	Olanzapine	–0.8125	1.10868	17.69	.86
	Placebo	–0.7368	1.88096	18.26	

Abbreviation: CGI-BPD = Clinical Global Impressions scale modified for borderline personality disorder.

Safety

Weight increase was greater in the olanzapine-treated patients relative to placebo, as shown in Figure 5. Endpoint weight gain was 8.25 ± 7.56 lb (3.71 ± 3.40 kg) for olanzapine-treated patients versus 0.17 ± 10.66 lb (0.08 ± 4.80 kg) for placebo-treated patients (F = 5.40, df = 1,32; p = .027). The difference in weight gain was significant at all timepoints. Treatment assignment did not have a significant effect on AIMS, Barnes Akathisia

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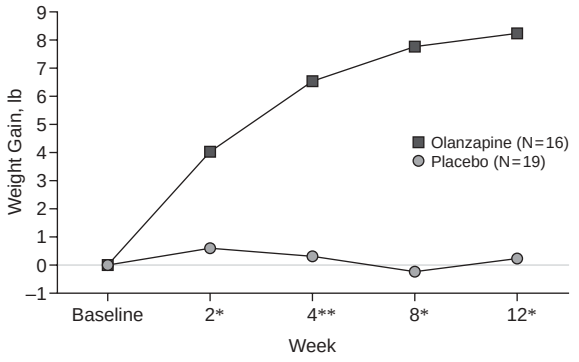
Figure 5. Weight Gain in Borderline Personality Disorder Patients (N = 35, LOCF)



*p < .05.
**p < .005.
Abbreviation: LOCF = last observation carried forward.

Scale, or Simpson-Angus Scale scores at any timepoint. There were no serious adverse events and no clinically significant unexpected study-related adverse events in the course of the study. Four patients taking olanzapine quit the study early due to side effects, 2 due to weight gain and 2 due to sedation. No patient taking placebo quit due to side effects (p = .11, Fisher exact test).

DISCUSSION

Patients treated with olanzapine improved more than placebo-treated patients on the primary outcome measure, the CGI-BPD, beginning at 4 weeks and continuing to 12 weeks. This finding extends the evidence of efficacy of atypical antipsychotics in BPD to a mixed sample of men and women with significant comorbidity but no psychotic disorders. The broad spectrum of efficacy across BPD symptomatology is consistent with most previous studies of antipsychotic treatment of BPD.

The global CGI showed similar results to those of the CGI-BPD. The other secondary measures did not show significant treatment effects at endpoint, although some of them (the GAF, AIAQ, and HAM-D) showed significant differences at 8 weeks. Distributional characteristics required us to use nonparametric tests for some of the scales (OAS-M, ASI, AIMS, Simpson-Angus Scale), so we were unable to include the effect of baseline value in the analyses. Baseline ASI composite scores were very low (alcohol, 0.095 ± 0.122; drug, 0.027 ± 0.059) due to the fact that patients with fully active substance dependence were excluded from the study. Given the relatively small sample size and the large variances for these scales, it appears that the study may not have had adequate power consistently to detect differences on these scales. This argument is supported by the fact that the olanzapine group was numerically more improved on all of these measures at all timepoints with only 2 exceptions: the AIAQ at week 2 and the ASI alcohol composite score at week 4.

Several similarities and differences between the present study and that of Zanarini and Frankenburg[12] warrant discussion. The findings of the 2 studies were broadly similar in that both studies found a significant benefit of olanzapine over placebo across a broad range of BPD symptomatology measured by the primary outcome instrument. The endpoint olanzapine dose in the present study (6.9 mg) was only slightly higher than that in the earlier study (5.3 mg), in spite of the fact that we allowed doses of up to 20 mg. Weight gain in the present study was greater than that reported by Zanarini and Frankenburg[12] (2.87 lb), but comparable to that reported by Schulz et al.[10] (8.89 lb). The lack of significant effect on SCL-90 scores contrasts with the report of Zanarini and Frankenburg, who found significant differences on several of the SCL-90 subscales. We do not have a clear explanation for this discrepancy. Possibly, demographic factors played a role: our sample included men and was somewhat more ethnically diverse and possibly lower in socioeconomic status and education than the patients in the Zanarini and Frankenburg study.[12]

It is possible that some of the differences between the findings of the studies are related to the difference in duration of treatment (12 vs. 24 weeks). However, our results suggest that the treatment effect had leveled off by 8 weeks. In fact, an unexpected finding was that the treatment effect was stronger at 8 weeks than at 12 weeks. This result was due to greater improvement in the placebo group, and in some cases a slight worsening of symptoms in the olanzapine group, between weeks 8 and 12. It is not consistent with our expectations of the pharmacology of olanzapine in BPD that the effect would begin to wear off after 8 weeks. It also seems unlikely that this effect was due to increasing medication side effects over time in the olanzapine group. Medication dose was only slightly higher at 12 than at 8 weeks, and the side effects of olanzapine (e.g., sedation, weight gain) are unlikely to be mistaken for signs of BPD, although they could possibly affect ratings on symptoms of depression. It is more likely that these changes are due to the reactivity of symptoms and the subjectivity of interpretation of experiences that are characteristic of patients with BPD. With the relatively small number of subjects in this study, change in just a few patients could significantly alter the picture. However, the finding of a greater effect at 8 weeks raises the possibility that atypical antipsychotics may be useful for short-term treatment of exacerbation of BPD symptoms. No studies have directly addressed the optimal length of pharmacologic treatment of BPD. It is also possible that some BPD patients may experience a worsening of symptoms during the final weeks of the study in anticipation of termination from study participation. For this reason, it may be that the 8-week ratings are a better indi-

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cation of "steady-state" drug response than the endpoint ratings. The addition of an open-label continuation phase following the double-blind phase would be another methodological strategy to minimize this termination effect.

Overall, the study medication appeared to be well tolerated. No significant movement disorder symptoms were noted. Weight gain and sedation appeared to be significant side effects, each accounting for premature discontinuation of 2 olanzapine-treated patients. Weight gain was over 8 lb at endpoint in the olanzapine-treated group and was significantly greater than in the placebo-treated group, in spite of large standard deviations in both groups. These side effects have been reported with the use of olanzapine in other populations.[25]

The study has several limitations that restrict generalizability of the findings. Small sample size is a significant limitation that is shared with almost all published pharmacologic trials in patients with BPD. On the other hand, patient heterogeneity, inherent to BPD, and the inclusion of men were strengths in terms of generalizability. We did not include or control for psychosocial treatment in the present study. This is unlikely to have biased the results, as only 5 out of 40 patients were involved in therapy, 1 in the olanzapine group and 4 in the placebo group. However, our findings should not be extrapolated to situations in which medication is combined with psychosocial treatment. The treatment duration of 12 weeks is not sufficient to evaluate the efficacy of long-term treatment with olanzapine in BPD. Longer-term studies are essential to determine whether the effects of atypical antipsychotics persist, diminish, or increase with time. Such studies will be very challenging given the high dropout rates that have been found consistently in this population. Design features that minimize objectionable side effects (e.g., choice of medication, dosing, treatment of side effects, concurrent psychosocial treatment) may play a role in improving retention. Larger studies of atypical antipsychotics in BPD are needed, including a variety of medications, differing dosing regimens (e.g., p.r.n. dosing), combination of medication with empirically validated psychotherapies such as dialectical behavioral therapy,[26] and specific comorbid populations (e.g., patients with posttraumatic stress disorder, major depression, active substance use disorders).

Drug names: amitriptyline (Elavil and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others).

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