See article beginning on page 1353.

Randomized Controlled Trials of Olanzapine Treatment of Borderline Personality Disorder: Two Similar Studies With Different Results

H. George Nurnberg, MD

Borderline personality disorder, with origins in the psychodynamic literature, was a controversial addition to the official psychiatric nomenclature of *DSM-III* and became the most frequently diagnosed and extensively studied Axis II category. As defined in *DSM* nosology, borderline personality disorder is a prototypal construct with the following characteristics: (1) different polythetic criteria combinations constitute category membership heterogeneity (5 of 9 criteria lead to 225 potential combinations), (2) some individual criteria or combinations have a greater weight for making a diagnosis, (3) category members may simultaneously meet defining criteria for other Axis I and Axis II disorders, (4) homogeneity for diagnostic covariates is not expected, and (5) boundaries are imprecise. Borderline personality disorder is one of the more common and difficult-to-treat disorders in psychiatric practice and adversely affects treatment outcomes of other Axis I disorders when concurrent with them. Although there are no Food and Drug Administration (FDA)–approved pharmacologic treatments for *DSM-IV* borderline personality disorder, approximately 80% of patients in outpatient and inpatient treatment take medication (eg, antipsychotics, antidepressants, mood stabilizers, and sedatives) for the different facets of the pathological spectrum, which includes affective instability, impulsivity, dissociative states, cognitive difficulties, or disturbed interpersonal relations.[1] Treatment recommendation guidelines on pharmacologic treatment of borderline patients have predominantly relied on "expert" opinion (which diverges from more recently reported meta-analyses of small studies) and revision.[1,2]

The randomized placebo-controlled trial[3] of fixed-dose (2.5 mg/d and 5–10 mg/d) olanzapine treatment of borderline personality disorder reported in this issue of the *Journal* is the second report on 2 large, concurrently conducted industry-sponsored pharmacotherapy trials using essentially the same protocols and outcome measures and differing primarily on fixed-dose versus flexible-dose medication administration for treatment.

The results of the current fixed-dose trial[3] with 451 subjects (clinicaltrials.gov Identifier NCT00088036[4]) need to be considered together with the prior 2.5- to 20-mg/d flexible-dose report[5] published in 2008 involving 314 patients (clinicaltrials.gov Identifier NCT00091650[6]). The olanzapine 5- to 10-mg/d fixed-dose group, in comparison to the 2.5-mg/d fixed-dose and placebo groups, showed a statistically significant difference in the baseline-to-endpoint outcome measure (Zanarini Rating Scale for Borderline Personality Disorder [ZAN-BPD][7] score) for improvement of overall borderline psychopathology (−8.5 vs −8.0 vs −6.8, respectively; $P = .01$), with a small clinical effect size (0.29; 95% CI, 0.06–0.52).[3] The magnitude of change (mean improvement in baseline-to-endpoint ZAN-BPD total scores) versus placebo was less in the prior 2.5- to 20-mg/d flexible-dose trial (0.31) than in this 5- to 10-mg/d fixed-dose trial (1.71), without a significant difference between treatment groups (−6.56 for olanzapine vs −6.25 for placebo; $P = .66$).[5] In the current fixed-dose trial, olanzapine 2.5 mg/d did not produce significant results (change in ZAN-BPD score) relative to placebo (−8.0 vs −6.8; $P = .06$) but had a 0.19 (95% CI, −0.04 to 0.42)[3] effect size that exceeded the effect size of 0.03 (95% CI, −0.20 to 0.25)[5] in the 2.5- to 20-mg/d flexible-dose trial. The differences in treatment outcomes between the 2 reports are interesting and are not explained simply by the differences in medication dose; 5 mg/d was the most common daily dose of olanzapine during both double-blind trial periods,[3,5] with 7.09 mg/d being the mean modal dose in the 2.5- to 20-mg/d flexible-dose group,[5] compared to a 6.7-mg/d mean modal dose in the 5- to 10-mg/d fixed-dose group (distinct from the 2.5-mg/d fixed-dose group).[3]

On secondary last-observation-carried-forward outcome measures, the rate of response (*response* defined as a ≥ 50% decrease from baseline ZAN-BPD total score) for the olanzapine 5- to 10-mg/d fixed-dose treatment relative to the placebo treatment was 73.6% vs 57.8%, which was significant, with a number needed to treat (NNT) of 6 (95% CI, 4–21; $P = .03$),[3] and greater than the response rate for the 2.5- to 20-mg/d flexible-dose olanzapine treatment relative to placebo treatment (64.7% vs 53.5%; $P =$ not significant), with an NNT of 9 (95% CI, 7–24).[5] For other secondary outcome measures, such as the Modified Overt Aggression Scale irritability, Sheehan Disability Scale family life, and Symptom Checklist-90-Revised hostility scores, both studies were generally consistent for significant mean baseline-to-endpoint improvements in the olanzapine treatment groups; however, there were no significant depression score changes between groups according to the Montgomery-Asberg Depression Rating Scale.

Submitted: January 6, 2011; accepted January 13, 2011.
Online ahead of print: April 5, 2011 (doi:10.4088/JCP.11com06844).
Corresponding author: H. George Nurnberg, MD, Department of Psychiatry, University of New Mexico School of Medicine, 2400 Tucker NE, Albuquerque, NM 87131 (gnurnberg@salud.unm.edu).

J Clin Psychiatry 2011;72(10):1363–1365

Measures of individual items for the 9 *DSM-IV* criteria for borderline personality disorder showed significant last-observation-carried-forward mean scale reductions compared to placebo for the inappropriate anger item, with effect sizes of 0.26 (95% CI, 0.08–0.44; $P = .002$) and 0.13 (95% CI, 0.05–0.41; $P = .08$) for the olanzapine 5- to 10-mg/d and 2.5-mg/d fixed-dose groups, respectively, and 0.23 (95% CI, 0.05–0.41; $P = .01$) for the 2.5- to 20-mg/d flexible-dose group.[5] The 5- to 10-mg/d fixed-dose design showed additional, significantly reduced mean change for affective instability and paranoid dissociation items, with smaller effect sizes ($d = 0.18$ and $d = 0.28$, respectively), but similar findings did not occur in the prior flexible-dose trial. Additionally, in the flexible-dose trial, the placebo group showed a greater reduction (improvement) (not statistically significant) for suicidality/self-harm in comparison to the olanzapine 2.5- to 20-mg/d group (−0.6 vs −0.3, respectively). However, in the fixed-dose trial, the mean change of −0.3 for the 2.5-mg/d and 5- to 10-mg/d groups was greater than the mean change of −0.2 for the placebo group on suicidality/self-harm.

Assessment for effectiveness must include evaluation of adverse events and premature treatment discontinuation. Premature discontinuation due to adverse effects favors placebo relative to active drug treatment outcomes and becomes an additional consideration vis-à-vis benefit to understand differences between treatment outcomes and whether it is beneficial to treat with medication or not. In 12 weeks of double-blind treatment, a 35% overall premature discontinuation rate occurred among the 3 fixed-dose groups[3] compared to a 48% rate in the flexible-dose groups, with a number needed to harm (NNH) of 8 (95% CI, 6–21; $P = .02$).[3,5] Incidence of ≥ 7% weight gain, a concern with use of second-generation antipsychotic agents, was significant for fixed-dose olanzapine 5–10 mg/d (30.6%) or 2.5 mg/d (20.3%) over placebo (4.8%; $P = .002$, $P = .045$, respectively), with a relative risk (RR) of 4.26 (95% CI, 1.93–9.38) and an NNH of 6.45 (95% CI, 4.38–12.23) for olanzapine 2.5 mg/d and an RR of 6.42 (95% CI, 2.99–13.77) and an NNH of 3.88 (95% CI, 2.94–5.71) for olanzapine 5–10 mg/d.[3] Therefore, the cost-benefit ratio is derived from likelihood of harm (NNH = 4) divided by likelihood of benefit (NNT = 6.3), yielding a cost-benefit ratio of 0.63 (95% CI, 0.46–0.67), which indicates a 3:2 greater likelihood of ≥ 7% weight-gain harm over the modest treatment response (effect size, 0.29; 95% CI, 0.06–0.52) with fixed-dose olanzapine 5–10 mg/d. Treatment-emergent weight gain ≥ 7% over baseline incidence was significant and greater for individuals treated with flexible-dose olanzapine 2.5–20 mg/d relative to placebo (34.2% vs 2.6%, respectively; $P = .001$), with an NNH of 2.6 (95% CI, 2–3), resulting in a less effective cost-benefit consideration of 0.33 compared to fixed-dose olanzapine 5–10 mg/d.[5]

It is understandable that the efficacy data and adverse effects data together would not support application for an FDA-approved indication to treat overall global borderline personality disorder psychopathology with olanzapine. However, it must be underscored that the failure to prove efficacy should not be taken as proof of failure of olanzapine to treat not all but some borderline patients effectively. These 2 studies provide a rich and valuable new data source to inform clinicians in practice on more specific applications available for treatment of borderline patients. However, one size does not fit all, and by further examination and understanding of the data, patient selection can be better matched to selected potential treatment benefits.

For example, absent a gold standard for identifying borderline personality disorder, patient selection for inclusion in the studies required borderline personality disorder diagnosis according to the Diagnostic Interview for *DSM-IV* Personality Disorders (DIPD-IV), together with a minimum total severity score of 9 on the ZAN-BPD,[7] a semistructured interview derived from the DIPD-IV with anchored ratings from 0 (no symptoms) to 4 (severe symptoms) on each of 9 items corresponding to the 9 *DSM-IV* criteria for borderline personality disorder. Given inherent construct heterogeneity with differences of up to 50%[8] in diagnostic agreement between different scales and instruments for diagnosis of borderline personality disorder (eg, the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, the DIPD-IV, the Personality Disorder Examination, and others), patient selection can be expected to result in highly variable borderline personality disorder samples with different severity ratings that will influence outcomes across studies. For example, heterogeneity of illness severity in this trial,[3] with a treatment effect size of 0.29 (95% CI, 0.06–0.52), indicates that half of the patients were lower-half treatment-effect responders, at an effect size of 0.06–0.29, while the other half had a more robust treatment effect of 0.30–0.52.

More stringent entry criteria (eg, higher severity cutoff) or selection of subjects with more specific target criteria (eg, high anger ratings and high paranoid ratings) can result in higher differential treatment effectiveness than would occur by selecting a borderline group with other symptoms (eg, fear of abandonment, impulsivity, and feelings of emptiness) or with lower severity, for which olanzapine efficacy effectiveness (increased NNT) would be lower than the adverse-event impact (lower NNH)—and comparatively less effective overall. It is to be expected in borderline personality disorder, in which 5 of 9 criteria lead to 225 potential combinations and heterogeneity, that large randomized controlled trials will show wide variability in demonstrating global efficacy. Broad heterogeneity poses a challenge to demonstrating global treatment efficacy by a drug with specific effects.

In conclusion, for clinicians in practice who are treating patients with borderline personality disorder, it would have been more parsimonious to have results of these 2 important trials presented together in the same journal instead of 2+ years apart in different journals. While the evidence from the 2 randomized controlled trials does not support an indication for overall efficacy of olanzapine for borderline personality disorder treatment, the evidence is consistent

© Copyright 2011 Physicians Postgraduate Press, Inc.

with suggestions that pharmacotherapy should be targeted at specific symptoms and that second-generation antipsychotics can be effective for treating a number of core symptoms and their associated psychopathology. The updated clinical guidelines by Oldham[9] reflect a suggestion for more specific treatments of borderline personality disorder by focusing on matching different drug classes to more specific symptom clusters rather than focusing on one drug for all. An evidence-based psychopharmacology is emerging, enabling clinicians to be able to better match patients by subsets of specific criteria to different classes of agents (mood stabilizers, selective serotonin reuptake inhibitors, atypical antipsychotics) rather than relying on opinion-based guidelines that need revision in concordance to new data on pharmacologic treatment of borderline personality disorder. This industry-sponsored study provides an important contribution supporting clinicians' use of atypical treatment for borderline personality disorder in the absence of an FDA indication. The planned revision for *DSM-5* suggests an additional caveat: the expected revisions in diagnostic criteria can be expected to influence whether the generalizability of prior drug study results will be concordant and apply to patients identified in the new classification system.

Drug names: olanzapine (Zyprexa).
Author affiliation: Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque.
Potential conflicts of interest: None reported.
Funding/support: None reported.

REFERENCES

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Borderline Personality Disorder. *Am J Psychiatry*. 2001; 158(10 suppl):1–52.
2. Binks CA, Fenton M, McCarthy L, et al. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database Syst Rev*. 2006;(1):CD005653.
3. Zanarini MC, Schulz SC, Detke HC, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2011;72(10):1353–1362.
4. Eli Lilly and Company. Clinical Study Summary: Study F1D-MC-HGKK. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized double-blind comparison with placebo. http://www.clinicalstudyresults.org/documents/company-study_2339_0.pdf. Verified February 18, 2011.
5. Schulz SC, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. *Br J Psychiatry*. 2008;193(6): 485–492.
6. Eli Lilly and Company. Clinical Study Summary: Study F1D-MC-HGKL. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized, flexible-dose, double-blind comparison with placebo. http://www.clinicalstudyresults.org/documents/company-study_3631_0.pdf. Verified February 21, 2011.
7. Zanarini MC, Vujanovic AA, Parachini EA, et al. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of *DSM-IV* borderline psychopathology. *J Pers Disord*. 2003;17(3): 233–242.
8. Kavoussi RJ, Coccaro EF, Klar HM, et al. Structured interviews for borderline personality disorder. *Am J Psychiatry*. 1990;147(11):1522–1525.
9. Oldham JM. Guideline watch: practice guideline for the treatment of patients with borderline personality disorder. Arlington, VA: American Psychiatric Association; 2005. http://www.psychiatryonline.com/pracGuide/PracticePDFs/Borderline.watch.pdf. Verified February 21, 2011.

© Copyright 2011 Physicians Postgraduate Press, Inc.

A Dose Comparison of Olanzapine for the Treatment of Borderline Personality Disorder: A 12-Week Randomized, Double-Blind, Placebo-Controlled Study

Mary C. Zanarini, EdD; S. Charles Schulz, MD; Holland C. Detke, PhD; Yoko Tanaka, PhD; Fangyi Zhao, PhD; Daniel Lin, PhD; Walter Deberdt, MD; Ludmila Kryzhanovskaya, MD; and Sara Corya, MD

ABSTRACT

Objective: To examine the efficacy and safety of olanzapine at low and moderate doses for the treatment of borderline personality disorder.

Method: In this 12-week randomized double-blind placebo-controlled trial, 451 outpatients aged 18–65 years with *DSM-IV* borderline personality disorder received olanzapine 2.5 mg/d (n = 150), olanzapine 5–10 mg/d (n = 148), or placebo (n = 153). The trial was conducted from February 2004 through January 2006 at 59 community-based and academic study centers in 9 countries (United States, Italy, Poland, Romania, Turkey, Chile, Peru, Argentina, and Venezuela). The primary efficacy measure was mean change from baseline to last-observation-carried-forward endpoint on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) total score. Secondary measures included the Montgomery-Asberg Depression Rating Scale, the Modified Overt Aggression Scale, the Global Assessment of Functioning, the Symptom Checklist-90-Revised, and the Sheehan Disability Scale.

Results: An overall mean baseline ZAN-BPD total score of 17.2 (SD = 4.9) indicated moderate symptom severity. Only treatment with olanzapine 5–10 mg/d was associated with significantly greater mean change from baseline to endpoint in ZAN-BPD total score relative to placebo (−8.5 vs −6.8, respectively; $P = .010$; effect size = 0.29; 95% CI, 0.06–0.52). Response rates (response indicated by ≥ 50% decrease from baseline in ZAN-BPD total score) were significantly higher for olanzapine 5–10 mg/d (73.6%) versus olanzapine 2.5 mg/d (60.1%; $P = .018$) and versus placebo (57.8%; $P = .006$). Time to response was also significantly shorter for patients taking olanzapine 5–10 mg/d than for placebo-treated patients ($P = .028$). Treatment-emergent adverse events reported significantly more frequently among olanzapine-treated patients included somnolence, fatigue, increased appetite, and weight increase (all P values < .05). Mean weight change from baseline to endpoint was significantly greater for olanzapine-treated than for placebo-treated patients (olanzapine 2.5 mg/d: 2.09 kg; olanzapine 5–10 mg/d: 3.17 kg; placebo: 0.02 kg; $P < .001$). The overall completion rate for the 12-week double-blind treatment period was 65.2% (ie, 64.7% for olanzapine 2.5 mg/d, 69.6% for olanzapine 5–10 mg/d, and 61.4% for placebo).

Conclusions: Olanzapine 5–10 mg/d showed a clinically modest advantage over placebo in the treatment of overall borderline psychopathology. This advantage in effectiveness should be weighed against the risk of adverse events (particularly weight gain), which were consistent with the known safety profile of olanzapine.

Trial Registration: clinicaltrials.gov Identifier: NCT00088036

J Clin Psychiatry 2011;72(10):1353–1362

See also Commentary on page 1363.

Submitted: *February 18, 2008; accepted May 21, 2010.*
Online ahead of print: *April 5, 2011 (doi:10.4088/JCP.08m04138yel).*
Corresponding author: *Mary C. Zanarini, EdD, McLean Hospital, 115 Mill St, Belmont, MA 02478 (zanarini@mclean.harvard.edu).*

Despite the frequency with which newer antidepressants, mood stabilizers, and antipsychotics are prescribed for patients with borderline personality disorder,[1] the empirical evidence for the efficacy of most of these medications is not particularly robust. Among these classes of medication, atypical antipsychotics have been studied the most extensively for borderline personality disorder, with 10 published studies.[2–11] Five studies have examined the atypical antipsychotic olanzapine: 1 open-label trial[8] and 4 placebo-controlled or comparator-controlled trials.[3,9–11] Taken together, these 5 studies suggest that low to moderate doses of olanzapine may be effective in treating a range of symptoms common among patients with borderline personality disorder, although olanzapine is not currently approved to treat borderline personality disorder.

However, all of the above 5 trials have limitations that hinder the ability of clinicians to generalize from their findings to everyday practice, such as small sample size or the exclusion of men with borderline personality disorder. An additional limitation is that 4 of the 5 studies[8–11] focused on specific symptoms associated with borderline personality disorder, such as anxiety and aggression, rather than on the symptoms of borderline personality disorder per se or on some overall measure of the severity of borderline psychopathology.

The current study is the largest pharmacotherapy trial for borderline personality disorder that has been conducted to date, involving community-based as well as academic sites. It is also the first study to compare different doses of olanzapine to placebo. In addition, it is one of the first studies to use a psychometrically proven outcome measure designed specifically to assess the severity of overall borderline psychopathology over time.

METHOD

This study was one of 2 multicenter, parallel, double-blind, randomized, placebo-controlled clinical trials (clinicaltrials.gov Identifier NCT00088036) comparing olanzapine with placebo in patients with borderline personality disorder: one was a fixed-dose study and the other a variable-dose study. The results of the fixed-dose study are presented here and provide data on a low dose (2.5 mg/d) and a moderate dose (5–10 mg/d) of olanzapine. Results from the variable-dose study (2.5–20 mg/d) are presented in a separate article.[12]

This study was conducted from February 2004 through January 2006 at 59 community-based and academic study centers in 9 countries (United States, Italy, Poland, Romania, Turkey, Chile, Peru, Argentina, and Venezuela). All patients provided written informed consent before study participation. The appropriate ethics review boards approved the study before recruitment.

Study Design

This study consisted of 3 periods: (1) 2- to 14-day screening (visits 1–2); (2) 12-week double-blind acute treatment (visits 3–14); and (3) 12-week open-label extension. This report presents the results of the 12-week double-blind acute treatment period. The 12-week duration was considered sufficient to confirm a sustained difference between treatment groups, surpassing temporary variability in condition.

To minimize patient dropout, clinic visits alternated with telephone visits to maintain weekly contact with the patient. Telephone visits were conducted by site personnel, and if a dose decrease was deemed necessary, or if the patient reported a serious adverse event, a study physician also called the patient. If an investigator believed that a dose increase was necessary between clinic visits, the patient could be brought into the clinic for an unscheduled visit.

Patients who met enrollment criteria at visit 2 were randomly assigned in a 1:1:1 ratio, stratified by study center, to receive treatment with olanzapine 2.5 mg/d, olanzapine 5–10 mg/d, or placebo. All patients, study site personnel, and investigators were blinded to randomization codes. For all patients assigned to treatment with olanzapine 2.5 mg/d or olanzapine 5–10 mg/d, the starting dosage was 2.5 mg/d. For patients assigned to treatment with olanzapine 5–10 mg/d, the dosage was adjusted to 5.0 mg/d after 1 week and could be increased subsequently up to 10 mg/d at the investigator's discretion.

Diagnostic Interviews

All patients were administered 2 semistructured diagnostic interviews: the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[13] and the Diagnostic Interview for *DSM-IV* Personality Disorders (DIPD-IV).[14]

Outcome Assessments

Four clinician-rated measures were administered at baseline and at subsequent clinic visits: the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD),[15] the Montgomery-Asberg Depression Rating Scale (MADRS),[16] the Overt Aggression Scale-Modified (OAS-M),[17] and the Global Assessment of Functioning (GAF).[18] Two self-report measures were also administered: the Symptom Checklist-90-Revised (SCL-90-R)[19] and the Sheehan Disability Scale.[20]

The ZAN-BPD is a semistructured interview with anchored ratings from 0 (no symptoms) to 4 (severe symptoms) on each of 9 items corresponding to the 9 *DSM-IV* criteria for borderline personality disorder. Thus, ZAN-BPD total scores can range from 0 to 36. Its discriminant and convergent validity, interrater and test-retest reliability, and sensitivity to change have all been found to be good to excellent.[15]

Rater Training

All raters received a training guide and a videotape pertaining to the SCID-I and the DIPD-IV. Each rater also received a training guide and live training on the ZAN-BPD by the scale's author (M.C.Z.). As part of the training, raters watched a videotape of the scale's author conducting an interview with a subject and discussed the ratings. Subsequently, each rater viewed a second videotaped interview and scored the subject independently. If the scoring met established criteria (sum of squared differences between the gold standard and the rater's score < 8), the rater was considered certified to administer the ZAN-BPD. If the rater did not meet certification criteria, he or she received a second training and then took another test. The vast majority of raters passed the first test, and all raters who had to take a second test passed it and received certification to administer the scale.

Inclusion/Exclusion Criteria

Male and female outpatients 18 to 65 years of age who met *DSM-IV* criteria for borderline personality disorder as determined by the DIPD-IV, with a ZAN-BPD total score ≥ 9 at visit 2, were included in this study. It should be noted that the DIPD-IV assesses symptoms and behaviors that were characteristic of the subject over the past 2 years (and much of his or her adult life). To gain entrance into the study, each subject needed to meet at least 5 of the 9 *DSM-IV* criteria for borderline personality disorder. In contrast to the DIPD-IV, the ZAN-BPD pertains to the past week only and rates severity of symptom expression (and not the presence or absence of a borderline personality disorder diagnosis or the presence or absence of any of the 9 *DSM-IV* criteria for borderline personality disorder).

Patients were excluded from the study if they had ever met criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, or delusional disorder as assessed by the SCID-I. Patients could not have a diagnosis of major depressive disorder, bipolar II disorder, or substance dependence within the previous 3 months; could not currently meet *DSM-IV* criteria for posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder; could not be actively suicidal; and could not have a body mass index < 17. In addition, they could not meet criteria for a cluster A personality disorder. Subjects with a psychotic disorder, bipolar I disorder, or recent substance dependence were excluded because their Axis I state (ie, psychosis, mania, or intoxication/withdrawal) would quite likely interfere with assessments of their more enduring personality traits or symptoms.

Patients entering the study could not have begun any type of psychotherapy within the 3 months prior to visit 1, nor could they begin any during the acute phase of the study. Patients with ongoing psychotherapy for > 3 months at the time of visit 1 were eligible for the study. However, they were discontinued from the study if there was an increase in psychotherapy frequency or a change in type of psychotherapy during study periods 1 or 2.

Concomitant use of benzodiazepines or hypnotics was allowed during the study at a dose equivalent to ≤ 1.0 mg lorazepam per day. Episodic use of anticholinergics was permitted at a dose of ≤ 6.0 mg/d for benztropine mesylate or biperiden, or ≤ 12.0 mg/d for trihexyphenidyl, to treat extrapyramidal symptoms; however, the use of anticholinergic medication as prophylaxis for extrapyramidal symptoms was not allowed.

Safety Measures

Safety was assessed by evaluating adverse events, vital signs, electrocardiogram findings, laboratory values, and extrapyramidal symptoms. Laboratory tests included clinical chemistry, electrolytes, lipid profile, prolactin, and hematology panels. These tests were performed at the protocol-specified time points, when clinically indicated, and any time a patient completed the double-blind acute period or discontinued the study. Extrapyramidal symptoms were assessed using the Simpson-Angus Scale,[21] the Barnes Akathisia Scale,[22] and the Abnormal Involuntary Movement Scale.[23] All adverse events were recorded as actual terms and were coded to terms of the Medical Dictionary for Regulatory Activities.[24]

Efficacy Outcomes

The primary efficacy variable was last-observation-carried-forward mean change from baseline to endpoint in ZAN-BPD total score. Additional analyses included rate of response (defined a priori as ≥ 50% decrease at endpoint in ZAN-BPD total score from baseline) and time to response.

Secondary efficacy variables included mean baseline-to-endpoint changes on the MADRS total score; the Global Severity Index of the SCL-90-R[19]; the OAS-M aggression, irritability, and suicidality scores; the Sheehan family, social, and work/school scores; and the current GAF score.

Statistical Methods

All patient data were analyzed on an intent-to-treat basis. Patient characteristics at baseline, including demographics (gender, age, and race), illness characteristics, efficacy scores, and quality-of-life scores, were summarized for all 3 study groups. Three-way frequencies were compared using the Fisher-Freeman-Halton test, and 2-way comparisons were conducted using the Fisher exact test. Means for continuous data were compared by analysis of variance, with treatment and investigator as independent factors.

For analysis of last-observation-carried-forward mean change from baseline to endpoint, only patients with a baseline and at least 1 postbaseline measurement were included in the analyses. Changes in continuous efficacy data were analyzed with analysis-of-covariance models, which included terms for the fixed effects of baseline, investigator, and treatment. All reported ZAN-BPD, OAS-M, Sheehan, SCL-90-R, GAF, and MADRS mean change scores represent least-squares means. Cohen effect-size estimates were used when comparing baseline-to-endpoint changes in efficacy scores between treatments. Analysis of visitwise ZAN-BPD total scores used a mixed-effects model repeated-measures method, which included independent factors for baseline, therapy, visit, and therapy-by-visit interaction. Frequency of treatment response was analyzed using the Fisher exact test. Relative risk, number needed to treat for rates of response, and number needed to harm for weight gain ≥ 7% of baseline were calculated with corresponding 95% confidence intervals. Time to response was calculated using the Kaplan-Meier technique, with treatment comparisons made using the log-rank test. Last-observation-carried-forward mean changes from baseline to endpoint for continuous safety measures were analyzed using analysis-of-variance models, including terms for the fixed effects of investigator and treatment.

Categorical analyses of safety data were analyzed using the Fisher-Freeman-Halton test for 3-way frequencies and the Fisher exact test for 2-way comparisons. Analyses of incidences of treatment-emergent abnormal metabolic parameters included patients with both fasting baseline and fasting postbaseline assessments. A shift analysis was performed to examine changes from baseline to endpoint in the total number of abnormal parameters that could be potential indicators of metabolic dysregulation. The 4 parameters examined were body mass index, fasting glucose, fasting high-density lipoprotein cholesterol, and fasting triglycerides, and the criteria used to define normal and abnormal ranges for these parameters are listed in the footnote to Table 5.

All hypotheses were tested at a 2-sided $\alpha = .05$. The software used for all statistical analyses was SAS Version 8.2 (SAS Institute Inc; Cary, North Carolina).

RESULTS

A total of 451 patients were randomly assigned to receive olanzapine 2.5 mg/d (n = 150), olanzapine 5–10 mg/d (n = 148), or placebo (n = 153). Table 1 details the baseline demographic and illness characteristics of those in each group. No statistically significant differences between groups and no significant gender differences were observed on any of these baseline measures, except eating disorders, which were found exclusively in female subjects.

Baseline scores indicate moderate symptom severity and moderate functional impairment consistent with an outpatient population. Over 60% of the subjects in each study group completed the trial (Figure 1). Overall, no statistically significant between-group differences were observed with regard to patient disposition.

The mean modal dose of olanzapine in the olanzapine 5- to 10-mg/d group was 6.7 mg/d, with 5 mg/d being the most common daily dose. The incidence of benzodiazepine use did not differ significantly between treatment groups (olanzapine 2.5 mg/d, 22.0%; olanzapine 5–10 mg/d, 27.0%; placebo, 26.1%; $P = .558$), nor did the mean daily benzodiazepine dose (olanzapine 2.5 mg/d, 0.97 mg; olanzapine 5–10 mg/d, 1.34 mg; placebo, 1.82 mg; $P = .925$) or mean days of use (olanzapine 2.5 mg/d, 50.67 days; olanzapine 5–10 mg/d, 38.95 days; placebo, 46.33 days; $P = .584$).

Table 1. Baseline Demographic and Illness Characteristics by Treatment Group (N = 451)

Characteristic	Olanzapine 2.5 mg/d, n = 150	Olanzapine 5–10 mg/d, n = 148	Placebo, n = 153	*P* Value
Sex, female, n (%)	109 (72.7)	106 (71.6)	117 (76.5)	.798[a]
Age, mean (SD), y	32.6 (11.2)	32.8 (10.0)	33.5 (11.3)	.914[b]
Ethnicity, n (%)				.604[a]
White	102 (68.0)	87 (58.8)	106 (69.3)	
African descent	7 (4.7)	11 (7.4)	14 (9.2)	
East/Southeast Asian	1 (0.7)	4 (2.7)	2 (1.3)	
Western Asian	1 (0.7)	0 (0)	0 (0)	
Hispanic	36 (24.0)	45 (30.4)	30 (19.6)	
Other origin	3 (2.0)	1 (0.7)	1 (0.7)	
Test scores, mean (SD)				
ZAN-BPD total score[c]	17.0 (5.0)	17.4 (4.5)	17.1 (5.0)	.724[b]
MADRS total score	11.7 (4.8)	12.0 (4.7)	11.5 (4.8)	.680[b]
Current GAF score	55.1 (9.4)	55.7 (8.9)	55.4 (9.7)	.798[b]
Sheehan Disability Scale total score	18.6 (6.8)	18.4 (7.0)	18.1 (7.1)	.885[b]
Unemployed due to study disease, n (%)	18 (12.0)	19 (12.8)	21 (13.7)	.966[a]
Lifetime Axis I disorders, n (%)				
Major depression	30 (20.0)	33 (22.8)	32 (21.3)	.846[a]
Other mood disorders	4 (2.7)	6 (4.1)	9 (6.0)	.359[a]
Substance use disorders	13 (8.7)	11 (7.6)	14 (9.3)	.864[a]
Anxiety disorders	11 (7.3)	12 (8.3)	8 (5.3)	.597[a]
Eating disorders	4 (2.7)	8 (5.5)	9 (6.0)	.340[a]
Axis II disorders, n (%)				
Odd cluster	1 (0.7)	4 (2.8)	3 (2.0)	.391[a]
Anxious cluster	20 (13.3)	17 (11.7)	23 (15.3)	.661[a]
Non–borderline personality disorder dramatic cluster	3 (2.0)	10 (6.9)	9 (6.0)	.117[a]

[a] χ^2 test.
[b] Means analyzed using type III sum of squares analysis of variance: model = investigator, therapy.
[c] For all randomized patients (N = 451), ZAN-BPD total score mean (SD) = 17.2 (4.9).
Abbreviations: GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Efficacy

On the primary outcome measure, the olanzapine 5- to 10-mg/d group showed a statistically significantly greater mean baseline-to-endpoint decrease in ZAN-BPD total score relative to the placebo group ($P = .010$). The corresponding effect size was 0.29 (95% CI, 0.06–0.52). The difference between the olanzapine 2.5-mg/d group and the placebo group on this measure approached significance ($P = .062$), with an effect size of 0.19 (95% CI, −0.04 to 0.42) (Figure 2). Subgroup analysis of this measure by gender did not reveal a significant treatment-by-gender interaction ($P = .140$). When visitwise data were analyzed using mixed-effects model repeated-measures methods, statistically significant differences in mean change from baseline ZAN-BPD total score were observed between the olanzapine 5- to 10-mg/d and placebo treatment groups at the 2-, 4-, 6-, 8-, and 10-week time points. The results pertaining to this comparison were more robust at week 6 than at week 12. More specifically, the comparison between the olanzapine 5- to 10-mg/d and placebo treatment groups was not significant at endpoint ($P = .051$).

The rate of response (*response* defined as ≥ 50% decrease from baseline ZAN-BPD total score) was significantly higher for the olanzapine 5- to 10-mg/d group (73.6%) relative to the olanzapine 2.5-mg/d (60.1%; $P = .018$) and placebo (57.8%; $P = .006$) treatment groups. The olanzapine 5- to 10-mg/d group showed significantly greater mean reductions compared with the placebo group on the anger, affective instability, and paranoid ideation or dissociation items of the ZAN-BPD, with a trend toward a significantly greater mean reduction on the suicidal/self-mutilating behavior item. Patients in the olanzapine 2.5-mg/d group had significantly greater reductions compared with the placebo group on 2 individual ZAN-BPD item scores (identity disturbance and suicidal/self-mutilating behavior). Relative risk (RR) and number needed to treat (NNT) for response rates were as follows: olanzapine 2.5 mg/d versus placebo: RR = 1.19 (95% CI, 0.92–1.54), NNT = 12.77 (95% CI, 5.22–undefined); olanzapine 5–10 mg/d versus placebo: RR = 1.40 (95% CI, 1.10–1.78), NNT = 6.20 (95% CI, 3.64–20.87). Time to reach response was statistically significantly shorter for the olanzapine 5- to 10-mg/d group relative to the placebo group ($P = .028$) (Figure 3).

Table 2 shows the mean change results for ZAN-BPD total and individual item scores, and Table 3 shows the mean change results for the secondary outcome measures. Mean baseline-to-endpoint improvements were statistically significantly greater in both olanzapine treatment groups relative to the placebo group on OAS-M irritability, OAS-M suicidality, and Sheehan family life. In addition, a statistically

© Copyright 2011 Physicians Postgraduate Press, Inc.

Figure 1. Flow Diagram of Patient Progress Through the 12-Week Study

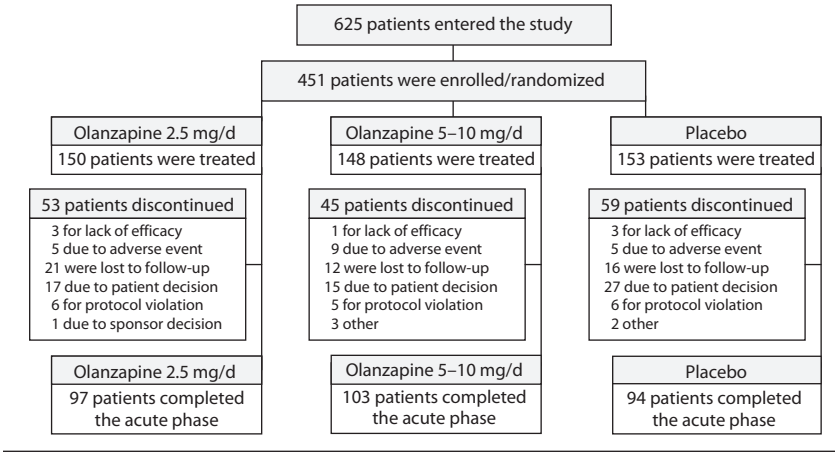
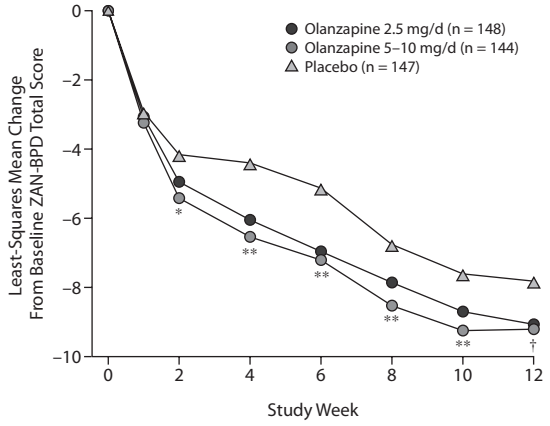


Figure 2. Mean Visitwise Changes in ZAN-BPD Total Scores (mixed-effects model repeated measures)[a]



[a]Olanzapine 5–10 mg/d versus placebo: *P < .05, **P < .01, †P = .051.
Abbreviation: ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

significantly greater decrease was found for the olanzapine 2.5-mg/d group relative to the placebo group on the Sheehan social life item, and a similar pattern was found for the olanzapine 5- to 10-mg/d group on the SCL-90-R total score and Sheehan work/school item. There were no statistically significant differences between treatment groups in GAF or MADRS scores.

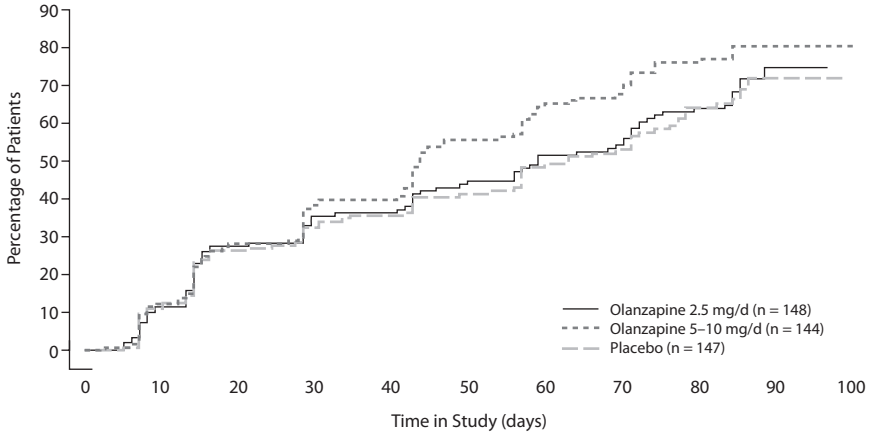
Safety

Adverse events. Among treatment-emergent adverse events reported with a frequency ≥ 5% in any treatment group, somnolence, fatigue, increased appetite, and weight increase were reported significantly more frequently in the olanzapine 5- to 10-mg/d group compared with the placebo group (Table 4). Somnolence, increased appetite, and weight increase were reported significantly more frequently, and nasopharyngitis significantly less frequently, in the olanzapine 2.5-mg/d group compared with the placebo group. The incidence of reported serious adverse events (this section refers to a separate analysis of serious adverse events, available in the clinical study summary[25]) was 3.4% for the olanzapine 5- to 10-mg/d group, 0.7% for the olanzapine 2.5-mg/d group, and 5.9% for the placebo group. Only the comparison between the olanzapine 2.5-mg/d group and placebo was statistically significant (P = .020). Among olanzapine-treated patients, none of the serious adverse events was reported by > 1 patient. Two patients in the placebo group attempted suicide. No deaths occurred during the double-blind phase of the study.

Weight and vital signs. Mean baseline-to-endpoint change in weight was significantly different in the olanzapine 2.5-mg/d and olanzapine 5- to 10-mg/d groups versus the placebo group (olanzapine 2.5 mg/d: 2.09 ± 2.93 kg and olanzapine 5–10 mg/d: 3.17 ± 3.28 kg versus placebo: 0.02 ± 2.47 kg; both P values < .001). The incidence of weight gain ≥ 7% of baseline was significantly higher for the olanzapine 2.5-mg/d and olanzapine 5- to 10-mg/d groups relative to the placebo group (olanzapine 2.5 mg/d: 20.3% [30/148] and olanzapine 5–10 mg/d: 30.6% [44/144] versus placebo: 4.8% [7/147]; both P values < .001). Mean weight gain was significantly greater, and the incidence of weight gain ≥ 7% of baseline was significantly higher, for the olanzapine 5- to 10-mg/d group relative to the olanzapine 2.5-mg/d group (P = .002 and P = .045, respectively). Relative risk and number needed to harm (NNH) for weight gain ≥ 7% of baseline were as follows: olanzapine 2.5 mg/d versus placebo: RR = 4.26 (95% CI, 1.93–9.38), NNH = 6.45 (95% CI, 4.38–12.23); olanzapine 5–10 mg/d versus placebo: RR = 6.42 (95% CI, 2.99–13.77), NNH = 3.88 (95% CI, 2.94–5.71). No significant group differences were observed for blood pressure or pulse measures.

Metabolic parameters. Mean ± SD baseline-to-endpoint increases in fasting triglycerides were significantly greater for the olanzapine 2.5-mg/d group compared to the placebo group (0.20 ± 0.79 mmol/L vs −0.06 ± 0.66 mmol/L, respectively; P = .018). Mean ± SD baseline-to-endpoint changes were significantly greater for the olanzapine 5- to 10-mg/d group relative to the placebo group in high-density

Figure 3. Time to First Response (≥ 50% reduction from baseline in ZAN-BPD total score)[a,b]



[a]Response is defined as a 50% reduction in ZAN-BPD total score from baseline to any postbaseline visit.
[b]Log-rank test: $P = .028$ for placebo versus olanzapine 5–10 mg/d.
Abbreviation: ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Table 2. Mean Change From Baseline to Endpoint (last observation carried forward) on ZAN-BPD Total and Individual Item Scores by Treatment Group

	Olanzapine 2.5 mg/d		Olanzapine 5–10 mg/d		Placebo		
Borderline Personality Disorder Criteria	Baseline, Mean (SD), N = 148	Least-Squares Mean Change, N = 148	Baseline, Mean (SD), N = 144	Least-Squares Mean Change, N = 144	Baseline, Mean (SD), N = 147	Least-Squares Mean Change, N = 147	Overall *P* Value[a]
Primary efficacy measure							
ZAN-BPD total score	17.1 (5.0)	−8.0	17.4 (4.5)	−8.5[b]	17.1 (5.0)	−6.8	.029
ZAN-BPD individual items							
Intense anger	2.3 (0.9)	−1.0	2.3 (0.7)	−1.1[b]	2.4 (0.8)	−0.8	.007
Affective instability	2.7 (0.8)	−1.3	2.7 (0.8)	−1.3[b]	2.7 (0.8)	−1.1	.055
Chronic feelings of emptiness	1.9 (1.2)	−0.8	2.2 (1.2)	−0.9	2.0 (1.2)	−0.7	.433
Identity disturbance	1.8 (1.1)	−1.1	1.9 (1.1)	−1.0	1.7 (1.1)	−0.9	.135
Paranoid ideation or dissociation	1.7 (1.0)	−0.9	1.8 (1.0)	−1.0[b]	1.7 (1.0)	−0.7	.050
Frantic efforts to avoid abandonment	1.7 (1.1)	−0.9	1.9 (1.2)	−1.0	1.8 (1.0)	−0.9	.602
Suicidal or self-mutilating behavior	0.6 (0.9)	−0.3[b]	0.5 (0.8)	−0.3[b]	0.5 (0.9)	−0.2	.043
Impulsivity that is self-damaging	2.1 (1.1)	−0.9	2.0 (1.1)	−0.9	2.0 (1.1)	−0.8	.509
Unstable interpersonal relationships	2.3 (0.9)	−0.9	2.2 (0.9)	−1.0	2.3 (1.0)	−0.8	.353

[a]Type III sum of squares analysis of covariance: model = baseline, investigator, therapy.
[b]Versus placebo: $P < .05$.
Abbreviation: ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Table 3. Mean Change From Baseline to Endpoint (last observation carried forward) on Secondary Efficacy Measures by Treatment Group

	Olanzapine 2.5 mg/d			Olanzapine 5–10 mg/d			Placebo			
Secondary Efficacy Measure	Total N	Baseline, Mean (SD)	Least-Squares Mean Change	Total N	Baseline, Mean (SD)	Least-Squares Mean Change	Total N	Baseline, Mean (SD)	Least-Squares Mean Change	Overall *P* Value[a]
OAS-M aggression score	139	50.9 (68.9)	−28.1	144	36.8 (53.2)	−32.9	142	44.0 (77.1)	−25.4	.140
OAS-M irritability score	139	5.7 (1.8)	−2.2[b]	144	5.6 (1.6)	−2.4[b]	143	5.4 (2.0)	−1.6	.009
OAS-M suicidality score	139	0.7 (0.9)	−0.5[b]	144	0.7 (1.0)	−0.5[b]	143	0.6 (1.1)	−0.1	< .001
Sheehan family life score	139	6.4 (2.7)	−3.0[b]	144	6.4 (2.6)	−2.8[b]	143	6.2 (2.6)	−2.1	.014
Sheehan social life score	139	6.3 (2.6)	−2.9[b]	144	6.2 (2.9)	−2.6	143	6.2 (2.9)	−2.2	.096
Sheehan work/school score	108	5.8 (2.9)	−2.5	127	5.8 (3.1)	−2.6[b]	113	5.5 (2.8)	−1.8	.072
SCL-90-R score	131	1.6 (0.8)	−0.7	138	1.6 (0.7)	−0.7[b]	136	1.5 (0.7)	−0.6	.035
Current GAF score	131	55.2 (9.6)	10.5	138	56.0 (8.9)	10.1	137	55.4 (9.8)	7.8	.111
MADRS total score	131	11.8 (4.8)	−2.9	138	12.0 (4.6)	−1.4	136	11.9 (4.8)	−1.8	.196

[a]Type III sum of squares analysis of covariance: model = baseline, investigator, therapy.
[b]Versus placebo: $P < .05$.
Abbreviations: GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, OAS-M = Overt Aggression Scale-Modified, SCL-90-R = Symptom Checklist-90-Revised.

Table 4. Treatment-Emergent Adverse Events by Treatment Group (N = 451)

Treatment-Emergent Adverse Event	Olanzapine 2.5 mg/d, n = 150, n (%)	Olanzapine 5–10 mg/d, n = 148, n (%)	Placebo, n = 153, n (%)	*P* Value[a]
Patients with ≥ 1 treatment-emergent adverse events	98 (65.3)	99 (66.9)	93 (60.8)	.525
Increased appetite	25 (16.7)[b]	35 (23.6)[b]	11 (7.2)	< .001
Somnolence	25 (16.7)[b]	29 (19.6)[b]	10 (6.5)	.002
Headache	20 (13.3)	13 (8.8)	22 (14.4)	.283
Weight increase	12 (8.0)[b]	28 (18.9)[b]	1 (0.7)	< .001
Insomnia	11 (7.3)	11 (7.4)	13 (8.5)	.927
Fatigue	10 (6.7)	14 (9.5)[b]	4 (2.6)	.039
Anxiety	7 (4.7)	7 (4.7)	10 (6.5)	.778
Nausea	6 (4.0)	9 (6.1)	8 (5.2)	.718
Dry mouth	7 (4.7)	11 (7.4)	4 (2.6)	.153
Nasopharyngitis	2 (1.3)[b]	6 (4.1)	10 (6.5)	.065

[a]Fisher-Freeman-Halton test.
[b]Versus placebo: $P < .05$ (Fisher exact test).

lipoprotein cholesterol (−0.04 ± 0.20 mmol/L vs 0.02 ± 0.23 mmol/L, respectively; $P = .040$) and fasting triglycerides (0.21 ± 0.80 mmol/L vs −0.06 ± 0.66 mmol/L, respectively; $P = .014$). No significant differences were observed between treatment groups in the incidence of treatment-emergent abnormal fasting glucose or fasting lipids at any time during treatment, although the incidence of treatment-emergent abnormal body mass index was significantly higher for the olanzapine 5- to 10-mg/d group relative to the olanzapine 2.5-mg/d and placebo groups ($P = .045$ and $P = .003$, respectively) (Table 5). The shift analysis of baseline-to-endpoint changes in the number of parameters with abnormal values among the 4 parameters that could be potential indicators of metabolic dysregulation revealed no significant group differences (olanzapine 2.5 mg/d vs placebo: $P = .494$; olanzapine 5–10 mg/d vs placebo: $P = .120$). In the olanzapine 2.5-mg/d group, the number of these parameters with values that changed from normal at baseline to abnormal at endpoint increased by 1 parameter in 13 patients (12.3%) and by 2 parameters in 1 patient (< 1%), whereas 56 patients (53.3%) did not change and 35 patients (33.3%) experienced a decrease by ≥ 1 parameter. In the olanzapine 5- to 10-mg/d group, 14 patients (13.6%) experienced an increase by 1 parameter, 1 patient (< 1%) experienced an increase by 2 parameters, 61 patients (59.2%) did not change, and 27 patients (26.2%) experienced a decrease by ≥ 1 parameter. In the placebo group, 9 patients (8.7%) experienced an increase by 1 parameter, 54 patients (52.4%) did not change, and 40 patients (38.8%) experienced a decrease by ≥ 1 parameter.

Prolactin and other laboratory values. Mean ± SD baseline-to-endpoint increases in prolactin levels were significantly greater for the olanzapine 5- to 10-mg/d group (9.26 ± 19.2 μg/L) relative to the olanzapine 2.5-mg/d group (2.25 ± 13.23 μg/L; $P = .001$) and the placebo group (0.03 ± 17.35 μg/L; $P < .001$). The incidence of treatment-emergent abnormally high levels of prolactin at endpoint was statistically significantly higher for the olanzapine 2.5-mg/d group (14.7% [15/102]; $P = .007$) and the olanzapine 5- to 10-mg/d group (31.5% [35/111]; $P < .001$) relative to the placebo group (3.6% [4/111]) and for the olanzapine 5- to 10-mg/d group relative to the olanzapine 2.5-mg/d group ($P = .006$). Mean ± SD baseline-to-endpoint changes in hepatic enzymes were significantly greater for the olanzapine 5- to 10-mg/d group relative to the placebo group (alanine aminotransferase/serum glutamic pyruvic transaminase: 6.78 ± 18.07 U/L vs −0.45 ± 9.22 U/L, $P < .001$; and γ-glutamyltransferase: 2.48 ± 12.90 U/L vs −0.48 ± 9.89 U/L, $P = .041$). The incidence of treatment-emergent abnormally high levels of alanine aminotransferase/serum glutamic pyruvic transaminase at any time was significantly higher for the olanzapine 5- to 10-mg/d group relative to the placebo group (5.1% [7/137] vs 0% [0/131]; $P = .015$).

Electrocardiogram. No significant differences were observed between treatment groups on any of the electrocardiogram measures. Analysis of potentially clinically significant changes in QTc intervals did not reveal any significant differences between treatment groups.

Extrapyramidal symptoms. No significant group differences were observed with respect to baseline-to-endpoint changes in extrapyramidal symptoms.

DISCUSSION

Four main findings have emerged from this study. The first is that moderate doses (5–10 mg/d) of olanzapine were more effective than placebo in reducing the overall severity of borderline psychopathology. This result was found across multiple analyses, including last-observation-carried-forward mean change from baseline ZAN-BPD total score, response rate, and time to response. In contrast, low-dose olanzapine (2.5 mg/d) did not differ significantly from placebo on any of these 3 outcomes. However, it should be noted that there is some evidence that the effect of olanzapine at a moderate dose may become attenuated over time.

The second major finding is that both low and moderate doses of olanzapine ameliorated the severity of irritability and suicidality symptoms to a greater degree than did placebo. These symptom-specific findings are consistent with those of prior controlled studies of olanzapine and borderline personality disorder.[3,10–12] These findings are also clinically important because irritability and suicidality are among the most problematic symptoms for patients with borderline personality disorder, their families, and the clinicians treating them.

The third major finding is that patients treated with low and moderate doses of olanzapine improved to a greater extent in various areas of psychosocial functioning relative to placebo. Both dose levels were superior to placebo in terms of improved family functioning. Moderate-dose olanzapine was also superior to placebo in improving work/school achievement. In addition, low-dose olanzapine improved social functioning significantly more than placebo; however, the fact that this last finding was not corroborated with a similar finding at the higher dose suggests that this finding should be interpreted with caution. Nevertheless, these psychosocial results are not surprising, as one might

Table 5. Treatment-Emergent Categorical Changes in Body Mass Index and Glucose and Lipids Parameters[a,b]

	Olanzapine 2.5 mg/d			Olanzapine 5–10 mg/d			Placebo		
Measure	Total N	Baseline Abnormal, n (%)	Postbaseline Abnormal, n (%)[c]	Total N	Baseline Abnormal, n (%)	Postbaseline Abnormal, n (%)[c]	Total N	Baseline Abnormal, n (%)	Postbaseline Abnormal, n (%)[c]
Body mass index ≥ 25	148	68 (45.9)	7 (8.8)	144	64 (44.4)	17 (21.3)[d,e]	146	75 (51.4)	3 (4.2)
High glucose	104	0 (0)	1 (1.0)	104	2 (1.9)	1 (1.0)	105	5 (4.8)	4 (4.0)
Low HDL cholesterol	105	45 (42.9)	15 (25.0)	103	55 (53.4)	11 (22.9)	103	56 (54.4)	12 (25.5)
High LDL cholesterol	100	69 (69.0)	0 (0)	101	68 (67.3)	0 (0)	102	71 (69.6)	0 (0)
High triglycerides	105	32 (30.5)	2 (2.7)	103	32 (31.1)	2 (2.8)	103	29 (28.2)	0 (0)

[a]Approximately 30% of patients had no fasting measures of glucose and lipids at baseline or postbaseline, and could not be included in these analyses.
[b]Categorical definitions for changes from normal at baseline to abnormal at any time postbaseline:
Body mass index: baseline < 25, postbaseline ≥ 25;
Glucose: baseline < 100 mg/dL, postbaseline ≥ 126 mg/dL[26];
LDL cholesterol: baseline < 100 mg/dL, postbaseline ≥ 160 mg/dL[27];
HDL cholesterol (men): baseline ≥ 40 mg/dL, postbaseline < 40 mg/dL[27];
HDL cholesterol (women): baseline ≥ 50 mg/dL, postbaseline < 50 mg/dL[27];
Triglycerides: baseline < 150 mg/dL, postbaseline ≥ 200 mg/dL.[27]
[c]Among those who were normal at baseline.
[d]Olanzapine 5–10 mg/d versus placebo: $P = .003$.
[e]Olanzapine 5–10 mg/d versus olanzapine 2.5 mg/d: $P = .045$.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

expect interpersonal role-related functioning to improve as the severity of borderline psychopathology declines. However, the mechanism or mechanisms that underlie this relationship are not clear.

The fourth major finding is that the adverse events observed during olanzapine treatment were consistent with those reported in previous studies of olanzapine in other patient populations,[28,29] as well as those found in the variable-dose olanzapine–borderline personality disorder study.[12] Weight gain has been very commonly reported during treatment with olanzapine. Both olanzapine treatment groups experienced significantly greater mean weight gain and a higher incidence of weight gain ≥ 7% of baseline relative to the placebo group, with patients in the olanzapine 5- to 10-mg/d group showing greater weight gain than those in the olanzapine 2.5-mg/d group. In addition, a greater proportion of patients with a baseline body mass index < 25 who received olanzapine 5–10 mg/d gained enough weight to have a postbaseline body mass index ≥ 25 in comparison with the olanzapine 2.5 mg/d and placebo groups (21% vs 9% and 4%, respectively). It should be noted that over 40% of the patients in each group were overweight at baseline. No significant differences were observed between treatment groups in the incidence of treatment-emergent abnormal fasting glucose or lipids at any time during treatment. Again, it should be noted that over 60% of those in each group had high low-density lipoprotein cholesterol at baseline, over 40% had low high-density lipoprotein cholesterol, ≈ 30% had high triglycerides, and over 10% had elevated glucose levels at baseline. A large proportion of patients (≈ 32%) experienced decreases in the total number of abnormal parameters that may be associated with metabolic dysregulation, which may be due in part to participation in the structured clinical trial environment.

A risk-benefit ratio or likelihood of help or harm derived from the number-needed-to-harm and number-needed-to-treat estimates for ≥ 7% weight gain and treatment response (olanzapine 5–10 mg/d: 3.88/6.20 = 0.63) suggests that, although the probability of responding modestly is good, the probability of gaining weight is even greater. Given this finding, patients with borderline personality disorder and their prescribing physicians would be well advised to discuss the potential efficacy benefits of olanzapine relative to the potential risks of weight gain. Further, although no significant differences were observed between treatment groups with regard to glucose or lipids, close monitoring of these metabolic parameters in addition to changes in weight is recommended during treatment with olanzapine.

A number of limitations to the study should be noted. First, this study employed particularly stringent exclusion criteria. While borderline patients meeting criteria for psychotic disorders, bipolar disorder, and current depression have routinely been excluded from pharmacotherapy trials, the current study also excluded patients meeting current criteria for posttraumatic stress disorder, panic disorder, and obsessive-compulsive disorder, as well as odd cluster Axis II disorders, to focus results more clearly on any changes to borderline personality disorder and not some underlying comorbid disorder. However, in reality, many patients with borderline personality disorder do suffer from comorbid disorders. Thus, the results of this study may not generalize to patients with these concomitant disorders. Second, this study was limited to current outpatients. Along these lines, it should also be noted that surprisingly few of the patients in the study were receiving concomitant psychotherapy (n = 10). Third, while over 60% of each study group completed the trial, the 30%–39% dropout rates that were found limit the confidence that we can place in our findings. Specifically, incomplete data pose concerns about potential selection bias. Although selection bias cannot be ruled out, we note that the dropout rates were comparable across study groups. Fourth, the issue of treatment resistance was not assessed in the current study. Recent research has shown that younger age (less than 26 years) is one of the best predictors of a faster time to remission of borderline personality disorder,[30] while older

age may be associated with greater treatment resistance. Mean age of the patients in the current study was 33 years.

The present findings should be considered alongside those from a second study, conducted in parallel, comparing variably dosed olanzapine (2.5–20 mg/d) with placebo.[12] No significant differences were observed between the treatment groups in mean change from baseline to last-observation-carried-forward endpoint in ZAN–BPD total score or in the percentage who experienced at least a 50% decline in their ZAN-BPD total score. However, time to reach the ≥ 50% response criterion was statistically significantly shorter for patients treated with olanzapine relative to placebo. In addition, mean last-observation-carried-forward improvements from baseline to endpoint were statistically significantly greater for olanzapine-treated than for placebo-treated patients on ZAN-BPD intense anger, OAS-M irritability, Sheehan family life, and SCL-90-R hostility scores.

The reasons for these between-study differences on our primary outcome are unclear. However, the authors of the variably dosed study[12] speculated that, when given the flexible dosing option, the investigators may not have increased doses sufficiently to achieve optimal efficacy. Results from the present study would appear to lend some support to that hypothesis in that the 2.5-mg/d dose was less effective than the 5- to 10-mg/d dose. Thus, future studies might use a starting dose of 5 mg/d or, if starting at 2.5 mg/d, ensure titration to at least 5 mg/d. Nevertheless, both studies found that olanzapine was modestly superior to placebo in decreasing anger and irritability and improving functioning as a family member, and, regardless of dose group, mean ZAN-BPD total scores indicated mild symptom severity at 12 weeks of treatment.

Taken together, the results of this study suggest that olanzapine 5–10 mg/d may be a modestly effective tool in the treatment of overall borderline psychopathology. These results also suggest that the types of adverse events observed in those patients treated with olanzapine, particularly weight gain, appeared similar to those seen previously in other diagnostic groups treated with olanzapine.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), lorazepam (Ativan and others), olanzapine (Zyprexa).

Author affiliations: McLean Hospital, Harvard Medical School, Boston, Massachusetts (Dr Zanarini); Department of Psychiatry, University of Minnesota Medical School, Minneapolis (Dr Schulz); and Lilly Research Laboratories, Indianapolis, Indiana (Drs Detke, Tanaka, Zhao, Lin, Kryzhanovskaya, and Corya), and Brussels, Belgium (Dr Deberdt).

Study investigators: Lawrence W. Adler, MD, Clinical Insights, Inc, Glen Burnie, MD, USA; G. Asnis, MD, Montefiore Medical Center, Bronx, NY, USA; Jason Baron, MD, Medlab, Houston, TX, USA; Ronald Brenner, MD, Neurobehavioral Research, Inc, Lawrence, NY, USA; Emil F. Coccaro, MD, University of Chicago, Chicago, IL, USA; John M. Downs, MD, Clinical Trials of Memphis, Inc, Memphis, TN, USA; Robert Friedel, Panic, Anxiety, & Depression Center, Richmond, VA, USA; Saleem Ishaque, MD, Synergy Clinical Research, National City, CA, USA; Arif A. Khan, MD, Northwest Clinical Research Center, Bellevue, WA, USA; Anne Gilbert, MD, Indianapolis Psychiatric Associates, Indianapolis, IN, USA; James Knutson, MD, Eastside Therapeutic Resources, Kirkland, WA, USA; Joseph Kwentus, MD, University of Mississippi School of Medicine, Jackson, MS, USA; Michael T. Levy, MD, Behavioral Medical Research of Staten Island, Staten Island, NY, USA; Thomas H. McGlashan, MD, Yale Psychiatric Research, New Haven, CT, USA; Denis B. Mee-Lee, MD, Hawaii Clinical Research Center, Honolulu, HI, USA; Ziad Nahas, MD, Medical University of South Carolina, Charleston, SC, USA; Bruce Pfohl, MD, University of Iowa, Iowa City, IA, USA; Brady J. Schroer, MD, Stormont-Vail West Outpatient, Topeka, KS, USA; David Rissmiller, MD, UMDNJ-New Jersey Medical School, Cherry Hill, NJ, USA; Angelo Sambunaris, MD, Atlanta Institute of Medicine and Research, Marietta, GA, USA; Fred Schaerf, MD, PhD, Neuropsychiatric Research Center of Southwest Florida, Fort Meyers, FL, USA; S. Charles Schulz, MD, University of Minnesota Medical School, Minneapolis, MN, USA; Scott Segal, MD, Segal Institute for Clinical Research, North Miami, FL, USA; Paras Harshawat, MD, Clinico, Terre Haute, IN, USA; Andrew Winokur, MD, PhD, University of Connecticut School of Medicine, Farmington, CT, USA; Mary Zanarini, EdD, McLean Hospital, Belmont, MA, USA; Benny L. Barnhart, MD, Grayline Clinical Drug Trials, Wichita Falls, TX, USA; William McEntee, MD, Roskamp Institute, Sarasota, FL, USA; Perdro Gargoloff, MD, Clinica San Juan, Buenos Aires, Argentina; Gerardo M. Garcia Bonetto, MD, Clinica Saint Michael, Cordoba, Argentina, Miguel Marquez, CRF Investigaciones Clinicas, Buenos Aires, Argentina; Alberto Bertoldi, Clinica San Agustin, Buenos Aires, Argentina; Carlos Alberto Finkelsztein, MD, Hospital Italiano, Buenos Aires, Argentina; Antonio Menchaca, MD, Instituto Neuropsiquiatrico de Chile, Santiago, Chile; Sergio Gloger, MD, Psychomedical Research Group, Santiago, Chile; Pablo Arancibia, MD, Clinica Psiquiatrica de la Universidad de Chile, Santiago, Chile; Prof Alberto Siracusano, Clinica Sant' Alessandro, Rome, Italy; A/Prof Carlo Maggini, Istituto Di Clinica Psichiatrica-Ospedale Ugolina Da Neviano, Parma, Italy; A/Prof Francesco Barale, Universita Di Pavia, Pavia, Italy; Maria Elena Ridolfi, MD, ASUR Marche Zona Distrettuale 3, Fano, Italy; Luis A. Vilchez, MD, Asociacion Civil Lazos, Lima, Peru; Carlos E. Mendoza, MD, Consultorio Privado, Lima, Peru; William Aguilar, MD, Asociacion Civil Lazos, Lima, Peru; Julio Acha, MD, Consultorio Particular Julio Acha, Lima, Peru; Isabel Aspilcueta, MD, Consultorio Particular I. Aspilcueta, Arequipa, Peru; Hector Chue, MD, Clinica Pinel, Lima, Peru; Zoila Pacheco, MD, Hospital Nac Guillermo Almenara Irigoyen, Lima, Peru; Jaroslaw Laczkowski, MD, Wojewodzki Osrodek Lecaznictwa Psychiatriyczengo, Turon, Poland; Andrzej Czernikiewicz, MD, Samodzielny Publiczny Psychiatryczny Zaklad Opieki Zdorwotne, Choroszcz, Poland; Prof Petru Boisteanu, MD, Spitalul Clinic de Psihiatrie Socola, Iasi, Romania; Prof Dan Prelipceanu, MD, Spitalul Clinica de Psihiatrie Al. Obregia, Bucharest, Romania; Mirela Manea, MD, Spitalul Clinic de Psihiatrie Al. Obregia, Bucharest, Romania; Prof Bilgin Saydam, Istanbul University, Istanbul, Turkey; Celso Gonzalez, MD, Hospital Universitario De Caracas, Caracas, Venezuela; Xiorella Mazarella, MD, Proyecto Redes, Caracas, Venezuela; Eloy Silvio Pomenta, Instituto Medico Psicologico Campo Alegre, Caracas, Venezuela; Isabel Laprea, Consulta Privada, Barcelona, Venezuela; Alfonso Idalberto, MD, Grupo Medico Santa Rosalia, Barcelona, Venezuela; Yepez Aglay, Unidad De Psicopedgogia "Aprendiendo A Crecer," Caracas, Venezuela.

Potential conflicts of interest: **Dr Zanarini** has received grant/research support from Eli Lilly. **Dr Schulz** has been a consultant for Eli Lilly and has received grant/research support from Eli Lilly and AstraZeneca. **Drs Detke**, **Tanaka**, **Deberdt**, and **Kryzhanovskaya** are employees and stock shareholders of Eli Lilly. **Drs Zhao**, **Lin**, and **Corya** are employees of Eli Lilly.

Funding/support: This work was sponsored by Eli Lilly and Company.

Disclaimer: The findings described in this article are based on a single trial, and olanzapine is not approved by any regulatory agency for the treatment of borderline personality disorder.

Previous presentation: Presented at the 160th Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, California.

Acknowledgments: The authors thank the F1D-MC-HGKK Study Group investigators for their significant contributions to site management and data collection. We also thank the F1D-MC-HGKK clinical operations team, who are all employees of Eli Lilly and Company, for project management.

REFERENCES

1. Zanarini MC, Frankenburg FR, Hennen J, et al. Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. *J Clin Psychiatry*. 2004;65(1):28–36.
2. Benedetti F, Sforzini L, Colombo C, et al. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. *J Clin Psychiatry*. 1998;59(3):103–107.
3. Bogenschutz MP, George Nurnberg H. Olanzapine versus placebo

in the treatment of borderline personality disorder. *J Clin Psychiatry*. 2004;65(1):104–109.
4. Chengappa KN, Ebeling T, Kang JS, et al. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. *J Clin Psychiatry*. 1999;60(7):477–484.
5. Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. *Compr Psychiatry*. 1993;34(6):402–405.
6. Nickel MK, Muehlbacher M, Nickel C, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2006;163(5):833–838.
7. Rocca P, Marchiaro L, Cocuzza E, et al. Treatment of borderline personality disorder with risperidone. *J Clin Psychiatry*. 2002;63(3):241–244.
8. Schulz SC, Camlin KL, Berry SA, et al. Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. *Biol Psychiatry*. 1999;46(10):1429–1435.
9. Soler J, Pascual JC, Campins J, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am J Psychiatry*. 2005;162(6):1221–1224.
10. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. 2001;62(11):849–854.
11. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry*. 2004;65(7):903–907.
12. Schulz SC, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. *Br J Psychiatry*. 2008;193(6):485–492.
13. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for* DSM-IV-TR *Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2001.
14. Zanarini MC, Frankenburg FR, Sickel AE, et al. *The Diagnostic Interview for* DSM-IV *Personality Disorders (DIPD-IV)*. Belmont, MA: McLean Hospital; 1996.
15. Zanarini MC, Vujanovic AA, Parachini EA, et al. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of *DSM-IV* borderline psychopathology. *J Pers Disord*. 2003;17(3):233–242.
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
17. Coccaro EF, Harvey PD, Kupsaw-Lawrence E, et al. Development of neuropharmacologically based behavioral assessments of impulsive aggressive behavior. *J Neuropsychiatry Clin Neurosci*. 1991;3(2):S44–S51.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:34.
19. Derogatis LR. *SCL-90-R, Brief Symptom Inventory, and Matching Clinical Rating Scales. The Use of Psychological Testing for Treatment Planning and Outcome Assessment*. New York, NY: Lawrence Erlbaum; 1994:41–80.
20. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(suppl 3):89–95.
21. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand*. 1970;45(S212): 11–19.
22. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154(5):672–676.
23. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:534–537.
24. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109–117.
25. Eli Lilly and Company. Clinical Study Summary: Study F1D-MC-HGKK. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized double-blind comparison with placebo. http://www.clinicalstudyresults.org/documents/company-study_2339_0.pdf. Verified February 18, 2011.
26. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2004;27(suppl 1):S15–S35.
27. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143–3421.
28. Tohen M, Sanger TM, McElroy SL, et al; The Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry*. 1999;156(5):702–709.
29. Tohen M, Jacobs TG, Grundy SL, et al; The Olanzipine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2000;57(9):841–849.
30. Zanarini MC, Frankenburg FR, Hennen J, et al. Prediction of the 10-year course of borderline personality disorder. *Am J Psychiatry*. 2006;163(5):827–832.