Olanzapine Plus Dialectical Behavior Therapy for Women With High Irritability Who Meet Criteria for Borderline Personality Disorder: A Double-Blind, Placebo-Controlled Pilot Study

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Objective: This double-blind study examined whether olanzapine augments the efficacy of dialectical behavior therapy (DBT) in reducing anger and hostility in borderline personality disorder patients.

Method: Twenty-four women with borderline personality disorder (DSM-IV criteria) and high levels of irritability and anger received 6 months of DBT. Subjects were randomly assigned to receive either low-dose olanzapine or placebo and were assessed with standardized measures in a double-blind manner. The study was conducted from September 2000 to December 2002.

Results: Intent-to-treat analyses indicated that both treatment conditions resulted in significant improvement in irritability, aggression, depression, and self-inflicted injury ($p < .01$ for each). Irritability and aggression scores tended ($p < .10$) to decrease more quickly for the olanzapine group than for the placebo group. Self-inflicted injury tended ($p < .10$) to decrease more for the placebo group than for the olanzapine group.

Conclusions: Olanzapine may promote more rapid reduction of irritability and aggression than placebo for highly irritable women with borderline personality disorder. Effect sizes were moderate to large, with the small sample size likely limiting the ability to detect significant results. Overall, there were large and consistent reductions in irritability, aggression, depression, and self-injury for both groups of subjects receiving DBT.

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Borderline personality disorder is characterized by emotional dysregulation, chaotic interpersonal functioning, and self-destructive and impulsive behaviors. Irritability and anger are particularly high among these individuals and may be an underlying factor that compromises treatment in this extremely difficult-to-treat population. Anger is both one of the highest sources of therapist stress and a predictor for early dropout from treatment.[1,2] Low-dose regimens of antipsychotics, like haloperidol, have been shown to be efficacious in reducing hostility and irritability in borderline personality disorder patients.[3,4]

Olanzapine, a novel antipsychotic, has been shown to be more efficacious than haloperidol in decreasing mean hostility scores and suicidal thinking in patients with schizophrenia.[5] The advantages of olanzapine in the treatment of borderline personality disorder are that it is both safe and generally has fewer side effects than conventional antipsychotic medications. In an open trial of olanzapine (mean dose = 7.73 mg) for patients with borderline personality disorder and dysthymia, Schulz and

colleagues[6] found that global ratings of anger went down over time. Since then, there have been 4 double-blind randomized trials evaluating olanzapine as a treatment for borderline personality disorder. Zanarini and colleagues have conducted 2 trials finding olanzapine efficacious in reducing anger and hostility[7] (average dose = 3.3 mg), as well as impulsive aggression[8] (average dose = 5.3 mg), in borderline personality disorder patients without concurrent major depressive disorder. Bogenschutz and Nurnberg[9] found olanzapine (mean dose = 6.9 mg) efficacious in reducing the inappropriate anger borderline personality disorder criterion. Soler and colleagues[10] found olanzapine (mean dose = 8.8 mg) efficacious in reducing impulsive aggression in a study in which all subjects were enrolled in concomitant dialectical behavior therapy (DBT). This latest finding is particularly important because the reductions in impulsive aggression were over and above the effects of DBT, which, at present, is the best-researched psychosocial treatment for borderline personality disorder with 6 randomized trials to date indicating its effectiveness.[11,12] DBT has also been shown to reduce anger and hostility among borderline personality disorder patients.[12–14] To date, however, no studies of olanzapine nor of DBT have selected borderline personality disorder patients specifically with excessive anger. Although inappropriate, intense anger or lack of control of anger is a criterion behavior of borderline personality disorder, meeting this criterion is not necessary to have the diagnosis. Given the important role of anger in interfering with treatment success, the current study explores the efficacy of olanzapine on reducing anger, irritability, and assaultive behaviors among angry women being treated with a 6-month regimen of DBT.

METHOD

Patients

Individuals were recruited from mental health clinics and by newspaper advertisements in Seattle area newspapers. For inclusion in the study, patients were required to be women aged 18 to 60 who met the following criteria: (1) diagnosis of borderline personality disorder according to 2 structured interviews, the Personality Disorder Examination[15] and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)[16]; (2) met borderline personality disorder criterion for inappropriate anger on the SCID II; and (3) scored 6 or higher on the irritability subscale of the Overt Aggression Scale-Modified for Outpatients (OAS-M).[17] Individuals were excluded if they (1) had a present diagnosis of schizophrenia, bipolar I disorder, schizoaffective disorder, major depressive disorder with psychotic features or other psychotic disorder, mental retardation or seizure disorder, or a diagnosis of substance dependence in the last 6 months according to the DSM-IV[18]; (2) had an episode of self-inflicted injury (including a suicide attempt) in the 8 weeks prior to the screening interview; or (3) were pregnant, breastfeeding, or planning to become pregnant. All patients provided informed consent using protocols approved by the University of Washington Human Subjects Division. The study was conducted from September 2000 to December 2002 and prior to general requirements for clinical trial database registration.

Following a brief telephone screening interview, potential patients were invited for an in-person screening interview. Patients then had a physical examination and laboratory analyses, including serum chemistry studies, hematologic indices, a drug screen, and a pregnancy test. Of 44 in-person interviews, 24 (55%) were accepted into the study, with the remaining deemed ineligible for one of the following reasons: did not meet criteria for borderline personality disorder (N = 5), met criteria for an excluded mental disorder (N = 2), did not complete pretreatment and/or medical evaluation (N = 5), completed pretreatment but never returned (N = 2), or other (N = 6). The initial sample of 24 patients was randomly assigned to DBT plus olanzapine or DBT plus placebo, with 12 in each condition.

Olanzapine and Placebo Conditions

A psychiatrist acted as the pharmacotherapist throughout the study. At treatment start, all patients were given 1 tablet per day of study medication. Each tablet contained either 5 mg of olanzapine or matching inert placebo as determined by a random number sequence. After the first week of treatment, the daily dose was adjusted upward or downward in response to perceived response and side effects by 2.5 to 5 mg with an allowed dosage range of 2.5 to 15 mg per day. To enhance compliance, tablets were given in RemindRx (IBV Technologies, Seattle, Wash., 2003) prescription bottles programmed to sound a sequence of alarms when medications were due, terminating only when the medication top was removed. During treatment, dosage adjustments were made as necessary. The final mean ± SD daily dose for patients in the olanzapine condition was 4.46 ± 1.16 mg. Patients, psychotherapists, pharmacotherapist, and assessment interviewers were kept naive to medication assignment. At the end of the study, the pharmacotherapist and interviewers were unable to guess group assignment above chance ($\kappa \leq .00$, not significant).

Behavioral Treatment

All patients were provided DBT, a comprehensive cognitive-behavioral intervention developed specifically for borderline personality disorder. DBT was applied according to treatment manuals developed by M.M.L. and adapted to address irritation and aggressive behavior patterns.[19,20] DBT applies directive, problem-oriented techniques that are balanced with supportive techniques, such

as reflection, empathy, acceptance, and emphasis on the client's inherent ability to access an internal "wise mind." In addition, dialectical strategies are employed, including balancing acceptance with change, alternating validation with problem solving, and using paradox and metaphor. Individual DBT targets dysfunctional behaviors in hierarchical order (suicidal, therapy-interfering, and quality-of-life interfering behaviors) and replacing those behaviors with skillful behaviors learned in a psychoeducational skills group. In treating patients identified as having high levels of irritability, irritable response patterns become the primary quality-of-life behavior target, particularly irritability that leads to aggressive acts. Within this category of behaviors, a series of targets were identified that were the focus of individual sessions in the following order of importance: (1) stopping physical assaults; (2) decreasing verbal assaults or "abuse"; (3) decreasing expressed irritability; (4) decreasing experienced anger, irritability, and hostility; and (5) decreasing willfulness. DBT skills taught included mindfulness, interpersonal effectiveness, distress tolerance, and emotion regulation. Those skills particularly likely to decrease the experience of irritation or inhibit or block aggression were highlighted in skills coaching and teaching.

Assessment Procedure

The OAS-M was used to measure irritability/anger, aggression, and suicidality during the week preceding the assessment interview.[17] We computed OAS-M subscale scores on physical aggression, a weighted sum of the number of physically aggressive acts against objects and others, and verbal aggression, a weighted sum of the number of verbally aggressive acts. For irritability/anger, we used the OAS-M Global Subjective Irritability score, which is an interviewer rating (on a 6-point Likert scale) of the intensity and frequency of feelings of anger and irritability. Suicidality is measured on the OAS-M with an interviewer rating (on a 7-point Likert scale) of the intensity and frequency of suicidal thoughts and actions. For intentional self-injury, we used the OAS-M Assaults Against Self score, which is a weighted sum of the number of acts such as hitting, biting, cutting, and bruising oneself. The Therapist Monitoring Record, which includes the OAS-M aggression items, was coded after each psychotherapy session (by the therapist) indicating whether each aggressive behavior occurred since the last session. Physical and verbal aggression Therapist Monitoring Record scores were computed in the same manner as the OAS-M. The Therapist Monitoring Record also includes ratings of suicidality, self-injury, hospitalization, and other important outcomes such as substance use. Depression was measured with the Hamilton Rating Scale for Depression (HAM-D).[21] The Somatic Symptom Scale (available from the authors on request) was rated by the pharmacotherapist at each medication visit. The OAS-M and HAM-D were given at pretreatment (time 0) and at weeks 7 (time 1), 14 (time 2), and 21 (time 3). Independent clinical interviewers, naive to the subjects' treatment conditions, administered the OAS-M and the HAM-D.

Data Analysis Methods

Outcomes were intent-to-treat analyses using random-effects regression models (RRMs; also known as hierarchical linear models, random coefficient models, and multilevel linear models), methods that are appropriate with data having a nested or hierarchical structure: a within-subject level and a between-subject level.[22,23] These models compute the responses of each patient as a line with intercept (e.g., baseline response) and slope (e.g., rate of change over time) that is specific to each individual.[24] RRM makes use of all available data for all patients for a particular dependent variable, and subject-specific intercepts and slopes are treated as random effects. Differences in rates of change from baseline (i.e., the slopes) were compared for the 2 treatment groups (i.e., the time by condition interaction). A piecewise RRM was also tested to examine if the olanzapine group showed improvement faster (i.e., larger slopes within the first 7 weeks or the first 3 months) even if the slopes for both groups did not differ across the whole study.[25] Analyses were performed using HLM-5 (Scientific Software International, Lincolnwood, Ill.) and the SPSS MIXED procedure (SPSS, Inc., Chicago, Ill.). Due to skewed distributions, the OAS-M and the Therapist Monitoring Record were analyzed with RRM for ordinal data.[26] Following the approach of Hedeker and Mermelstein,[26] we categorized these variables at specified ordinal cut points. All tests were 2-tailed tests using robust standard errors. For the RRM analyses, we attempted to fit model with both a random intercept and a random slope. For many outcomes, there was insufficient between-person variability in the rate of change to model the random slope term, in which case we modeled solely a random intercept term, which accounts for the within-subject correlation by assuming any pair of data points within a subject are equally correlated (i.e., compound symmetry covariance structure).

RESULTS

Sample Description

Of the 24 patients, none reported a previous olanzapine trial. Mean ± SD age of patients was 36.8 ± 9.0 years. The majority of patients were white (79%, N = 19), 1 (4%) was African American, 1 (4%) was Native American, 1 (4%) was Latino, and 2 (8%) indicated "other." Seven patients were separated or divorced (29%), 4 patients were currently married (17%), and the remainder had never been married (54%). All patients completed high school or obtained a general equivalency diploma (GED), and 9 (38%) were college graduates.

Patients met criteria for a mean of 2.5 (SD = 1.7) current comorbid Axis I diagnoses, with 63% (N = 15) meeting criteria for major depressive disorder or dysthymic disorder, 83% (N = 20) for a current anxiety disorder, 13% (N = 3) for an eating disorder, and 4% (N = 1) for a current substance use disorder. On Axis II, 17% of the patients (N = 4) met criteria for antisocial personality disorder, 33% (N = 8) for avoidant personality disorder, 4% (N = 1) for dependent personality disorder, 4% (N = 1) for histrionic personality disorder, 0% (N = 0) for narcissistic personality disorder, 33% (N = 8) for obsessive-compulsive personality disorder, 25% (N = 6) for paranoid personality disorder, 0% (N = 0) for schizoid personality disorder, and 0% (N = 0) for schizotypal personality disorder. The mean global assessment of functioning (GAF) score was 43.7 (SD = 6.1), indicating serious impairment across the sample. The majority of the sample (71%, N = 17) reported a history of at least 1 suicide attempt or intentional self-injury, and 38% (N = 9) reported both behaviors. More patients in the placebo group met criteria for an anxiety disorder (100% [N = 12] vs. 67% [N = 8], $\chi^2 = 4.80$, df = 1, p = .028), but no other significant between-group differences were detected for other diagnoses, level of general functioning (GAF ratings), or self-inflicted injuries prior to treatment.

Treatment Retention

Eight patients (33%: 4 olanzapine, 4 placebo) dropped out of DBT and consequently were not continued on medication. Five of those (21% of total) also dropped out of the assessment sequence before the final assessment; 4 (17%) missed the time-2 and time-3 assessments and 1 missed only the time-3 assessment. One patient, assigned to the olanzapine condition, dropped out due to pregnancy (at week 10). In addition, 1 patient assigned to the olanzapine condition was removed from the study at week 7 due to psychotic symptoms (she was not counted as a dropout). Although she was subsequently treated effectively with a higher dose of olanzapine, no further assessments were conducted. There was no statistically significant between-condition difference in dropout rate.

Anger and Aggression Outcomes

Table 1 presents a summary of the descriptive data, and Table 2 presents all the RRM analyses. Analyses of overall slopes indicated that scores on the aggression and irritability variables improved significantly during treatment for both conditions. Verbal aggression, physical aggression, and irritability decreased significantly over time. Medium effect sizes for the differences in overall slopes of physical aggression, verbal aggression (Therapist Monitoring Record), and irritability scores suggest larger decreases in scores for olanzapine-treated subjects during the study; however, between-condition differences on these variables were not significant. Piecewise RRM analyses indicated that irritability scores of subjects assigned to the olanzapine treatment tended to reduce more quickly than the scores of those assigned to placebo by the assessment at week 7. Similarly, according to the weekly Therapist Monitoring Record, physical aggression scores tended to decrease more quickly for olanzapine-treated subjects than subjects assigned to placebo through the third month.

Table 1. Descriptives for Aggression and Irritability Variables in Irritable Women With Borderline Personality Disorder (N = 24)

Variable	Olanzapine (N = 12)	Placebo (N = 12)
Physical aggression score, median (IR)[a]		
Overt Aggression Scale		
Pretreatment	5.5 (0.5–13.5)	6.0 (2.0–42.5)
Week 7	2.0 (0.0–6.0)	7.0 (0.5–25.3)
Week 14	2.0 (0.0–5.8)	1.0 (0.0–6.8)
Week 21	0.0 (0.0–0.0)	2.0 (0.0–16.0)
Therapist Monitoring Record		
Month 1	0.0 (0.0–1.4)	1.1 (0.0–5.3)
Month 2	0.0 (0.0–0.0)	0.0 (0.0–3.0)
Month 3	0.0 (0.0–0.0)	0.0 (0.0–1.1)
Month 4	0.0 (0.0–0.0)	0.0 (0.0–0.5)
Month 5	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Verbal aggression score, median (IR)		
Overt Aggression Scale		
Pretreatment	20.0 (8.3–30.8)	23.0 (11.5–69.8)
Week 7	9.0 (5.0–24.5)	27.5 (10.5–40.3)
Week 14	4.0 (2.0–14.3)	15.5 (3.8–50.3)
Week 21	9.0 (3.0–13.8)	9.0 (3.0–25.0)
Therapist Monitoring Record		
Month 1	1.3 (0.6–2.9)	1.9 (0.4–3.9)
Month 2	1.0 (0.0–2.8)	2.5 (0.0–3.0)
Month 3	0.8 (0.0–1.8)	1.2 (0.6–3.3)
Month 4	0.2 (0.0–2.1)	0.8 (0.3–1.8)
Month 5	0.8 (0.0–1.6)	0.2 (0.0–1.8)
Irritability score: Overt Aggression Scale, median (IR)		
Pretreatment	7.0 (6.0–8.0)	6.5 (6.0–8.0)
Week 7	5.0 (2.3–6.0)	6.5 (5.0–7.0)
Week 14	5.0 (4.0–6.0)	5.5 (3.8–7.3)
Week 21	3.5 (3.0–5.0)	4.5 (4.0–7.5)
High[b] suicidality: Overt Aggression Scale, %		
Pretreatment	41.7	50.0
Week 7	33.4	9.3
Week 14	37.5	0
Week 21	25.0	12.5
Intentional self-injury, % yes		
Pretreatment	33.3	33.3
Week 7	16.7	25.0
Week 14	12.5	0
Week 21	25.0	12.5
Hamilton Rating Scale for Depression score, mean (SD)		
Pretreatment	20.4 (9.0)	19.3 (7.1)
Week 7	14.7 (8.4)	15.2 (7.3)
Week 14	11.5 (7.1)	13.3 (7.0)
Week 21	12.6 (7.2)	15.4 (5.8)

[a]Physical aggression includes physical aggression against objects and other people (i.e., assault), but does not include self-harm.
[b]High suicidality is defined as a report of frequent suicide ideation and/or planning or behavior.
Abbreviation: IR = interquartile range.

Table 2. Effect Size Estimates for Aggression and Irritability Variables[a]

Variable	Overall Slopes[b]				Piecewise RRM Analyses of Slopes for First Time Phase[c]		
	Pooled	Olanzapine	Placebo	Difference[d]	Olanzapine	Placebo	Difference[d]
Physical aggression							
Overt Aggression Scale	–1.02****	–1.33***	–0.77**	–0.56	–0.44	–0.33	–0.11
Therapist Monitoring Record	–1.39***	–1.82*	–1.30***	–0.52	–2.12***	–0.84**	–1.35*
Verbal aggression							
Overt Aggression Scale	–1.11****	–1.05***	–1.23****	0.18	–0.41	–0.17	–0.23
Therapist Monitoring Record[e]	–1.40***	–1.79***	–1.11	–0.68	–1.16****	–0.50	–0.65
Irritability: Overt Aggression Scale	–1.32****	–1.70****	–0.99***	–0.72	–1.37****	–0.51	–0.86*
Suicidality: Overt Aggression Scale	–0.49	–0.07	–0.93*	0.85	…	…	…
Intentional self-injury	–1.12***	–0.52	–1.99***	1.48*	…	…	…
Hamilton Rating Scale for Depression[f]	–0.80**	–0.69**	–0.44	–0.20	…	…	…

[a]All variables were analyzed with RRMs. Slopes represent the amount of change over time with a negative sign indicating that scores decreased over time. The pooled slope represents the overall amount of change regardless of treatment condition. Effect size estimates reported here indicate the total amount of pre-to-post change: 0.2 = small effect; 0.5 = moderate effect; 0.8 = large effect. For all analyses, robust standard errors were used, and 2-tailed p values are reported.
[b]These analyses examined slopes based on all available data across all time points.
[c]These piecewise RRM analyses examined slopes across the first 3 months for Therapist Monitoring Record data and slopes comprising the pretreatment and week 7 Overt Aggression Scale-Modified for Outpatients data.
[d]The difference in slopes between the olanzapine and placebo groups was tested by the treatment-by-time interaction effect, estimated by RRM. A negative sign indicates that the decrease in the score was larger in the olanzapine condition.
[e]Slope and intercept both included as random effects in the model. All variables without this notation were tested with random intercept models (i.e., without slope as a random effect).
[f]This variable was analyzed with standard linear RRM. All variables without this notation were analyzed with ordinal RRM.
*p < .10.
**p < .05.
***p < .01.
****p < .001.
Abbreviation: RRM = random-effects regression model.
Symbol: … = not applicable.

Suicidality, Self-Injury, and Depression Outcomes

Suicidality was low throughout the study and did not decrease significantly over time for the sample as a whole (see Tables 1 and 2). Large effect sizes for the differences in overall slopes for both suicidality and self-injury suggest larger reductions in both suicidality and intentional self-injury in the placebo condition; these differences in overall slopes, however, were not significant. There was, however, a trend indicating a decrease in suicidality in the placebo condition, but there was no decrease in the olanzapine condition. Over the sample as a whole, there was a significant decrease in self-inflicted injury over time with a trend toward a significantly greater decrease in the placebo condition than in the olanzapine condition (see Table 2). There were no suicide attempts during the treatment period. The self-injurious behaviors were hitting, biting, scratching, head banging, and hitting fists against a wall. Depression scores improved, but there was no significant difference between conditions. There was, however, a significant decrease in depression in the olanzapine condition with no corresponding significant decrease in the placebo condition.

Olanzapine Side Effects

Patients reported a variety of somatic symptoms. Twice as many patients assigned to olanzapine reported dizziness than did patients assigned to placebo (67% [N = 16] vs. 33% [N = 8]), although the difference was not statistically significant (Fisher exact test, 1-tailed p = .110), and more olanzapine patients also reported more dizziness before the start of olanzapine (42% [N = 10] vs. 17% [N = 4]; Fisher exact test, 1-tailed p = .185). Patients assigned to olanzapine reported significantly distressing or incapacitating sedation more often than those assigned to placebo (42% [N = 10] vs. 8% [N = 2]; Fisher exact test, 1-tailed p = .077). Significantly more placebo patients reported severe nervousness than olanzapine patients (0% [N = 0] vs. 42% [N = 10]; Fisher exact test, 1-tailed p = .019), but this difference was present before the start of olanzapine (0% [N = 0] vs. 33% [N = 8]; Fisher exact test, 1-tailed p = .047). Olanzapine patients more often reported sexual dysfunction (33% [N = 8] vs. 0% [N = 0]; Fisher exact test, 1-tailed p = .047) and muscle stiffness (83% [N = 20] vs. 42% [N = 10]; Fisher exact test, 1-tailed p = .045), and the groups equally reported these symptoms before the start of olanzapine. More olanzapine-treated patients reported weight gain (92% [N = 22] vs. 58% [N = 14]; Fisher exact test, 1-tailed p = .077), and those assigned to olanzapine gained a mean of 2.3 lb (SD = 4.9 lb) whereas those assigned to placebo lost a mean of 2.9 lb (SD = 10.7 lb; t = 1.52, df = 22, p = .143). Patients who dropped out did not endorse any individual side effect significantly more than those patients who did not drop out.

DISCUSSION

Analyses of both significance levels and effects sizes suggest that olanzapine may be beneficial for reducing irritability and physical aggression in highly irritable women meeting criteria for borderline personality disorder. Patients assigned to olanzapine tended to have both larger and faster reductions in irritability over the course of medication treatment. Effect sizes for reductions in irritability by week 7 and over the entire treatment were quite large, near the 0.8 level noted by Cohen as a large effect.[27] On measures of physical aggression, effect sizes were slightly over 0.5, indicating a moderate effect of olanzapine over placebo. The failure to find statistical significance here was most likely due to the very small sample size resulting in low power to detect a medium treatment effect. When between-session behaviors were coded by therapists, however, the effect size was quite large (greater than 1), and patients assigned to olanzapine had a trend toward significantly faster reduction in overt physical aggression. Therapist-coded verbal aggression also showed medium effect sizes in favor of olanzapine. DBT, whether patients were receiving olanzapine or placebo, demonstrated large and consistent effect sizes, indicating reductions in physical and verbal aggression, irritability, and depression in DBT. Olanzapine was well tolerated in this population with dropout rates identical for the 2 conditions. Thus, the promise implicit in our findings is that olanzapine may provide an additive benefit in reducing aggression and irritability over and above the benefits of behavioral treatments.

Unexpected findings were that clinical evaluations of both self-inflicted injury and suicidality produced large effect sizes for differences in slopes, indicating that olanzapine might have slowed down improvements in suicidality compared to improvements found for DBT plus placebo. The incidence of intentional self-injury went down significantly in the placebo condition but not in the olanzapine condition. Over time, there was a trend for fewer people receiving placebo than olanzapine to report self-injury. Although suicidal ideation was extremely low to begin with, ideation went down at a trend level in the placebo condition but not in the olanzapine condition. These findings are interesting in light of the recent study by Meltzer et al.,[28] who found significantly greater reductions in suicidality among schizophrenic and schizoaffective patients taking clozapine versus olanzapine. While it might be tempting to interpret our results as suggesting a dampening effect of olanzapine on treating suicidality and self-injury among borderline personality disorder patients, it would be premature to do so. The small sample size, the low suicidality and self-injury, and findings that were opposite to predictions suggest that it would be wiser to test such new hypotheses in a subsequent study. Given the significant reductions in aggression with olanzapine, it is possible that both aggressive behavior and self-injurious behaviors function to regulate irritability and that as one goes down, the other goes down more slowly. The data are simply not sufficient in this study to test this hypothesis.

Our findings are very similar to those reported by Soler et al.,[10] who also compared olanzapine to placebo among patients in DBT. Although they found no significant differences in suicidal behaviors between the 2 conditions, the absolute score for suicidal behaviors was lower in the placebo condition. Unfortunately, they did not compare changes in outcome slopes over time and instead used posttest t tests, a procedure that might have missed important effects.

A limitation in this study is the small sample size. The random regression/hierarchical linear model is an advanced statistical framework. The extension to ordinal/binary outcomes puts even more sophistication on a complex modeling paradigm. While one may consider creating summary scores over longitudinal period, this approach does not use all the available data to gain a more complete understanding of the treatment dynamics. Despite the small sample size in our sample of 24 patients, the Institute of Medicine[29] provides guidelines to maximize information from this small trial in order to obtain reliable and valid results. They recommend several statistical approaches for small trials including our analytic approach, hierarchical models. The discussion of sufficient sample size for these models is still an active area of research.[30] Hedeker and Mermelstein[26] note that there is no global recommendation to what sample size should be in these models. On the basis of our study design, we examined Hedeker et al.,[31] Raudenbush,[32] and Raudenbush and Xiao-Feng[33] to confirm whether or not our design had sufficient power to detect clinically meaningful effects. Despite the low sample size, the design is sufficient to detect large effects. Nonetheless, reproducibility of these findings in a larger sample would be beneficial. Model diagnostics of residuals and model-based assumptions indicated no influential observations or outliers. It appears, for all outcomes, the models were appropriate and sufficiently modeled the data.

Drug names: clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.