Reduced Suicidal Ideation in Bipolar I Disorder Mixed-Episode Patients in a Placebo-Controlled Trial of Olanzapine Combined With Lithium or Divalproex

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Objective: To identify symptoms associated with suicidality in bipolar I disorder patients, and to assess suicide risk during treatment with olanzapine in combination with lithium or divalproex.

Method: We used data from a study (conducted from September 1997 to October 2000) in which DSM-IV bipolar I manic or mixed-episode patients who were partially responsive to at least 2 weeks of lithium or divalproex monotherapy prior to study entry were randomly assigned to augmentation therapy with olanzapine (5–20 mg/day) or placebo. Among mixed-episode patients with residual suicidality (Hamilton Rating Scale for Depression-item 3 [HAM-D-3] score of 1 or above) at randomization to cotherapy, we identified items in the Young Mania Rating Scale, Positive and Negative Syndrome Scale, and Barnes Akathisia Rating Scale that correlated with HAM-D-3 scores. We used factor analysis of correlated items to identify symptom domains associated with suicidality ratings and assessed changes in symptom factors and HAM-D-3 scores during 6 weeks of combination therapy with olanzapine versus placebo.

Results: In 58 mixed-episode patients, mean ± SD HAM-D-3 scores averaged 1.36 ± 0.55 after at least 2 weeks of initial mood stabilizer monotherapy prior to study entry. Factors associated with the HAM-D-3 appeared to represent somatic discomfort, agitated depression, and psychotic features. Combination therapy with olanzapine (N = 36) versus placebo (N = 22) differentially reduced HAM-D-3 scores by 58% versus 29% ($p < .05$) within 1 week, and all 3 associated symptom factors within 2 weeks by averages of 31% versus 12% ($p < .05$).

Conclusions: Suicidality in adult, mixed-episode, bipolar I disorder patients was associated with somatic discomfort, agitated depression, and psychosis. Overall, these findings suggest that the addition of an atypical antipsychotic-antimanic agent in some bipolar disorder patients may help to reduce suicidal ideation.

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Suicide rates in patients diagnosed with bipolar disorder are at least 20 times higher than in the general population.[1] Clinical factors associated with suicidal behavior in bipolar disorder include depression, dysphoric-agitated states, hopelessness,[1,2] and mixed episodes.[2–5] Suicidal ideation, ranging from ambivalence toward life to serious contemplation and planning for suicide, is more common in bipolar depressive (79%) or mixed states (26%–55%) than in pure mania (2%–7%).[2–5]

A recent meta-analytic review[6] of randomized, controlled trials of treatment for bipolar and other major mood disorders consistently revealed markedly lower rates (≥ 80%) of suicide and attempts with lithium, and a decreased ratio of suicides/attempts that suggests reduced lethality of attempts. This effect of lithium on suicide behavior appears to be superior to that of some anticonvulsants, which are widely employed also for proposed mood-stabilizing effects.[1,7–9] Reduced suicidal risk with long-term lithium treatment may reflect improvement in depressive symptoms or reduction in impulsivity, hostility, or aggressive tendencies.[9]

Except for clozapine,[10–12] no antipsychotic drug treatment has shown effectiveness in reducing suicidal risk.

Various types of antidepressants, including tricyclics and serotonin reuptake inhibitors, have shown superiority to placebo in reducing suicidal thinking[13–20] as documented with suicidality items in standard depression rating scales such as Hamilton Rating Scale for Depression,[21] item 3 (HAM-D-3), and Montgomery-Asberg Depression Rating Scale[22] (MADRS), item 10. There is also evidence that clozapine[10,23] and olanzapine[24,25] may reduce suicidal ideation among patients diagnosed with schizophrenia. However, the potential efficacy of atypical antipsychotics in the treatment of suicidal risk in bipolar disorder patients remains untested.

Tohen et al.[26] previously reported that suicidality ratings in olanzapine cotherapy groups versus placebo cotherapy groups were significantly more reduced in a randomized trial of adding olanzapine or placebo to the treatment regimen of subjects who had responded partially to initial treatment with lithium or divalproex prior to study entry. We focused on a post hoc analysis of change in baseline non-zero suicidality ratings (HAM-D-3 scores) obtained from the subset of mixed-episode bipolar I disorder patients in this study with initial non-zero suicidality ratings.

We propose that this prospective approach may minimize inaccuracies that arise in retrospective gathering of information following suicidal outcomes. We reasoned that an analysis of prospectively collected psychiatric rating scale item scores correlated with HAM-D-3 would identify specific clinical symptoms associated with suicidal ideation and would support assessment of the efficacy of adding olanzapine to lithium or divalproex in reducing suicidality ratings and associated symptoms.

METHOD

Study data were obtained from a double-blind, randomized trial conducted from September 1997 to October 2000 to determine the efficacy of adding 6 weeks of olanzapine versus placebo to ongoing monotherapy with lithium (steady-state daily trough serum concentration, 0.6–1.2 mEq/L) or divalproex (serum concentration, 50–125 μg/mL [350–870 μmol/L]) after at least 2 weeks of partial clinical response in patients with acute DSM-IV bipolar I mania (N = 165) or mixed episode (N = 169).[26] Diagnoses were based on the Structured Clinical Interview for DSM-IV–Patient Version[27] (SCID-P). Partial clinical response was indicated by Young Mania Rating Scale[28] (YMRS) total scores of 16 or above at week 2. Patients were randomly assigned 2:1 to receive olanzapine (5–20 mg/day) or placebo as an experimental adjunctive cotherapy. The study site institutional review board approved the protocol, and written informed consent was obtained from each subject prior to study participation.

This study was a post hoc analysis of 58 mixed-episode patients who had non-zero HAM-D-3 suicidality ratings at randomization to olanzapine or placebo cotherapy. Our intent was to identify residual symptoms that might be associated with suicidal thinking in mixed-episode patients, a diagnostic group with a high risk for suicidal behavior, and to observe changes in these symptoms during supplemental treatment with olanzapine versus placebo. We excluded mixed-episode patients with baseline zero HAM-D-3 suicidality ratings from the factor analysis, but separately evaluated increases in post-baseline HAM-D-3 scores for all mixed-episode patients during supplemental treatment. We also excluded patients with pure mania because they have low rates of suicidal ideation or behavior.[2–5]

At randomization, Pearson's correlation coefficients (r) were estimated for scores of the HAM-D-3 and individual items from clinical rating scales used in the original trial: HAM-D (21-item), YMRS, Positive and Negative Syndrome Scale[29] (PANSS), and Barnes Akathisia Rating Scale[30] (BARS). Significantly correlated items ($p < .05$) then underwent principal components factor analysis of variation. Resulting components with eigenvalues greater than 1.0 were retained, and rotated factors were calculated using the varimax method. Scores for each factor were calculated based on the loadings from the factor analysis at randomization. A mixed-effects model of repeated measures evaluated the impact of olanzapine versus placebo treatment across time on the HAM-D-3 and each factor score. The dependent variable was mean score, and the model included terms for investigator, treatment group, use of lithium versus divalproex, visit, and interaction of treatment group with visit. A random patient effect was included in the model to account for potential covariance of ratings from the same subjects over time and to reduce bias from dropouts. Percent reductions from baseline in the HAM-D-3 suicidality score and each factor score were calculated using pooled baseline values generated from the mixed model.

The proportion of patients with a score of zero ("absent") on HAM-D-3 suicidality ratings was compared between treatment groups at each visit (Fisher exact test). All statistical comparisons were conducted at a 2-tailed $\alpha = .05$ significance level. Statistical analyses employed standard commercial software (SAS 2005, SAS Institute, Cary, N.C.).

RESULTS

Patients

Initial characteristics of patients (N = 58) in a mixed episode with a HAM-D-3 suicidality score of 1.0 or above at the time of randomization to olanzapine versus placebo cotreatment with divalproex or lithium are summarized in Table 1. Most patients were white (84%), women (60%), aged 40 to 45 years, and nonpsychotic (66%). No patient left the trial due to suicidality; 42 of 58 eligible patients

Table 1. Characteristics of 58 Bipolar I Disorder Patients in Mixed Episodes With Residual Suicidality at Randomization to Adjunctive Treatment With Olanzapine vs. Placebo

Characteristic	Olanzapine Cotherapy (N = 36)	Placebo Cotherapy (N = 22)
Age, mean (± SD), y	40.2 (8.35)	41.2 (9.58)
Male, N (%)	13 (36.1)	10 (45.5)
White, N (%)	29 (80.6)	20 (90.9)
Nonpsychotic, N (%)	23 (63.9)	15 (68.2)
Baseline HAM-D item 3 (suicidality) score, mean (± SD)[a]	1.44 (0.61)	1.23 (0.43)
Baseline HAM-D total score, mean (± SD)	24.5 (7.64)	21.7 (5.19)
Baseline YMRS total score, mean (± SD)	23.1 (4.87)	21.9 (3.87)
Baseline BARS total score, mean (± SD)	0.64 (1.02)	0.41 (0.67)
Baseline PANSS score, mean (± SD)	75.8 (18.9)	72.3 (16.8)
Lithium therapy, N (%)	10 (27.8)	5 (22.7)
Divalproex therapy, N (%)	26 (72.2)	17 (77.3)

[a]Overall HAM-D item 3 (suicidality) score averaged 1.36 ± 0.55 at randomization to olanzapine vs. placebo cotherapy. None of these comparisons differs statistically between subjects randomized to olanzapine or placebo cotherapy.
Abbreviations: BARS = Barnes Akathisia Rating Scale, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

completed the trial (81% [29/36] given olanzapine versus 59% [13/22] given placebo). The mean ± SD daily dose of olanzapine was 11.9 ± 5.5 mg; divalproex and lithium were continued at doses yielding the previously stated range of serum drug concentrations.

HAM-D-3: Suicidality

Of the 58 patients with non-zero HAM-D-3 suicidality scores at randomization to cotherapy (overall mean ± SD score = 1.36 ± 0.55 of a potential maximum score of 4; olanzapine, 1.44 ± 0.61; placebo, 1.23 ± 0.43; $p = .148$), 39 (67%) had scored 1 (life is not worth living); 17 (29%) had scored 2 (wishes of death); 2 (3%) had scored 3 (thoughts of suicide); and none had scored 4 (suicide attempt). After 1 week of adjunctive treatment, mean ± SD suicidality scores were reduced significantly more with supplemental olanzapine (0.61 ± 0.17; 57.6% reduction) versus placebo (1.02 ± 0.19; 29.2% reduction; $p < .05$; Figure 1), and, respectively, 64% (23/36) versus 50% (11/22) of patients had HAM-D-3 suicidality scores of zero (absent; $p = .41$). Reductions in HAM-D-3 suicidality scores were greater with olanzapine versus placebo cotherapy at week 2 (0.43 ± 0.14 [70.1% reduction] versus 1.19 ± 0.18 [17.4% reduction]; $p < .001$) and week 3 (0.50 ± 0.15 [65.3% reduction] versus 1.44 ± 0.20 [0.0% reduction]; $p < .001$). Differences between cotherapies were not significant at weeks 4 to 6. The overall main treatment effect of olanzapine versus placebo was highly significant ($p = .005$), with no differences between adding supplemental treatment to lithium or divalproex ($p = .40$).

Mixed-episode patients with initial non-zero HAM-D-3 scores experienced at least 1 instance of increased (worsening) suicidality ratings during follow-up visits 3 times more often with placebo versus olanzapine supplementation (45.5%, 10/22 versus 13.9%, 5/36; $p = .013$), and this difference remained significant when similar patients with zero baseline HAM-D-3 scores were included in the analysis (44.4%, 24/54 versus 25.6%, 31/121; $p = .021$).

Factor Analysis

Of a combined total of 66 items from the HAM-D, YMRS, PANSS, and BARS rating scales, 9 were significantly correlated with the HAM-D-3 at randomization (Table 2). Principal components analysis of scores from these 9 items yielded 3 clusters of associated symptoms. These symptom factors appeared to represent the following clinical features: factor 1, somatic discomfort; factor 2, agitated depression; factor 3, psychotic features (Table 3). Factor 1 included the HAM-D items rating gastrointestinal discomfort, weight loss, and sexual dysfunction (loss of libido or menstrual disorder). Factor 2 included PANSS items rating depression and uncooperativeness and the BARS item rating subjective awareness of restlessness. Factor 3 involved PANSS items rating delusions and bizarre thoughts.

Changes in Suicidality Symptom-Factor Scores During Treatment

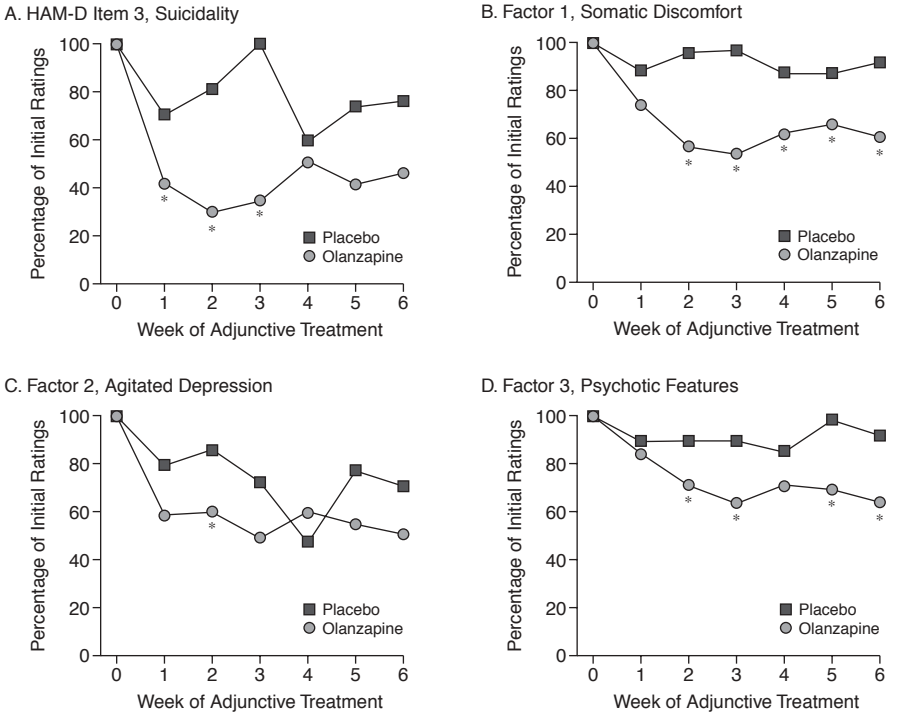
Possible scores for symptom factors calculated from individual rating scale items ranged as follows: factor 1, 0 to 13.4; factor 2, 0 to 15.5; factor 3, 0 to 16.5. At randomization to olanzapine versus placebo, the mean (and percentage of maximum possible) factor scores were as follows: factor 1, 4.6 (34.3%); factor 2, 1.8 (11.6%); factor 3, 6.0 (36.4%).

There were statistically significant improvements among patients randomized to olanzapine versus placebo cotherapy on all 3 symptom factors at week 2 of treatment. This olanzapine versus placebo cotherapy difference was sustained through week 6 for factor 1 (somatic discomfort) and, with the exception of week 4, for factor 3 (psychotic features). There were no significant differences between treatments in factor 2 (agitated depression) after week 2 (Figure 1).

DISCUSSION

Factor analysis of rating scale data from 58 DSM-IV bipolar I disorder patients in an acute mixed episode, who had HAM-D-3 scores of 1 or above after at least a 2-week pretrial phase with standard doses of divalproex or lithium, yielded 3 symptom factors associated with suicidality at the point of randomization to 6 weeks of placebo-controlled, combination therapy with olanzapine. These

Figure 1. Percent Change in Ratings of Suicidality and Associated Symptom Factors From Randomization in 58 Bipolar Mixed-Episode Patients Randomly Assigned to 6 Weeks of Supplemental Treatment With Olanzapine or Placebo After Only Partial Response to at Least 2 Weeks of Lithium or Divalproex Monotherapy[a]



[a]Subjects available (N) for analysis at weeks 1 through 6 were as follows: olanzapine (36, 34, 33, 31, 28, 29); placebo (22, 20, 19, 16, 14, 13).
*$p < .05$.

factors appeared to represent somatic discomfort (factor 1), agitated depression (factor 2), and psychotic features (factor 3), which are clinically plausible as being associated with suicidality.

Somatic discomfort (factor 1) had the strongest statistical association with suicidality. Such symptoms may well indicate clinically important states of subjective distress that may not be recognized clinically as risk factors for suicidal thinking or behavior. Somatic distress, including restlessness, has been suggestively associated with depression, mixed episodes, or suicidality in a number of studies.[31–34]

Agitated depression (factor 2) was intermediate in its association with suicidality. This factor combined 2 features, agitation and depression, each of which has been associated with suicidal behavior. Agitation, particularly when severe, may be an unusually strong short-term predictor of impending suicide.[35,36] In addition, bipolar disorder patients who attempt suicide are in a depressed state more often or more severely than patients without suicidal behavior.[1,37,38]

Psychotic features (factor 3) had the lowest loading on suicidality in the present analysis. This outcome probably reflects the low rate of psychosis (34%, 20/58) in this subsample of patients, as well as the entire sample included in the original trial.[26] The importance of psychotic features in mood disorder patients with suicidal thoughts and behavior has been suggested, but remains to be clarified.[35,39–42]

The lack of an association observed between suicidality and the clinical items not included in the 3 factors identified in this analysis merits further consideration. Some caution is appropriate with the PANSS items since this rating scale was developed for patients diagnosed with schizophrenia,[29] and patients with bipolar disorder would be expected to have low scores on items not characteristic of their disorder, particularly negative symptoms. On the other hand, it is striking and somewhat surprising that suicidality was not found to be associated with individual scale items rating mania (YMRS), nor with the HAM-D items dysphoria, insomnia, anhedonia, and decreased concentration or energy, particularly among mixed-episode patients who initially met full DSM-IV criteria for both major depression and mania.[26]

Residual suicidality in patients included in the present analysis involved mild suicidal ideation (HAM-D-3 scores

Table 2. HAM-D, PANSS, and BARS Rating Scale Items Correlated With HAM-D-3 Suicidality Ratings at Randomization to Adjunctive Treatment[a]

Scale Item	Symptom	Correlation (r)	Probability (p)
HAM-D, item 12	Somatic, gastrointestinal	0.48	< .001
PANSS, item 20	Depression	0.40	.002
HAM-D, item 14	Somatic, genital	0.34	.010
BARS, item 2	Aware of restlessness	0.33	.012
HAM-D, item 16	Somatic, weight loss	0.33	.012
PANSS, item 1	Delusional	0.28	.033
HAM-D, item 19	Depersonalization	0.28	.036
PANSS, item 23	Bizarreness	0.28	.036
PANSS, item 22	Uncooperative	0.28	.037

[a]Correlations with all other rating scale items including the YMRS (not shown) were statistically nonsignificant.
Abbreviations: BARS = Barnes Akathisia Rating Scale, HAM-D = Hamilton Rating Scale for Depression, HAM-D-3 = Hamilton Rating Scale for Depression-item 3, PANSS = Positive and Negative Syndrome Scale.

Table 3. Symptoms Derived From Principal Components Analysis of Variation in Scores at Randomization for Items Identified by Correlation Analysis[a,b]

Scale Item	Factor 1	Factor 2	Factor 3
HAM-D, item 3, suicide	0.59	0.38	0.23
HAM-D, item 12, gastrointestinal	**0.65**	0.31	0.22
PANSS, item 20, depression	0.27	**0.71**	–0.12
HAM-D, item 14, sexual dysfunction	**0.78**	–0.02	0.12
HAM-D, item 16, weight loss	**0.63**	0.36	–0.10
BARS, item 02, aware of restlessness	0.19	**0.60**	0.37
PANSS, item 01, delusions	0.10	0.13	**0.87**
HAM-D, item 19, depersonalization[c]	0.49	–0.32	0.45
PANSS, item 22, uncooperativeness	0.03	**0.75**	0.11
PANSS, item 23, unusual thought content	0.13	0.09	**0.91**

[a]Factor 1 = somatic discomfort, Factor 2 = agitated depression, and Factor 3 = psychotic features.
[b]Symptom item loads > 0.50 are in boldface.
[c]Depersonalization was distributed relatively evenly across the 3 factors.
Abbreviations: BARS = Barnes Akathisia Rating Scale, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale.

of 1–2 at randomization). It is also important to emphasize that patients who later attempt or commit suicide may not be considered suicidal at intermittent, cross-sectional clinical assessments, let alone on a single rating scale item rated weekly. Instead, such clinical features as anxiety, restlessness, or agitation may be associated with suicidality.[35,36,43,44] If this formulation is valid, we suggest that close consideration of measures of subjective distress, including somatic discomfort, may be important in assessing potential suicidal risk and, moreover, may represent potential therapeutic targets.

Finally, we would emphasize that studies of the therapeutics of suicide may need to consider the possibility that treatment responses of suicidal ideation and suicidal behavior may not be the same. The present findings suggest that adding olanzapine to lithium or divalproex in partially responsive, mixed-episode bipolar I patients reduces the HAM-D-3 suicidality scores representing suicidal ideation, but these findings do not suggest that olanzapine reduces suicidal behavior. Furthermore, the findings do suggest that adding olanzapine reduces factors associated with such suicidality, including somatic distress, agitated depression, and perhaps psychotic features. Only lithium has been associated with reductions of suicides and attempts in bipolar disorder patients,[6] and use of clozapine in schizophrenia patients has been associated with reductions of suicide attempts or interventions aimed at preventing suicide, but not suicide itself.[10,11] In striking contrast, treatment of depressed patients with antidepressants of all types has not been associated with reductions of suicidal acts,[9] but as noted above, has been strongly and consistently associated with reductions of scores on depression rating scale items for suicidality, including in randomized contrasts to placebo treatment.[13–20]

Several limitations of this study should be considered. This was a post hoc analysis of a subset of a limited number of mostly middle-aged inpatients during DSM-IV mixed episodes of bipolar I disorder, as diagnosed by the SCID-P, selected as partially responding after at least 2 weeks of monotherapy with either divalproex or lithium. They were further selected as having non-zero initial ratings of suicidal ideation on the HAM-D-3 (suicidality). None of the patients exhibited actual suicidal behaviors at any time during the study, although worsening of suicidality scores occurred at least once in 31% of the subjects. In addition, the method of assessing suicidality based on a single rating scale item in a study not explicitly designed to examine suicidal thoughts or behaviors clearly constrains generalization from the present findings. The narrow range of the HAM-D-3 scores encountered (1–2) potentially limited correlations and might explain the lack of significant association of HAM-D-3 scores and mood ratings. However, the symptom clusters from our factor analysis were consistent with findings from other studies, which support this approach to understanding suicidality.

The therapeutic response component of the present study was limited by the partial recovery status of all patients prior to adding olanzapine and the tendency for all patients, who were also receiving divalproex or lithium, to continue toward recovery. In addition, the lack of suicide attempts is inconclusive regarding a potential beneficial effect of olanzapine on suicidal behavior. The substantial dropout rates during adjunctive treatment (41% with placebo versus 19% with olanzapine) further confounded assessment of treatment responses. However, when comparing the discontinued versus completing subjects (all of whom had non-zero HAM-D-3 scores at baseline), 14.3% (1/7) versus 41.4% (12/29) of olanzapine-treated and 77.8% (7/9) ver-

sus 46.2% (6/13) of placebo-treated subjects had non-zero HAM-D-3 scores at endpoint. This finding suggests that early discontinuation tended to eliminate placebo-treated but not olanzapine-treated patients with higher suicidality scores. If this impression is valid, then early discontinuation does not account for the differences between olanzapine and placebo in suicidality score reduction.

Finally, there were insufficient numbers of patients for separate analyses of efficacy of adding olanzapine or placebo to treatment with lithium versus divalproex. To better understand relationships between particular antecedent or coincident clinical symptoms and suicidal thinking or behavior, further studies are warranted with larger, more diverse, and more severely ill or more severely suicidal patients with bipolar disorder, with explicit outcome measures aimed at assessing suicidality.

CONCLUSIONS

Fifty-eight mixed-episode bipolar I disorder patients only partially responsive to at least 2 weeks of monotherapy with divalproex or lithium showed rapid improvement in suicidality scores (specifically, item 3 of the HAM-D, "suicidal ideation") within a week of adding treatment with olanzapine compared with placebo. This result is congruent with a finding in the initial report arising from this study of significantly greater improvement in HAM-D-3 suicidality ratings in all patients given olanzapine versus placebo, including manic as well as mixed-state patients, and those with zero or greater initial item 3 suicidality scores.[26] A significant new finding is that scores of suicidality-associated rating scale items representing somatic discomfort, agitated depression, and psychosis improved along with suicidality ratings after adding olanzapine, with a particularly clear association between changes in somatic discomfort and suicidal thinking. Overall, these findings suggest that the addition of an atypical antipsychotic-antimanic agent in some bipolar disorder patients may help to reduce suicidal ideation.

Drug names: clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

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