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A 13-Week, Randomized Double-Blind, Placebo-Controlled, Cross-Over Trial of Ziprasidone in Bipolar Spectrum Disorder

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Objective: Features of bipolarity in a major depressive disorder sample were used to define a "bipolar spectrum disorder" population for treatment with a neuroleptic agent, ziprasidone.

Methods: Forty-nine acutely depressed patients were randomized to ziprasidone-washout-placebo or placebo-washout-ziprasidone in this double-blind, prospective, 13-week crossover trial. All patients met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for a major depressive episode and were positive for at least 3 predictors of bipolarity: family history of bipolar disorder, antidepressant-induced mania, highly recurrent depressive episodes (>5), atypical depression, early onset of depression (<age 20), failure to respond to antidepressants or antidepressant tolerance. The most common bipolarity inclusion criteria were antidepressant tolerance and nonresponse, and atypical depression. Approximately 52% received ziprasidone in monotherapy, 48% as adjunct to antidepressants.

Results: There was a small statistically nonsignificant benefit with ziprasidone compared with placebo on Montgomery Asberg Depression Rating Scale change [−1.5 (p = 0.48)]. Statistical carryover effects were observed.

Conclusions: Ziprasidone, alone or added to antidepressants, was not more effective than placebo in this population. A false-negative finding due to the crossover design is suggested by statistical carryover effects. Alternatively, this definition of bipolar spectrum illness may have been too nonspecific to show neuroleptic benefit, unlike other definitions, like "mixed depression." Also, this study did not test potential neuroleptic efficacy without the potentially mood-destabilizing effects of antidepressants.

Key Words: depressive mixed state, ziprasidone, bipolar depression, major depressive disorder, mixed episodes, bipolar spectrum disorder

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Major depressive disorder (MDD) is a broad diagnostic category, including many forms of depressive illness: a single major depressive episode, episodic recurrence with intervening well states, chronic depressive/anxious states without intervening euthymia, and those with manic symptoms that do not meet threshold definitions of full mania/hypomania.

Within this heterogeneous diagnostic classification, important groups of patients do not seem to respond well to antidepressants and, conversely, based on observational studies, may respond well to neuroleptics.[1] These predictors of response have begun to be identified and may serve to better design studies of neuroleptics in depressive illnesses.

Among these predictors of response in MDD are clinical features that are more similar to bipolar than unipolar depression. These include a family history of bipolar disorder, antidepressant-induced mania, highly recurrent depressive episodes (>5), atypical depression, early age of onset of depression (age <20), failure to respond to antidepressants, and antidepressant tolerance (initial response followed by later loss of response).[2,3] Previously, we defined the presence of multiple such predictors as identifying "bipolar spectrum disorder."[3]

If a part of what is labeled "MDD" in fact represents a bipolar spectrum condition, then it is important to know whether treatments for bipolar illness, like mood stabilizers, are also effective for bipolar spectrum conditions (which are currently diagnosed in the DSM system as "MDD"). There are different definitions of the term *bipolar spectrum*,[4] but there has been only one previous randomized study of any agent for that condition.[5] In that study, conducted by our group, ziprasidone was more effective than placebo for "mixed depression," or depression with manic symptoms, which is one way of defining some subjects in the bipolar spectrum.[4,6]

Neuroleptics may not be mood stabilizers,[7] if by "mood stabilizer" we mean long-term prevention of mood episodes in bipolar illness.[7] However, some neuroleptics have been found to have some acute efficacy for depressive and manic episodes[8] and even in acute treatment of some bipolar spectrum definitions,[5] as described previously.

This study represents an attempt to examine another kind of bipolar spectrum definition using the neuroleptic ziprasidone.

METHODS

Following CONSORT guidelines, this 3-site, block randomized (1:1 ratio), double-blind, placebo-controlled, prospective crossover study analyzed 49 patients who were randomized to ziprasidone-washout-placebo or placebo-washout-ziprasidone for 13 weeks between November 2006 and September 2009. The washout period lasted 1 week. The study was approved by the institutional review board at each participating site (Tufts Medical Center, Cambridge Health Alliance, University of South Carolina, Northwestern University, and Duke University).

Inclusion criteria for the study were as follows: male or female subjects aged 18 to 70 years and currently meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of nonpsychotic current major depressive episode. At least three of the following predictors of bipolarity were required: a family history of bipolar disorder, antidepressant-induced mania, highly recurrent depressive episodes (>5), atypical depression, early age of onset of depression (age <20 years),

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failure to respond to antidepressants, and antidepressant tolerance (initial response followed by later loss of response). Inadequate response to antidepressants was identified as report of non-response after a retrospective confirmation of an adequate trial of a single antidepressant (defined as a ≥6-week trial of acceptable therapeutic dose [≥40 mg of fluoxetine, paroxetine, or citalopram; 20 mg of escitalopram; 60 mg of duloxetine, 37.5 mg of paroxetine CR, 150 mg of sertraline, 100 mg of fluvoxamine, 225 mg of venlafaxine XR, 30 mg of mirtazapine, 300 mg of bupropion, 75 mg of nortriptyline, 20 mg of protriptyline, and 100 mg of amitriptyline or imipramine]). Patients with bipolar disorder, ziprasidone use in the past 3 months, sensitivity or nonresponse to ziprasidone, substance abuse within the past 3 months, psychotic disorders, and scores of 3 or higher on the suicide item of Montgomery Åsberg Depression Rating Scale (MADRS) were excluded.

Existing antidepressant therapy was to be continued unchanged throughout the study. Concomitant medications for stable medical disorders were allowed to continue unchanged during the trial. The only class of medications not allowed in the study was neuroleptic agents, in the same class as ziprasidone, with the exception of extremely low-dose quetiapine (25–50 mg/d) if only used for sleep and if provided before the beginning of the study. No concomitant medication doses were changed once the study began.

Ziprasidone dosing began at 20 mg BID with flexible titration in increments of 20 to 40 mg weekly to a goal of 80 to 160 mg/d. Visits occurred at the screening visit and Weeks 0, 1, 2, 4, 6, 7, 8, 9, 11, and 13, with a 7-day washout between Weeks 6 and 7. Research scales included the Structured Clinical Interview for *DSM-IV* Axis I disorders, the MADRS, the Mania Rating Scale from SADS-C, the Clinical Global Impression for Bipolar Disorder, Global Assessment of Functioning, Barnes Akathisia Scale, Simpson Angus Scale (SAS), Hamilton Rating Scale for Anxiety, and the Temperament Scale of Memphis, Paris, Pisa, San Diego-Autoquestionnaire (TEMPS-A, 50-item version). The presence of an affective temperament was defined as meeting 75% or more of items on TEMPS-A. Family history was obtained in clinical interview, without using a structured instrument. No research procedures were performed without a patient first signing informed consent after all procedures, and possible side effects were explained to them. Laboratory tests, consisting of complete blood count (CBC) with differential, serum pregnancy test, echocardiogram, and biochemistry profile, were conducted at baseline, at the end of Phase I, and at termination, along with a physical examination and vital signs. Patient termination occurred if the patient experienced a worsening of MADRS scores greater than 30% above the baseline in two successive visits, if Mania Rating Scale scores were higher than 20 in 2 successive visits, if suicidality worsened, as determined by MADRS suicide item score of 3 or higher in 2 successive visits, or based on clinician judgment or patient preference.

Statistical Analysis

All baseline measures between treatment arms were compared with end point measures. Descriptive statistics were performed using mean and standard deviations for continuous variables and percentages of the total for binary ones. The main statistical analysis involved the use of a linear mixed effects repeated measures model. To account for the correlated nature of the data, we analyzed patients' data as repeated measures (using unrestricted covariance structure) and included site of data collection as a random effect. Backward selection procedure was used to select important predictors. The primary model was built using MADRS scores over time as the response variable, ziprasidone (drug) as the main explanatory variable, weeks (time) and its interaction with drug arm as the dependent variables in the model along with indicator variables for treatment order, being a value of 1 when drug was given in the first period and a value of 1 when patients had their second trial after the washout week. This variable assessed the eventual presence of a carryover effect. Sex was also included into the model, along with age and race.

A secondary exploratory analysis was performed using the primary model along with baseline MADRS measures. When analyzed with adjustment for baseline severity of depression, the overall results did not differ notably (results not shown). Model assumptions were verified. Sensitivity analysis assessing robustness of results excluding outliers' data points was conducted, again with no notable change in results. Analyses were completed in Stata 11 (StataCorp LP, College Station, TX), and SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The sample was 42.6 ± 11.4 years of age, 67.4% female, 54.2% college educated, and 69.4% non-white. Approximately 48.9% received antidepressants, mostly serotonin reuptake inhibitors (36.2% serotonin reuptake inhibitors, 10.6% bupropion, and 6.4% other).

Regarding bipolarity predictors, the most common features were tolerance (75.0%), antidepressant nonresponse (73.5%), high recurrence of major depressive episodes (72.3%), and atypical depression (52.9%). Among less common bipolarity predictors, 46.0% had a family history of bipolar disorder, 47.6% early age of onset of depression (age <20), and only small minority of the sample had experienced antidepressant-induced mania (8.8%). Duration of illness was 16.4 ± 11.7 years. Affective temperaments were 46.7% cyclothymic, 28.9% dysthymic, and 17.8% hyperthymic; given overlap between temperaments, 31.0% were normal, meaning not being defined as having any single affective temperament.

In the main outcome, there was no statistically significant difference between ziprasidone versus placebo over time in a linear mixed effects model with repeated measures ($p = 0.48$). As seen in Figure 1, drug response, whether in the first or second 6-week phase, was similar to placebo response, whether in the first or second 6-week phase. MADRS scores exhibited significant changes over time in both groups ($p < 0.001$), and there was marginally differential temporal changes between drug and placebo groups ($p = 0.28$). Absolute MADRS scores were 22.3 ± 8.3 at baseline, 11.6 ± 7.8 at the end of the first phase, and 7.4 ± 7.0 at the end of the crossover phase. Using a mixed effects regression model, ziprasidone decreased MADRS scores 1.57 ± 1.67 points greater than placebo, which is a small effect size benefit that was not statistically significant. The effect of the crossover phase (after the washout week) over MADRS scores was significant ($p < 0.001$). Order of treatment ($p = 0.1681$), sex ($p = 0.9341$), age ($p = 0.3678$), and race did not produce statistically significant effects on MADRS scores.

Regarding side effects, more than 80% of the sample remained in both phases of the study. Side effects occurred in about one-half of the sample, somewhat more in the first compared to the second crossover phase. In the first phase of the study (Weeks 0–6), the most common side effect at Week 6 was sedation (17.5%), followed by other nonspecific side effects (nausea and dry mouth, 7.5% each; constipation, 5%; and 1 patient each with salivation, anxiety, drooling, nightmares, irritability, and increased appetite). The only serious side effect was a seizure in 1 patient randomized to ziprasidone. In the second crossover phase (Weeks

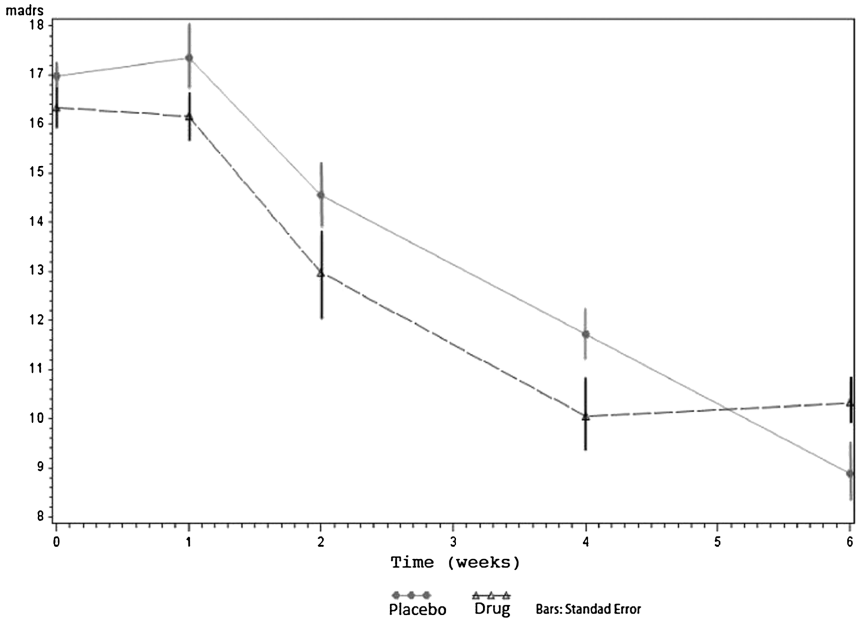

FIGURE 1. Graph of change of MADRS over time by treatment group. In cross-over studies, each patient serves as his or her control, receiving study drug or placebo in the first or second 6-week phase of the trial. This figure presents mean (±SE) drug response, whether in the first or second 6-week phase, versus placebo response, whether in the first or second 6-week phase. The similar parallel arms indicate similar efficacy for drug versus placebo.

7–13), there were somewhat fewer side effects, and the most common side effect at Week 13 was dry mouth (11.1%), followed by other nonspecific side effects (sedation, 8.3%; and one patient each with tinnitus, nausea, weight gain, and insomnia). The only serious side effect was marked akathisia in 1 patient randomized to switch from ziprasidone to placebo.

DISCUSSION

There was no meaningful depressive symptom benefit with ziprasidone over placebo in this randomized placebo-controlled cross-over trial of a type of bipolar spectrum illness.

It is important to realize that these negative results could partly relate to the validity of the bipolar spectrum illness definition used here. Other bipolar spectrum illness definitions, like the concept of "mixed depression," have shown therapeutic benefit with the neuroleptic ziprasidone, in contrast to this study.[5] It could be that the specific bipolar spectrum features that picked out many of the subjects in this sample—namely recurrent depressive episodes with antidepressant nonresponse and tolerance and frequent atypical depression – may not be specific enough to identify therapeutic benefit with neuroleptic or mood stabilizer agents. For instance, it seems atypical depression may not be very specific for bipolar spectrum illness,[9] as had been previously thought, whereas melancholic features may be a more specific bipolarity predictor.[10] Furthermore, the *DSM-IV* definition of atypical depression has been questioned as to its validity.[11] Also, antidepressant tolerance may be more common in unipolar depression than previously thought, occurring in about one-half of MDD subjects in the STAR*D trial,[12] and thus be less specific for bipolarity.[1] The 2 primary features of "bipolar spectrum disorder" as formally proposed by Ghaemi and colleagues[3]—antidepressant-induced mania and family history of bipolar illness—were present in only a minority of this sample.

Also half of this sample received antidepressants during the study, and thus, ziprasidone was being used as an adjunct, not by itself. If antidepressants can cause mania or mixed states or worsen bipolar spectrum illness, as some studies suggest,[13,14] then the continued use of antidepressants in this study might have impaired potential ziprasidone efficacy. In that case, this study is a test not of "mood stabilizer" efficacy in this definition of bipolar spectrum illness, but of combination of antidepressant plus neuroleptics efficacy in this condition. It may be that neuroleptics or mood stabilizers would be more effective without antidepressant agents in bipolar spectrum illness, as has been shown in some studies of Type I or II bipolar depression.[13,14]

Another major factor that should influence interpretation of these data has to do with the crossover design; it is well known that this design is potentially invalid when used with episodic, as opposed to chronic, conditions. This is because of the "carryover effect."[15–17] In a chronic illness, the condition would immediately relapse after stopping an effective drug. In an episodic condition, the symptoms might stay in remission naturally for weeks or months or longer before recurring. This could lead to overestimation of benefit of placebo and hence a negative treatment result. For instance, if ziprasidone is effective in the first 6-week phase, placebo may seem to be effective in the second 6-week phase because of a carryover of ziprasidone benefit weeks or even months after the drug was stopped. We tested this possibility by examining MADRS scores at baseline versus end of the first phase versus end of the second crossover phase. As described in the results, there was a decline in MADRS from 22.3 ± 8.3 at baseline to 11.6 ± 7.8 at the end of the first phase to 7.4 ± 7.0 at the end of the crossover phase, which suggests continued improvement over time, with persistence of improvement in the crossover phase such that there was a floor effect, with less room for improvement, in the second crossover phase. This phenomenon is consistent with carryover of benefit from the initial phase of the study, which would potentially reduce validity of the crossover design in this setting.

Despite these caveats, the actual results can be interpreted, to the extent they are valid, in relation to other neuroleptic studies as follows. The relevant previous literature mainly involves studies

of neuroleptics as adjuncts to antidepressants in MDD; randomized controlled trials (RCTs) with aripiprazole have demonstrated such benefit,[18,19] leading to FDA indication of that agent for adjunctive treatment of MDD.[20–23] Other studies have been conducted with risperidone, olanzapine, and quetiapine, with some benefit in MDD but not as markedly as with aripiprazole.[24]

Regarding ziprasidone in particular, 2 RCTs exist, one showing benefit in adjunctive therapy to antidepressants in MDD and the other finding no benefit with ziprasidone monotherapy.[25,26] As noted, our group previously showed benefit with ziprasidone over placebo in an RCT of the bipolar spectrum condition of "mixed depression": an acute major depressive episode in patients with concomitant manic symptoms; about half of that sample was diagnosed with MDD (they did not meet the *DSM-IV* criteria for a full mixed episode, and they never previously had manic or hypomanic episodes).[5]

Besides the diagnostic and design limitations mentioned previously, other potential limitations are as follows: the sample size was modest, thus confounding factors could potentially be nonrandomly distributed between treatment arms. We tried to adjust for some potential confounding effects in the adjusted regression model for the results, which made the ziprasidone effect size somewhat larger. Also, family history was not obtained using a structured instrument and, thus, may not have accurately identified, to a sufficient degree, the presence or absence of bipolar illness in relatives.

AUTHOR DISCLOSURE INFORMATION

Dr Ghaemi has the following conflicts: In the past 36 months, he has received a research grant from Takeda Pharmaceuticals and has made a one-time research consultation to Sunovion Pharmaceuticals. Neither he nor his family holds equity positions in pharmaceutical corporations. Dr Ashwin A. Patkar has read the journal's policy and has the following conflicts: Grant/Research Support: NIH (NIDANIAAA), Duke Endowment, Forest Labs, Dey Pharma, Janssen, Envivo, Lundbeck, Pfizer, Titan, Shire; Sunovion Consultant/Advisory Board: Forest Pharmaceuticals, Dey Pharmaceuticals, Gilead, TTK Pharma; Speakers Bureau: Alermes, Bristol Myers Squibb, Dey Pharmaceuticals; Pfizer, Sunovion. Dr Chi-Un Pae has read the journal's policy and has the following conflicts: Dr Pae has received research grant from Eisai Korea, Daewoong Pharmaceuticals, Otsuka Korea, AstraZeneca Korea, Otsuka International Asia and Arab (OIAA), Astellas, GlaxoSmithKline Korea, Hanlim Pharmaceuticals, Janssen Pharmaceuticals Korea, Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea, and Korean Research Foundation; has received honoraria from Pfizer Korea, GlaxoSmithKline Korea, Lundbeck Korea, AstraZeneca Korea, Janssen Pharmaceuticals Korea, Eisai Korea, Abott Korea, Novartis Korea, OIAA and Otsuka Korea. Dr Meera Narasimhan has the following grant and research support: National Institute of Mental Health, National Institute of Drug Abuse, National Institutes of Alcohol Abuse and Alcoholism, National Institutes of Health, Eli Lilly, Janssen Pharmaceuticals, Forest Labs, and Pfizer.

Dr Antony Loebel has the following conflicts: Dr Loebel is an employee of Sunovion Pharmaceuticals. He has no other disclosures or competing interests (eg, stock etc).

Dr Prakash S. Masand has read the journal's policy and has the following conflicts:

Consultant: Forest, Lundbeck, Merck, Pfizer, Sunovion; Research Support: Forest

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