Antidepressant Action of Atypical Antipsychotics: Focus on Ziprasidone Monotherapy, With a Few Twists in the Tale

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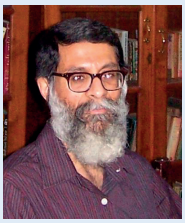

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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Clinical Problem

Mr J is a 44-year-old man who experienced a manic episode 8 years earlier. He discontinued sodium valproate maintenance therapy, because of weight gain, after about 1 year of medication use. He is presently experiencing his first major depressive episode, which is moderately severe in intensity. Mr J is reluctant to accept quetiapine because of the risks of sedation and weight gain associated with the drug. Ziprasidone is less likely to result in sedation and weight gain than quetiapine. Might Mr J respond to monotherapy with ziprasidone?

Why Consider an Atypical Antipsychotic for Patients With Bipolar Depression?

The use of antidepressant drugs is generally discouraged in bipolar depression because there is no clear evidence of antidepressant benefit (especially when the patient is receiving an adequate dose of a mood stabilizer)[1–3] and because there is a risk of manic switch and cycle acceleration.[4–6] Lamotrigine is a candidate treatment[7]; however, one concern is that lamotrigine needs to be slowly up-titrated to the target dose to reduce the risk of serious rash,[8] and another concern is that lamotrigine may not be a good antidepressant during the acute phase of illness because it was superior to placebo in only 1 of 5 randomized controlled trials (RCTs) conducted in patients with bipolar depression[9] and in none of 3 RCTs conducted in patients with major depressive disorder (MDD).[10]

Antipsychotic drugs are effective against mania; therefore, an advantage of using an atypical antipsychotic to treat a bipolar depressive episode is that the risk of manic switch could be expected to be lower. The atypical antipsychotic quetiapine is a serious first-line contender because it is effective in the acute phase of bipolar depression[3,11–13] and because it can afterward be continued as maintenance therapy.[14–16] Quetiapine has demonstrated efficacy when used as monotherapy[3,11–13,16] as well as when used to augment lithium or valproate.[14,15] Olanzapine is another atypical antipsychotic with possible efficacy in bipolar depression,[17,18] especially when used in combination with fluoxetine.[17]

Atypical antipsychotics, in fact, may also be helpful for MDD, both as monotherapy, as in the case of quetiapine,[19,20] and as antidepressant augmentation agents, as in the cases of quetiapine[21] and aripiprazole.[22] Quetiapine is also effective in the maintenance therapy of MDD.[23] Atypical antipsychotic agents as a class may be effective for antidepressant augmentation of nonpsychotic MDD[24,25] and may be more effective for antidepressant augmentation than the use of a second antidepressant.[26]

Preclinical Reasons Why Ziprasidone May Be Considered for Patients With Depression

Ziprasidone inhibits the synaptic reuptake of serotonin and norepinephrine and blocks 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1D} receptors.[27] Ziprasidone-induced agonism at 5-HT_{1A} receptors increases dopamine levels in the prefrontal cortex.[28] Ziprasidone may also block synaptic reuptake of dopamine.[29] All of these properties suggest antidepressant potential. For example, inhibition of the synaptic reuptake of

- Ziprasidone has established antimanic efficacy. It also has pharmacodynamic properties that suggest that it may have antidepressant action. Hypothetically, therefore, ziprasidone may be useful in depressive illness, especially bipolar depression.
- A recent RCT found ziprasidone to be no better than placebo in major depressive disorder. Earlier RCTs had found it ineffective in bipolar depression, as well.
- The results to date with ziprasidone suggest that clinicians should not rely too much on pharmacodynamic properties to guide expectations about the clinical efficacy of a drug. Due to limitations of the available RCT data, however, firm conclusions remain to be drawn regarding the use of ziprasidone in different contexts in depression.

monoamines is the proposed mechanism of action of tricyclic antidepressants, selective serotonin reuptake inhibitors, bupropion, and many other newer as well as older antidepressant drugs.[30,31] Blockade of 5-HT_{2A} and 5-HT_{2C} receptors results in increased levels of dopamine, serotonin, and norepinephrine in the prefrontal cortex,[32,33] which may also contribute to antidepressant action.[31]

Ziprasidone and Major Depressive Disorder

The best evidence for the clinical efficacy of a drug can come only from RCT data. In the only study to date on the subject, Papakostas et al[34] described an industry-sponsored, multicenter, 12-week, randomized, double-blind, placebo-controlled trial of ziprasidone in patients with *DSM-IV* MDD.

The sample comprised 120 adult outpatients, none of whom had significant medical, psychiatric, or substance use comorbidity. The mean age of the sample was 44 years, and the sample was 56% male. Patients were, on average, mildly depressed at baseline (mean 17-item Hamilton Depression Rating Scale [HDRS] score = 19.9).

These patients were randomized 2:3:3 to receive ziprasidone for 12 weeks, or placebo for 6 weeks followed by ziprasidone for 6 weeks, or placebo for 12 weeks. During the first 6 weeks (phase 1), there were 29 ziprasidone and 91 placebo patients. During the next 6 weeks (phase 2), when only phase 1 HDRS nonresponders were the subjects of interest, there were 21 ziprasidone and 25 placebo patients.

Ziprasidone was initiated at 40 mg/d, and the dose was raised by 40 mg/d at weekly intervals at the discretion of the treating clinician, with a ceiling of 160 mg/d. The mean maximum dose of ziprasidone was 81 mg/d during phase 1 and 114 mg/d during phase 2.

Response was defined as at least 50% improvement on the HDRS and the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR). Remission was defined as a final HDRS score of 7 or less or a QIDS-SR score of 5 or less.

Table 1. Important Findings of the Randomized, Placebo-Controlled Trial of Ziprasidone in Major Depressive Disorder[a]

In the ziprasidone group vs the placebo group, the dropout rates were 41% vs 16%, respectively, at the end of phase 1 and 33% vs 12% at the end of phase 2. Significantly more patients dropped out of ziprasidone treatment than placebo treatment
At the end of phase 1, HDRS response and remission rates were 45% vs 32% and 38% vs 25% in the ziprasidone group vs the placebo group, respectively. HDRS scores decreased by a mean of 8.8 vs 7.1 points with ziprasidone vs placebo, respectively. The groups did not differ significantly on these outcomes. The groups also did not differ significantly on QIDS-SR response, QIDS-SR remission, QIDS-SR change scores, or CGI-S change scores
At the end of phase 2, all of the above-mentioned outcomes again did not differ significantly between the 2 groups
When data from the 2 phases were pooled, outcomes once again did not differ significantly between the 2 groups
Ziprasidone was associated with significantly greater sedation and fatigue than placebo. Ziprasidone was also associated with a small (about 2.5 ng/mL) but significantly greater elevation of serum prolactin relative to placebo. Adverse events and laboratory results otherwise did not differ much between the 2 groups

[a]Data from Papakostas et al.[34]
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, HDRS = 17-item Hamilton Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

The findings of the study are summarized in Table 1. In brief, ziprasidone was not significantly superior to placebo on any efficacy outcome in either phase of the study or in a pooled analysis that employed a special, weighted statistical model. Notably, significantly more patients dropped out of ziprasidone treatment than placebo treatment.

The authors[34] offered several reasons why ziprasidone failed to demonstrate antidepressant efficacy; one was that the drug may have been underdosed, and another was that patients were not exposed to the highest dose for a sufficiently long period. The high dropout rate with ziprasidone and the sequential design also resulted in underpowered analyses. For all of these reasons and more, the findings of this study are not the last word on the subject. Nevertheless, the findings do not encourage the use of ziprasidone to treat a major depressive episode.

Ziprasidone and Bipolar Depression

Encouraging results were obtained in an open, uncontrolled study of ziprasidone monotherapy in bipolar II depression.[35] However, RCT results for ziprasidone in bipolar depression have disappointed academia and industry, alike. Sachs et al[36] described a 6-week RCT which found that ziprasidone (mean dose = 90 mg/d) augmentation of a mood stabilizer was ineffective in adults with bipolar depression. Lombardo et al[37] attempted to explain the failure of two 6-week RCTs comparing ziprasidone with placebo in adults with bipolar I depression. One of these studies examined 2 different doses of ziprasidone (40–80 mg/d and 120–160 mg/d), and the other examined flexible dosing with ziprasidone (40–160 mg/d). Response rates ranged from 46% to 53% in the first study and 51% to 53% in the second study;

ziprasidone was no better than placebo in either study. Sachs et al[36] and Lombardo et al[37] reported serious inconsistencies in clinical ratings and recruitment matters that may have limited the ability of the RCTs to detect a difference between ziprasidone and placebo. It is therefore uncertain whether these RCTs can contribute meaningfully to decision-making on the use of ziprasidone in bipolar depression.

Limitations of Pharmacodynamics as a Predictor of Clinical Actions

As reviewed earlier in this article, ziprasidone has many pharmacodynamic properties that are common to drugs with established antidepressant action. Ziprasidone also showed antidepressant efficacy in a 1-(*m*-chlorophenyl) piperazine animal model of depression.[38] Finally, other atypical antipsychotics show antidepressant action despite boasting of less impressive putative antidepressant mechanisms than ziprasidone. Yet, ziprasidone showed no antidepressant advantage over placebo in the MDD[34] and bipolar depression[36,37] RCTs described in the earlier sections. Important take-home messages are that preclinical research and circumstantial evidence can only guide hypothesis generation, and antidepressant action is not a class action of atypical antipsychotic drugs. Expressed as a delightfully mixed metaphor, the proof of the pudding can come only from the results of good clinical research.

Readers are reminded of how scores of prospective drugs with excellent preclinical credentials fail to make it to the market because of disappointing phase 2 and phase 3 clinical trial results. Thus, the failure of ziprasidone to separate from placebo in unipolar and bipolar depression is an outcome that academia and the industry must take in their stride.

An Evidence-Based Appraisal

It is incorrect to draw conclusions about apples from a study of oranges. The results of a study can only be generalized to the population from which the study was drawn, and then only if the same methods are employed. So, was the study of ziprasidone in MDD[34] appropriate to Mr J, the patient described at the start of this article? Perhaps not. The most important concern is diagnosis. Mr J has bipolar depression, and the Papakostas et al[34] study was conducted in patients with MDD. That diagnosis is a relevant issue should be evident from the lamotrigine RCT results for unipolar and bipolar depression, referred to in an earlier section.

Another important concern addresses severity of depression. The ziprasidone MDD study[34] was conducted in patients who were but mildly depressed (mean HDRS score at baseline = 19.9); this may be an important reason why the trial failed, for a meta-analysis of antidepressant RCTs submitted to the US Food and Drug Administration found that antidepressant drugs separate better from placebo only when depression is more severe.[39] Thus, given that Mr J has moderately severe depression, the ziprasidone MDD study[34] provides little guidance on how patients with moderately severe depression might fare on monotherapy with the drug. Finally, the study provides no information on possible benefits with faster up-titration or higher doses of ziprasidone (which, however, could result in even higher dropout rates than those recorded in the study).

The ziprasidone bipolar depression studies[36,37] were considered flawed by their authors themselves and therefore should not be used as evidence to guide decision-making. So, if the ideal evidence is unavailable, the next best evidence that is available should be applied to the clinical problem at hand. Under these circumstances, the ziprasidone MDD study[34] comes closest to providing guidance about the use of ziprasidone for Mr J. Readers are reminded here that using "next-best evidence" is widespread in clinical psychopharmacology. For examples, RCTs on which drug approvals are based almost always exclude very severely ill patients, those who are suicidal, those with significant medical or psychiatric comorbidities, those with substance use or personality disorders, and so on; that is, a substantial proportion of patients seen in everyday clinical practice.

Here are some additional notes on apples and oranges in the interpretation of research. What if Mr J had bipolar depression with psychotic features? It would seem that an atypical antipsychotic with proven antidepressant action would be even more appropriate as a monotherapy option because the antipsychotic action of the drug could take care of the psychotic symptoms and the antidepressant action could target the depression. However, patients with psychotic depression are generally excluded from RCTs, and so there is little to no high-quality evidence to support such a conjecture. In one RCT,[40] however, olanzapine monotherapy was inferior to an olanzapine-sertraline combination in psychotic depression.

Parting Notes

The preceding discussion explains why the last word remains to be written on the subject of the antidepressant efficacy of ziprasidone. Antidepressant drugs tend to separate from placebo only when depression is more severe.[39] Lamotrigine failed in MDD but enjoys a therapeutic role in bipolar depression.[41] Aripiprazole can be used for antidepressant augmentation in refractory MDD.[22] Ziprasidone remains to be studied in more severely depressed patients with MDD, in properly conducted RCTs in bipolar depression, and as an antidepressant augmentation agent—3 situations in which it may yet be found to have a role. As remarked earlier, for the best chance for successful trials, patients will need to be exposed to an adequate dose of the drug for an adequate duration.

On a positive note: a very recent RCT found that ziprasidone augmentation was superior to placebo augmentation in patients with a depressive mixed state.[42] And, on a negative note, aripiprazole, another atypical antipsychotic drug with good antidepressant credentials,[22] failed in two 8-week monotherapy RCTs in bipolar I depression,[43] reemphasizing the point that pharmacodynamics and circumstantial evidence do not necessarily indicate clinical efficacy.

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