

REVIEW

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Maintenance Treatment of Bipolar Disorder with Ziprasidone in Adjunctive Use with Lithium or Valproate

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Abstract: Ziprasidone is a second generation (“atypical”) antipsychotic drug that has been used alone and as an adjunct to standard mood stabilizers to reduce recurrence rates in bipolar disorder. Approval of ziprasidone as an adjunct to lithium or valproate in 2009 was based on an industry sponsored study of 584 outpatients with a current or recent manic episode; 240 of these subjects were randomized to adjunctive ziprasidone or placebo and 138 completed a six month trial. Patients enrolled in maintenance studies did not have refractory mood disorders, comorbid conditions or risk of dangerousness. Maintenance ziprasidone augmentation is an option for patients who do not respond to a single mood stabilizer rapidly, and possibly for those with residual psychotic symptoms, but there are insufficient data to prefer this approach to combinations of mood stabilizers or augmentation with other agents. Ziprasidone is generally well tolerated, with less sedation and weight gain than many other antipsychotic drugs; it should be taken with food. Primary interactions of concern are with other serotonergic medications, MAO inhibitors, and other medications that prolong the QT interval.

Keywords: bipolar, mania, maintenance, prophylaxis, antipsychotic drug

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Introduction

Bipolar disorder is a chronic or recurrent condition characterized by episodes of depression alternating or mixed with mania or hypomania. The current nomenclature defines three primary bipolar subtypes.¹ Bipolar I disorder is characterized by manic episodes with or without hypomania, while bipolar II disorder is associated with episodes of hypomania but not mania. Cyclothymia refers to chronic cycling of hypomania and mild depression. Additional categories undoubtedly exist. For example, brief hypomania is characterized by symptomatic criteria for hypomania but duration of 3 days or less and a high rate of recurrence.² Furthermore, within each category are many complex phenotypes, such as syndromes with early or late onset; intermittent, uncomplicated or chronic, mixed symptoms; frequent or occasional episodes; and with or without psychotic symptoms and comorbidity.³ Bipolar disorders therefore comprise a spectrum of conditions of varying severity with different courses, family histories, pathophysiology, and treatment response.

The lifetime prevalence of bipolar disorder has traditionally been reported to be in the range of 1%–2%, but when subsyndromal forms are included, the prevalence may be as high as 5.5%–6.5%.² Between 20% and 50% of depressed patients in specialty practice and at least 20% of depressed primary care patients have a bipolar rather than a unipolar mood disorder.^{4,5} Overall, bipolar disorder is associated with considerable morbidity and with a suicide rate as high as 15%.³

Acute mania responds to a variety of treatments, including lithium, anticonvulsants such as carbamazepine and valproate, benzodiazepines, all antipsychotic drugs, and electroconvulsive therapy.^{6–9} A recent meta-analysis of 38 industry-sponsored short-term atypical antipsychotic studies of acute treatment of acute mania with or without mixed depressive symptoms in 10,800 patients found that aripiprazole, asenapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone were all significantly more effective than placebo, with an overall number needed to treat (NNT) of 6.¹⁰ The NNT for ziprasidone was about the average, whereas the NNT for risperidone was somewhat lower than average, but no atypical antipsychotic drug was more effective than haloperidol. Ziprasidone, like most atypical

antipsychotic drugs, is approved for the treatment of acute mania.¹¹

A greater challenge than treating mania is the prevention of recurrences of mania, depression and mixed states, which tend to accelerate and become more complicated with time. Although a number of medications have been approved as “maintenance treatment” in bipolar disorder, according to strict criteria only lithium has had a sufficient number and quality of controlled studies to support its classification as a mood stabilizer, namely a treatment that ameliorates mania and depression and prevents recurrences of both poles of bipolar disorder.^{9,12} However, not all studies have consistently found an acute antidepressant effect of lithium. Conversely, lithium has been shown to reduce suicidality independent of its effect on mood.¹³ Valproate (divalproex) also appears to be effective as a maintenance treatment,^{14,15} although it is not as reliable as lithium for depression. Lamotrigine is commonly used for maintenance therapy, but evidence is much stronger for efficacy in depression than mania.¹⁶

American Psychiatric Association practice guidelines suggest that an attempt should be made to withdraw antipsychotic drugs unless they are clearly necessary for prevention of recurrence; however, there has been a marked trend toward use of atypical antipsychotic drugs as primary maintenance therapy in nonpsychotic bipolar disorder.¹³ This a trend has been accelerated by extensive marketing of atypical antipsychotic drugs to patients as well as practitioners, which has contributed to widespread use of these medications as first-line maintenance as well as acute therapies.¹⁷ Although the most controlled research for maintenance therapy of bipolar disorder has been with olanzapine,^{13,15,16,18} a 2009 review found that no atypical antipsychotic drug had yet been reliably demonstrated to be a mood stabilizer as defined above.¹⁹ Furthermore, a tendency of industry to report only positive studies makes it difficult to interpret the entire data set supporting the chronic use of any antipsychotic medication in bipolar disorder.²⁰ Virtually all studies of antipsychotic drugs for bipolar disorder define response as a 50% reduction in rating scale scores and remission as either a 2/3 reduction of symptoms or a mania or depression rating scale score below a certain level (eg, Young Mania Rating Scale Score \leq 12, with initial scores usually around 30–36)



at endpoint. No definition of remission in these studies specifies complete absence of symptoms or normal functioning, even though technically remission should refer to no more than one or two mild symptoms, normal functioning, and no longer meeting criteria for the disorder for at least 8 weeks.

Patients with less complex bipolar mood disorders frequently respond well to monotherapy with an established mood stabilizer. However, patients with more complex, chronic and refractory symptoms do not respond as well to a single treatment,⁹ and many patients need adjunctive treatment.²¹ Furthermore, while a significant number of patients are substantially improved with a mood stabilizer, many have residual symptoms that are overlooked compared to the previous severe episode but that impair functioning and quality of life. Indeed, dysfunction in professional and personal roles itself is a residual feature indicating that the active physiology of the disorder is not entirely suppressed. Yet any residual symptoms increase the risk of relapse and recurrence, and even subsyndromal symptoms are associated with continued functional impairment.²² As a result, there has been increased interest in combination therapy for maintenance treatment, especially using adjunctive atypical antipsychotic drugs added to standard mood stabilizers like lithium and valproate in achieving more complete remission and prevention of future recurrences. This review considers the data supporting the acute and chronic use of ziprasidone in bipolar disorder, in order to place into perspective its role as an adjunct to lithium and valproate in maintenance therapy.

Short-term placebo and haloperidol-controlled studies demonstrate the efficacy of ziprasidone acutely in mania.^{23–25} A post hoc analysis of two 3-week industry sponsored placebo controlled trials of ziprasidone in 399 patients with a manic or mixed episode (246 of whom were not psychotic) found that independent of effects on agitation, response of psychosis scores by day 4 (defined as at least 50% reduction) with ziprasidone or placebo predicted remission of mania by day 21 (defined as $\geq 50\%$ reduction in Mania Rating Scale scores and final Mania Rating Scale score ≤ 12).⁸ The use of ziprasidone in combination with lithium or valproate as maintenance treatment in bipolar disorder was approved by the FDA in 2009. Ziprasidone was also recommended as adjunctive

therapy by the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders.²⁶

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Ziprasidone is a benzisothiazolyl-piperazine type atypical antipsychotic drug with prominent dopamine D_2 and serotonin $5HT_{2A}$ antagonist and serotonin reuptake inhibitor properties. Ziprasidone has similar potency at serotonin $5HT_{2A}$ and dopamine D_2 receptors (K_i 0.42 nM). It has lower potencies at dopamine $D_{1,4}$ and histamine H1 receptors (K_i 525, 32 and 47 nM, respectively), and minimal effects on muscarinic cholinergic receptors ($K_i \geq 1000$ nM).²⁷ Antagonism of $5HT_2$ receptors mitigates the adverse effects of D_2 receptor blockade, and $5HT_{2A}$ antagonism may contribute to reduction of psychosis; $5HT_2$ blockade in turn may add to antipsychotic actions. Whereas serotonin uptake inhibition and $5HT_2$ antagonism may be associated with antidepressant effects, any contribution to mood stabilization is likely to be associated with as yet undefined actions on cell signaling and gene induction.

Absorption of ziprasidone is two-fold higher when it is taken with food (oral availability 59%); 100% is absorbed after intramuscular injection. Almost all available drug is protein bound. Peak serum concentration is 68 ± 20 ng/mL at a dose of 20 mg twice a day for a week and 156 ng/mL after a single 10 mg intramuscular dose, with times to peak concentrations being 4 and 0.7 hours, respectively as determined by repeated blood samples after the index dose. The elimination half-life of ziprasidone is 7.5 hours, as a result of which divided dosing is necessary. It is highly metabolized, only 5% of the total dose being excreted unchanged. About 2/3 of ziprasidone metabolism is attributable to reduction by aldehyde oxidase; the rest of its metabolism is by oxidation by CYP3A4. Ziprasidone has four major metabolites, one of which (S-methyldihydroziprasidone) is biologically active.²⁷

Clinical Efficacy

Industry-sponsored phase III adjunctive maintenance studies of ziprasidone, like those of other atypical antipsychotic drugs, have relied on sample enrichment, in which patients with a manic episode are



treated openly for several months with lithium or valproate plus ziprasidone. Those patients who do not respond or who relapse are excluded from the double-blind phase, in which the antipsychotic drug or placebo is combined with the mood stabilizer for 6–18 months, depending on the study.

Sample enrichment magnifies effect sizes that are small in randomly selected populations with a given illness (eg, all manic patients admitted to a psychiatric hospital regardless of comorbidity or complexity), but since about half the initial sample is lost during the open label phase of most such studies, and since patients with complex (eg, ultradian cycling, chronic unremitting symptoms, dangerousness), comorbid, and treatment refractory disorders are excluded, the generalizability of the results is limited.¹⁷ The most that can be concluded from studies of patients with relatively uncomplicated bipolar mood disorders is that if they do not have substantial rating scale evidence of relapse after 2–4 months of open treatment with the antipsychotic drug, it will take longer for them subsequently to require additional interventions for relapse if the antipsychotic drug is continued along with the mood stabilizer than if placebo is substituted. Another weakness of current research is that inferences are drawn from rating scale scores and analysis of secondary endpoints, often without correction for multiple statistical tests. While addition of the antipsychotic drug may produce better rating scale scores than placebo, some symptoms usually remain. Furthermore, nothing is known about subsyndromal states, functioning, or the response of the kinds of mood disorders seen in clinical practice such as mood disorders accompanied by suicidality, assaultiveness, chronicity, substance use and comorbid Axis I, Axis II and medical disorders.

In a manufacturer-sponsored study,^{11,28} 584 outpatients with a current or recent acute manic or mixed episode of bipolar I disorder who remained symptomatic after two or more weeks of treatment with lithium (mean level 0.7–0.9 mM) or valproate (mean level 67–73 mcg/mL) had open addition for a median of 60–77 days of ziprasidone (mean dose 160 mg/day). The mood stabilizer serum levels were lower than optimal levels for many manic patients. Patients with medical comorbidity, dangerousness, substance abuse, resistance to antipsychotic drugs, and 8 or more episodes in the previous year were excluded. Patients

in the open-label phase with a CGI-I score ≤ 3 for 8 weeks ($N = 240$) were randomized for six months (median actual time of treatment was 141 days for those on placebo and 167 days for those on ziprasidone) to the same dose of ziprasidone or placebo; ziprasidone was withdrawn over the first 2–6 days of randomization for those patients who were assigned to placebo.

During the double-blind phase, intervention for a mood episode was required by 18% of ziprasidone patients and 32% of placebo patients ($P = 0.0104$; $NNT = 8$); of the 61 patients who required such an intervention, median time to intervention (the primary endpoint) was 43 days with ziprasidone and 27 days for placebo ($P = 0.0104$). Discontinuation for any reason occurred in 34% of ziprasidone patients and 51% of placebo patients. Of 127 patients randomized to addition of ziprasidone, 84 completed the study, versus 54 of 113 patients randomized to addition of placebo. The difference between addition of ziprasidone or placebo in change in mean Mania Rating Scale score from baseline to the last observation was 3.27 points lower with addition of ziprasidone versus placebo ($P < 0.001$); there were no differences in changes in depression rating scale scores.

A retrospective claims-data analysis of commercially insured patients with bipolar mood disorders treated chronically with a mood stabilizer to which was later added an atypical antipsychotic drug found that the time to hospitalization over the 90 days after starting the antipsychotic drug was significantly longer with aripiprazole than with other adjunctive antipsychotics, including ziprasidone (H.R. 1.7).²⁹ However, doses of all antipsychotic drugs were lower than those indicated in manufacturer information and practice guidelines. The same group found that in the year after starting an atypical antipsychotic drug for bipolar disorder, ziprasidone, olanzapine and quetiapine had higher risks for hospitalization than aripiprazole, (hazard ratio 1.96, 1.55 and 1.56, respectively; $P < 0.05$); mental health treatment costs were significantly lower for aripiprazole than ziprasidone ($P = 0.004$).³⁰ Neither of these studies were designed to directly compare augmentation with the different antipsychotic drugs.

In one of two monotherapy maintenance studies, 65 patients (62 with complete data) who finished a 3-week placebo-controlled trial of ziprasidone for



pure or mixed mania entered a one-year open-label, flexible-dose extension.³¹ Scores upon entering the open-label phase indicated substantial illness at the end of the acute phase. The majority of subjects (86%) had at least a 50% reduction of Mania Rating Scale scores over the duration of the study, with no difference in response between psychotic and nonpsychotic patients. Most adverse effects were mild or moderate, with no serious cardiac effects. The open nature and the size of the study limit conclusions about efficacy or safety.

Of 127 patients who entered a two-year open-label extension of another 3-week placebo-controlled trial of ziprasidone in acute mania with an average daily dose of 122.4 mg/day, one-third remained in the study for the first year.³² Scores on the Mania Rating Scale and the CGI-S scale decreased over the two year study, but the majority of patients discontinued the study-88% of the time for reasons other than adverse medication effects. A small number of patients may have had a reduced likelihood of manic recurrence, but there was no evidence of prevention of depression in long-term treatment.¹³

Safety

Like other atypical antipsychotic drugs, at clinically relevant doses ziprasidone appears to be less likely than first generation neuroleptics to cause prolactinemia, sedation and parkinsonism, although akathisia is not uncommon. In the six-month study of placebo versus ziprasidone augmentation of lithium or valproate mentioned earlier,²⁸ the only treatment-emergent side effect that occurred more frequently with ziprasidone than placebo was tremor.

One significant concern that has been raised about ziprasidone is its suppression of expression of the human ether-a-go-go related gene (HERG), which results in inhibition of the delayed potassium rectifier current in cardiac conduction cells, prolonging depolarization and with it the QT interval.³³ Excessive QT prolongation has the potential to predispose to a risk of torsades de pointes. Very rare cases of this malignant arrhythmia have in fact been reported with ziprasidone;^{34,35} risk factors include congenital long QT syndrome, older age, female gender, cardiac disease, bradycardia, substance abuse, electrolyte disturbances, and concomitant use of other medications that prolong the QT interval such as tricyclic antidepressants,

a number of other antipsychotic drugs, erythromycin, trazodone and fluoxetine.³³ Although electrocardiographic evidence of QT prolongation is common with ziprasidone, clinically meaningful QT prolongation is not, and reports of adverse cardiac effects after considerable clinical use and a number of overdoses have been rare.³⁶ Lithium and valproate appear not to have the potential for additive QT prolongation with ziprasidone.

A few cases of neuroleptic malignant syndrome have been reported with ziprasidone.³⁷ Although weight gain with ziprasidone is less than with atypical antipsychotics such as olanzapine and risperidone,³⁸ as many as 7% of ziprasidone-treated schizophrenia patients have experienced clinically significant weight gain in some studies.³⁹ Metabolic effects such as elevated lipids and diabetes mellitus have appeared to be less common than with other atypicals, although no large case control studies of this problem involving ziprasidone versus other antipsychotics have been published. Because ziprasidone has serotonin reuptake inhibitor properties, combinations with other serotonergic agents such as selective serotonin reuptake inhibitor (SSRI) antidepressants, dextromethorphan, or meperidine carry the risk of serotonin syndrome. Dangerous serotonin syndrome can occur with combinations of ziprasidone and monoamine oxidase (MAO) inhibitors.

Patient Preference

Patients who cannot tolerate weight gain or sedation generally find ziprasidone to be preferable to other atypical antipsychotic drugs. Conversely, some people feel overstimulated or agitated with this medication.⁷ The manufacturer states that more rapid dosage escalation is better tolerated but prospective comparisons of rapid versus slow dosage adjustment in the maintenance treatment of bipolar disorder have not been published. In actual practice, some people do well with more rapid increases in dose, but others become dysphoric or uncomfortable and discontinue the medication. Twice a day dosing can be problematic for patients who do not keep track of medications well, but this is an issue with immediate release valproate, which also is administered twice daily. Lithium can usually be taken in one bedtime dose, and combining it with a twice daily medication is sometimes confusing.



Place of Ziprasidone in Maintenance Treatment of Bipolar Disorder

Whereas some patients with bipolar mood disorders do well with long-term monotherapy with a mood stabilizing medication such as lithium or valproate, a substantial number, especially those with frequent recurrences and mixed symptoms, have a more complex pathophysiology that requires combinations of treatments with different actions. Yet with the exception of studies of antipsychotic drugs added to lithium or valproate, there is little systematic research on combination therapy in bipolar disorder. Insofar as no single treatment or combination of two treatments has been shown to reliably eliminate all symptoms and disability or to totally prevent relapse and recurrence, there is a dearth of evidence for definitive maintenance treatments for bipolar disorder.

Although psychotic symptoms do not have to be present for ziprasidone and other antipsychotic drugs to be effective acutely for mania, these medications may be most useful in maintenance therapy when residual psychosis occurs. In the absence of any systematic comparisons between combinations of mood stabilizers and addition of an antipsychotic drug to a mood stabilizer, in bipolar disorder, and in view of the limited evidence of long-term efficacy of ziprasidone in this condition, combinations of mood stabilizers might be considered prior to addition of an antipsychotic drug. Antipsychotic augmentation might be most appropriately considered for patients with residual symptoms of dysphoric hypomania such as irritability, insomnia, hypervigilance or extreme interpersonal sensitivity that fail to respond to mood stabilizer combinations. There is no reason to expect that combinations of antipsychotic drugs have any role in maintenance therapy of bipolar disorder.

As has been true of maintenance studies of other antipsychotic drugs, longer-term treatment with ziprasidone has been superior to placebo in reducing recurrences of mania but not depression. This phenomenon may not be surprising since patients are entered in the study following a manic but not a depressive episode and the polarity of the index episode often predicts the polarity of the next recurrence.⁴⁰ Similarly, primary mood stabilizers are often more effective at preventing recurrences of mania than depression. In contrast,

chronic treatment with neuroleptics may increase the long-term risk of depressive relapse and the same could be true of the newer atypical antipsychotic drugs like ziprasidone. Interestingly, in two registration trials of maintenance lamotrigine,^{41,42} the time to a depressive recurrence was somewhat lengthened compared with placebo in each study, but apparent lengthening of time to a manic recurrence was not. However, when results of the two studies, which had different populations of patients, were combined, enough patients had lengthening of time to a manic episode to produce statistically if not clinically significant results.

Consistent with industry sponsored studies of other atypical antipsychotics using a similar methodology, addition of ziprasidone to lithium or valproate lengthens the time to intervention for recurrence or relapse, but in these studies even though lithium and valproate levels were technically in the reported therapeutic range they were not optimized.⁴³ It is therefore conceivable that higher levels of the primary mood stabilizer would have been as effective as the mood stabilizer plus ziprasidone, although a higher mood stabilizer dose might also result in more dropouts due to adverse effects. In the absence of comparisons of augmentation with ziprasidone or other antipsychotics to augmentation with a second mood stabilizer, clinical judgment is the only guide to which approach to choose.

If an antipsychotic drug is deemed to be appropriate as maintenance therapy in bipolar disorder, ziprasidone is a consideration for patients who cannot tolerate weight gain or sedation. It is less likely to be useful for patients with severe insomnia as it is not as sedating as some other atypicals, although there are no formal studies of this issue. Ziprasidone should not be combined with markedly serotonergic medications or monoamine oxidase inhibitors because of the risk of serotonin syndrome. Other medications that prolong the QT interval should probably be avoided. Although the absorption of ziprasidone is doubled by ingesting it with food, there is no research indicating reduced efficacy or side effects when the medication is taken without food. Nevertheless, if ziprasidone is not proving as effective as expected, clinicians should ensure that it is being taken with meals, and if adverse effects are excessive an attempt might be made not to take it with food.



Conclusion

Bipolar disorder is not a unitary illness but a heterogeneous group of conditions with different pathophysiologies, outcomes and treatments. Because maintenance treatments differ in their spectra of action, a single medication often is not fully effective in fully treating the mood disorder, and combination therapy is necessary in this context.⁷ Unfortunately, aside from industry sponsored add-on studies discussed earlier there is little systematic research into optimal combination maintenance treatment with complete mood stability over the years as the primary outcome.

A major limitation of all industry sponsored trials in bipolar disorder is the exclusion of patients with comorbid, complex and treatment-resistant bipolar mood disorders, who constitute a substantial proportion of patients seen in psychiatric practice. Indeed, many manic patients encountered in clinical practice do not continue to consent to routine established treatment, let alone sustain consent over the time necessary for participation in a long-term clinical trial. The relevance of currently available maintenance studies to actual practice therefore is not always apparent. Independently funded practical clinical trials comparing regimens with and without antipsychotic drugs and comparing antipsychotic drugs to each other are necessary to address this problem.

As research in maintenance therapy of bipolar disorder continues, specific markers of a response to an atypical antipsychotic and to ziprasidone in particular may emerge. In the meantime, experience and clinical judgment dictate treatment choice, and it is essential to remain objective in assessing whether the patient has responded and how completely, bearing in mind that the goal of treatment should be as complete resolution of symptoms as is possible.

Conflict of Interest Statement

Dr. S. Dubovsky has received grant support from Pfizer, Otsuka, Simitomo, Sunivion, Lilly and Biogen. Dr. A. Dubovsky has no conflicts of interest to disclose.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and

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