R E V I E W

Emerging treatment options in bipolar disorder in adolescents: focus on ziprasidone

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Abstract: Bipolar disorder is a debilitating, and chronic condition in adolescents. The rate of diagnosis and treatment is increasing in adolescents despite considerable controversy regarding criteria for diagnosis. Atypical antipsychotics have been studied extensively for adult and adolescent bipolar disorder. Ziprasidone is an atypical neuroleptic with novel receptor-binding activity and a favorable side effect profile. It has been marketed in the US since 2000, and now has several indications approved by the US Food and Drug Administration. Emerging case reports, open-label studies, and randomized controlled trials suggest that it may have a role in the management of adolescent bipolar disorder. Somnolence, akathisia, tachycardia, and prolonged corrected QT intervals are major safety concerns. There are no definitive guidelines for dosing ziprasidone in adolescents based on current literature. However, optimal treatment may involve dosages near the adult range. Given minimal data and understanding of its effects on cardiac conduction, it might be prudent to obtain electrocardiograms prior to initiation and during treatment. While not a first-line medication choice for adolescents struggling with bipolar disorder, it may be considered in certain situations in which metabolic side effects and weight gain are of concern.

Keywords: ziprasidone, bipolar disorder, atypical antipsychotics, mood stabilizer, mania, hypomania

Introduction

Bipolar disorder is a significant individual and public health challenge across the lifespan. It is often noted to have its origins in adolescence,[1] and has a poorer prognosis in these cases.[2] As with adults, the *Diagnostic and Statistical Manual of Mental Disorders* diagnosis of bipolar I disorder in adolescents involves an episode of mania or mixed mania with significant psychosocial impairment for a duration of one week or culminating in hospitalization. Symptoms of mania include a circumscribed period of elevated, expansive, or irritable mood with three additional symptoms (or four symptoms if the patient's mood is merely irritable) to include magnified self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased psychomotor activity, or goal-directed behavior, and involvement in gratifying activities with a high potential for harm. Individuals afflicted with mania also frequently have psychotic symptoms. Bipolar II disorder encompasses periods of manic symptoms with a shorter and less severe duration, which are termed hypomania, and the presence of at least one major depressive episode. Although it is an easily observable change from previous functioning, hypomania does not confer psychosocial impairment or involve psychotic symptoms.[3]

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Table 1 Receptor-binding affinities of ziprasidone and clinical relevance[12]

	D_2	5-HT_{2A}	5-HT_{1A}	$Alpha_1$	Muscarinic
Receptor-binding affinities pK_i (nanomolar)	3.1	0.39	2.5	13	–
Clinical implication	High $5\text{-HT}_{2A}/D_2$ affinity ratio which may confer less risk for EPS	High $5\text{-HT}_{2A}/D_2$ affinity ratio which may confer less risk for EPS	$5HT_{1A}$ agonism beneficial for cognitive and mood symptoms	Better tolerability and less likely to cause hypotension or sedation	Less anticholinergic side effects/GI disturbances

Abbreviations: GI, gastrointestinal; EPS, extrapyramidal symptoms.

Over the past 10 years, the number of adolescents diagnosed and treated for bipolar disorder has increased considerably in the US.[4] As with adults, there is considerable controversy about how narrow or broadly defined this diagnosis should be. Many young people with mood lability, dangerous behaviors, and aggressive outbursts are given the diagnosis of bipolar disorder in community settings. Optimum management involves a thorough diagnostic assessment with a consideration of psychosocial factors and comorbidities. However, pharmacotherapy is the principal treatment for depression and mania in well circumscribed bipolar I disorder.

For adolescents, the American Academy of Child and Adolescent Psychiatry Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder recommends initial treatment with a medication approved by the US Food and Drug Administration (FDA) for bipolar disorder in adults.[5] Presently this includes lithium for acute mania and maintenance treatment. Aripiprazole, asenapine, valproate, olanzapine, risperidone, quetiapine, and ziprasidone are also approved for the treatment of acute mania in adults, as is chlorpromazine. Lamotrigine, risperidone long-acting injectable (Risperdal® Consta®) and olanzapine are also approved for maintenance therapy in adults. Quetiapine, combined olanzapine and fluoxetine are also approved for bipolar depression in adults. For youth

with bipolar disorder, olanzapine was recently approved by the FDA for the acute treatment of bipolar I manic or mixed episodes in the age group 13–17 years. Quetiapine has been approved as monotherapy or in addition to lithium or divalproex for the acute treatment of manic episodes in patients aged 10–17 years. Aripiprazole and risperidone are also FDA-approved for the acute treatment of bipolar I manic or mixed episodes in patients aged 10–17 years. Otherwise, lithium is approved for patients aged 12 years and older for the acute and maintenance treatment of mania. Presently, ziprasidone does not have a pediatric indication and is not typically a first-line choice for the management of adolescent bipolar disorder. There is growing concern and data to indicate that even initial treatment with second-generation antipsychotics, such as olanzapine, risperidone, quetiapine, and aripiprazole leads to significant weight gain and metabolic changes.[6] Early evidence suggests that ziprasidone may pose less risk in this regard and hence could be an appropriate choice with some clinical presentations.[7]

Pharmacodynamics

Ziprasidone, a second-generation antipsychotic binds to a variety of serotonergic ($5\text{-HT}_{2a/2c}$, 5-HT_{1A}, 5-HT_{1D}) and dopaminergic (D_1, D_2, D_3) receptors (Table 1). To this end, ziprasidone has a particularly high affinity for the human 5-HT_{2A} receptor, and in vitro binding studies of human 5-HT receptors suggest that the affinity of ziprasidone at these receptors is higher than of the second-generation antipsychotics, olanzapine, quetiapine, and clozapine.[8] Similarly, binding of ziprasidone to human dopamine receptors is higher than that of olanzapine, quetiapine, and clozapine.[8] Additionally, ziprasidone exhibits moderate in vitro binding affinity for H_1 and α_1-adrenergic receptors. Functional studies in adults have suggested that ziprasidone antagonizes D_2, 5-HT_{2A}, and 5-HT_{1D} receptors and, like other second-generation antipsychotics, acts as an agonist at 5-HT_{1A} receptors.[9] In adults with schizophrenia, positron emission tomography imaging

Table 2 Comparison of pharmacokinetic properties of oral ziprasidone in pediatric and adult populations[9,11,15]

	Children/ adolescents	Adults
C_{max} (ng/mL)	36–51	56
T_{max} (hours)	5–5.5	4
$T_{1/2}$ (hours)	3.3–4.1	4.8
Area under the curve (ng × h/mL)	247–457	337
Apparent systemic clearance (mL/min/kg)	11.5	7.5
Kinetics	linear	linear

studies have revealed that ziprasidone saturates $5-HT_2$ receptors moreso than D_2 receptors across therapeutic dosages, and that $5-HT_2$ and D_2 receptor occupancy is directly related to plasma ziprasidone concentrations (Table 2).[10]

There are limited pharmacodynamic data on ziprasidone in children or adolescents. However, an interesting study which utilized clinical probes of dopaminergic activity (frequency of eye blinking) and dopamine receptor antagonism (acute, postdose changes in serum prolactin), suggested that ziprasidone might have functional agonist activity at cortical D_2 receptors in addition to D_2 receptor antagonism.[11,12]

Pharmacokinetics and metabolism

Ziprasidone is absorbed from the gastrointestinal tract, although its bioavailability is highly influenced by the presence of food.[9,13,14] Importantly, the absorption as indicated by C_{max}, C_{trough}, and area under the curve, does not appear to be related to the total fat content of a meal, but rather to its total caloric content.[14] Data from absorption studies in adults suggest that ziprasidone should be administered following a meal of at least 500 kcal for maximal absorption.[14] Peak plasma concentrations in adults are observed within 6–8 hours of oral administration, and the half-life is approximately five hours (terminal half-life seven hours) in adults. Because of the short half-life of ziprasidone, steady-state concentrations are generally reached within 1–3 days. Ziprasidone is highly (>99%) protein-bound (binding primarily to albumin and α_1-acid glycoprotein) and has a large volume of distribution (1.5 L/kg). The compound is extensively metabolized, about two-thirds by aldehyde oxidase and one-third in the liver by the cytochrome P450 3A4 and, to a lesser extent, the 1 A2 systems. This further explains why it has no effect with smoking and few drug interactions (eg, its dose is increased with carbamazepine while has no effect on lithium or valproate).[9]

There are few studies of ziprasidone pharmacokinetics in children and adolescents. In a study of 24 children and adolescents with tic disorder, aged 7–16 years, and treated with a single dose of ziprasidone 0.2–0.3 mg/kg (5 mg, 10 mg, or 20 mg), the area under the curve (a surrogate of bioavailability) was similar between adults and children/adolescents.[15,16] However, the half-life was slightly lower in children than in adults (3.3–4.1 versus 4.8).[15,16] This lower half-life, as well as the finding of increased ziprasidone clearance in children and adolescents, may be related to a reduced first-pass effect. Alternatively, it is likely that these pharmacokinetic differences might also be related to

lower rates of cigarette smoking in children and adolescents, because cigarette smoking induces the cytochrome P450 3A4 system. However, population-based studies of adults have failed to demonstrate significant pharmacokinetic differences between smokers and nonsmokers,[9] while Stimmel found that the pharmacokinetics of ziprasidone show no differences with regard to gender or age.[17] Ziprasidone is also available in an injectable formulation for intramuscular use, which is approved for the acute treatment of agitation associated with schizophrenia in adults. However, there are no published pharmacokinetic studies of this formulation in children or adolescents.[9]

Efficacy studies

In 2008, Delbello et al presented the results of a four-week, double-blind, placebo-controlled multicenter study of ziprasidone. This involved subjects aged 10–17 years having bipolar I disorder with a current manic or mixed episode. Diagnosis was based on an interview using the Kiddie-Schedule for Affective Disorders and Schizophrenia.[18] In this study, subjects were randomized in a 2:1 ratio to ziprasidone (n = 150) with a flexible dosing range (80–160 mg daily) or placebo (n = 88), with titration over 1–2 weeks. The primary outcome measure was change in the Young Mania Rating Scale (YMRS)[19] from baseline to endpoint, with Clinical Global Impressions-Severity scale (CGI-S)[20] reported as a secondary outcome. The estimated least squares mean change in YMRS was −13.83 for ziprasidone as compared with −8.61 for placebo ($P = 0.0005$). For the CGI-S, the estimated least squares change from baseline to endpoint was −1.43 for ziprasidone as compared with 0.74 for placebo ($P = 0.0001$).[21]

Versavel et al reported on a dosing study in children and adolescents with bipolar disorder, schizophrenia, and schizoaffective disorder in 2005 that involved treatment with ziprasidone over six months. This trial included subjects aged 10–17 years with bipolar I disorder (manic or mixed) and a baseline YMRS score >17 or a diagnosis of schizophrenia/schizoaffective disorder with a Brief Psychiatric Rating Scale (BPRS)[22] score ≥35. These subjects were randomized to monotherapy titrated over 7–10 days at a dose of 10–40 mg twice daily (Group 1) or 20–80 mg twice daily (Group 2). All subjects were treated with fixed dosages for three weeks and then continued flexible-dose treatment for six months. Other medications were allowed during the flexible-dose phase. There were 23 subjects enrolled in the Group 1 and 40 subjects enrolled in Group 2. After three weeks, Group 1 had a mean YMRS improvement of 14.9 and Group 2 had

a mean improvement of 11.1. Over 27 weeks, subjects with bipolar I disorder in Group 1 had a 1.47 mean reduction in CGI-S, while bipolar I subjects in Group 2 had a mean reduction of 1.33.[23]

Biederman et al published results from an eight-week, open-label, prospective study of ziprasidone as monotherapy at a mean dose of 57.3 (±33.9) mg/day in 21 subjects aged 6–17 years of age who were diagnosed with bipolar I disorder (manic or mixed) or bipolar disorder not otherwise specified. Outcome measures included the YMRS, CGI, and BPRS. In this group, 14 (67%) completed the study. Treatment was associated with statistically significant improvements in mean YMRS scores (−10.8 ± 8.4, $P < 0.0001$). Furthermore, 57% of the subjects had a CGI of ≤2 at the end of eight weeks.[24]

Barnett published a case series of four patients aged 7–16 years with bipolar disorder who were switched to ziprasidone from other psychotropic medications. These patients had resolution of symptomatology (hypomania, hallucinations, aggression, irritability, dysphoria, and insomnia) within three days. One of the patients received adjunctive loraze-pam for anxiety, but all others had monotherapy.[25] Another case series describes the treatment courses of a 12-year-old male and a 15-year-old male, both with bipolar disorder, who were treated with a combination of ziprasidone and olanzapine. Both of these patients had dramatic, sustained improvements in functionality at home and at school on this combination.[26]

Safety

Blood level monitoring is not required with ziprasidone. However, as with other atypical antipsychotics, careful cardiometabolic monitoring is recommended. This includes an indepth individual and family history focused on obesity, hypertension, hyperlipidemia, diabetes, lifestyle, and adverse events. Height, weight, body mass index (percentile and z score) should be monitored at every visit. Blood pressure, pulse, fasting blood glucose, and lipids should be checked after the first three months of treatment and then every six months. Thyroid testing should be completed annually. Sexual dysfunction should be monitored and prolactin levels should be checked if the patient develops sexual side effects, gynecomastia, or galactorrhea.[6,27] Due to concerns regarding possible effects on cardiac conduction, it has been recommended that electrocardiograms are obtained both prior to initiation and during treatment.[28] Based on case series publications, open trials, and larger studies, ziprasidone

appears to be well tolerated. Side effects are generally mild and transient. Ziprasidone has been associated with a low incidence of sedative effects, a low likelihood of extrapyramidal symptoms, and postural hypotension, with minimal anticholinergic effects.[29]

Common treatment-emergent adverse effects

In 2008, Delbello et al studied 26 subjects on ziprasidone doses ranging from 80–160 mg in a three-week fixed and 24-week flexible-dose trial. Sedation was observed in approximately 32%, somnolence in 30%, and nausea and headache in 25% of this sample.[21] In 2007, Malone et al conducted an open-label pilot study of ziprasidone in 12 autistic subjects. In this case, investigators observed drowsiness in almost 42% of the patient population, with decreased appetite and agitation in 25%, and nausea and headache in 17% of cases.[30] Sallee et al reported that most of the sedation seen in their study was transient and decreased with dose reduction.[28]

Serious adverse effects

Unintentional overdose of ziprasidone has been reported in a few cases involving toddlers which commonly presented with serious respiratory depression, altered mental state, and drooling, but no deaths have been reported, and respiratory depression was treatable.[31,32] Lackey reported seven cases of ziprasidone overdose involving doses of 40–80 mg and needing activated charcoal and gastric lavage. The long-term consequences were not reported.[33]

Antidopaminergic adverse effects

Delbello et al reported dystonia, tremors, akathisia, and extrapyramidal symptoms in 22% and 16%, respectively, in separate treatment groups. Also, seven of 63 subjects in period 1 and 10 of 56 subjects in period 2 received benzotropine.[21] In 2007, Malone et al observed two subjects with acute dystonic reactions. This resolved in both instances and did not recur with reinitiation of ziprasidone.[30] In other work, Sallee et al measured patients' symptoms on objective scales for extrapyramidal symptoms at week 8, and reported that subjects treated with ziprasidone were similar to those in the placebo group.[28]

Hyperprolactinemia

In 2000, Sallee et al studied 28 subjects with Tourette's disorder, and found no difference in prolactin levels between those treated with placebo or ziprasidone.[28] However, there have been a few

case reports of hyperprolactinemia in female teenagers treated with ziprasidone. In these instances, hyperprolactinemia was transient and resolved upon stopping medication.[27,34]

Metabolic effects

With increasing concerns about childhood obesity, ziprasidone has a relatively safer side effect profile in comparison with other antipsychotics in terms of metabolic effects, eg, weight gain, serum lipid elevations, and glucose dysregulation.[35] For example, experts have concluded that the available information suggests that ziprasidone's risk of adverse metabolic effects is much less than that for other atypical antipsychotics, such as olanzapine.[36] Studies examining the impact of switching from risperidone or olanzapine to ziprasidone suggest that this switch is often accompanied by weight loss and improved lipid profiles.[36,37] For example, Sallee et al found a statistically significant decrease of 10.2 mg/dL in cholesterol, whereas triglycerides, high-density cholesterol, and low-density cholesterol showed no change.[28]

Effects on corrected QT interval

Ziprasidone apparently has a predisposition to cause QTc prolongation in some patients. Experts have recommended close cardiac monitoring in patients taking higher ziprasidone doses in combination with medication which could prolong QT_c interval.[6] Blair et al examined electrocardiographic changes in children and adolescents treated with ziprasidone and found QTc prolongation which was not dose-related in 20 subjects treated for six months with ziprasidone. This involved a mean change of 28 ± 26 msec, with three subjects showing prolongation more than 450 msec, and one subject displaying a 114 msec change from baseline.[38] However, in a letter to the editor, Loebel et al questioned the results of Blair's study based on data analysis and methodology (specifically the use of Bazett's correction formula because it overestimates QT_c duration in patients with elevated heart rates).[39,40] Sallee et al studied 24 subjects in an open-label, single-dose study of ziprasidone. They measured QT_c interval four hours postdose using both Bazett's and Fridericia's formulae, and did not find any statistically significant changes.[41] In 2002, Patel et al did a retrospective study on 10 day patient population in Austin State Hospital who received ziprasidone for mood disorder with psychosis, schizophrenia and bipolar disorder in children and noted that 9 of the 13 subjects had a baseline and follow-up electrocardiogram. They observed only one child with a QT_c prolongation of 119 msec.[42] Studies in adults examining the impact of intramuscular ziprasidone suggest that QT_c prolongation is minimal.[37,38] There were no changes noted in QT_c interval in a case series of children with autism treated with ziprasidone.[43]

Discussion

The treatment of bipolar disorder in adolescents is complex and challenging. The majority of adults with bipolar disorder consistently report their first episodes prior to the age of 20 years.[44,45] Hence it is important for clinicians to have a high index of suspicion for the diagnosis and skill in addressing this chronic condition early in the life cycle. Screening, careful interview, evaluation, and consideration of other psychiatric comorbidities are important steps in the management of this illness in developing adolescents. Pharmacotherapy is essential for bipolar disorder across the lifespan. In teenagers, treatment typically consists of a mood stabilizer, such as lithium or an atypical antipsychotic. Ziprasidone is an atypical antipsychotic with unique receptor-binding properties and a favorable side effect profile (Table 1). Stewart et al have also examined changes in global functioning scales, such as the Child Health Questionnaire[46] and the Children's Global Assessment Scale,[47] with adolescents during treatment with ziprasidone. This demonstrated improvements from baseline in subjects treated with ziprasidone.[48] Harvey et al reported functional gains measured on quality of life scales with ziprasidone when compared with haloperidol.[49] Currently, ziprasidone does not have a pediatric indication. Given that there is a paucity of literature in adolescents, further clinical studies are essential. However, at present, the evidence does suggest that ziprasidone may play a role in the management of bipolar disorder in children and adolescents. Given that ziprasidone appears to have minimal metabolic effects, such as weight gain, lipid elevation, or impact on glucose metabolism, it may be increasingly considered in certain clinical situations. However, as with other atypical antipsychotics, close cardiometabolic monitoring is recommended. Experts have also advised that a thorough personal and family cardiac history is essential, as well as baseline and follow-up electrocardiograms.[50]

Disclosure

The authors report no conflicts of interest in this work.

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