Atypical Antipsychotics for Acute Manic and Mixed Episodes in Children and Adolescents with Bipolar Disorder
Efficacy and Tolerability

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Abstract

The diagnosis of bipolar disorder (BD) in children is increasing, and often requires a comprehensive treatment plan to address a complex array of symptoms and associated morbidities. Pharmacotherapy, in combination with psychotherapeutic interventions, is essential for the treatment and stabilization of disrupted mood. Current evidence collectively demonstrates, by randomized controlled design, that atypical antipsychotics have efficacy for the treatment of acute manic or mixed symptoms in children and adolescents with BD. Additional longitudinal and biological studies are warranted to characterize the effects of atypical antipsychotics on all phases and stages of bipolar illness development in children and adolescents.

Children and adolescents are increasingly being diagnosed with bipolar disorder (BD). Recent US national trends suggest a 40-fold increase in the diagnosis of BD in youth in office-based settings over the last 10 years,[1] and a 4-fold increase in BD-related inpatient hospitalizations among adolescents,[2] suggesting a rapidly in-creasing clinical identification of this disorder in paediatric populations. An early onset of BD in youth has been linked with a more severe course of illness, rapid cycling, an increased risk for psychosis, suicide attempts and substance abuse, as well as the presence of co-morbidities and complications such as poor academic and job

performance, interpersonal conflicts or legal problems.[3-7] Despite vigorous efforts to find effective treatments for this condition in children and adolescents, treatment challenges are frequent and illness carries a high morbidity and mortality.[8]

Comprehensive treatment plans are often required for individuals with BD to address a complex array of symptoms and associated morbidities. In general, a multimodal treatment approach combining pharmacological agents and psychosocial interventions is suggested, with the goal to improve symptoms, provide psychoeducation about BD, and promote treatment adherence for relapse prevention and attenuation of long-term complications from the illness.[9] Clinicians are encouraged to advocate for prevention, early intervention, and biopsychosocial treatments that promote the healthy growth and development of all children affected by BD, in any cultural context.

This article concentrates on the use of atypical antipsychotics for the treatment of BD in children and adolescents, and reviews some new controlled trials that have recently emerged, primarily for the treatment of acute manic or mixed BD episodes with this class of drugs. Studies were found through a systematic search on PubMed and in conference proceedings, and compared for analysis of efficacy and safety where there was clinical homogeneity and comparable trial duration.

1. Antipsychotics in Bipolar Disorder (BD)

Expert opinion, including the American Academy of Child and Adolescent Psychiatry (AACAP)[10,11] guideline for the treatment of paediatric BD, endorses the use of a either a mood stabilizer such as lithium, divalproex sodium (valproate semisodium) or carbamazepine, or an atypical antipsychotic such as olanzapine, risperidone or quetiapine as optimal first-line agents for the treatment of acute mania. Since the AACAP practice parameters were published, new data with other atypical antipsychotics such as ziprasidone and aripiprazole have emerged, necessitating an update on existing clinical parameters and guidelines. Clinicians are currently

being recommended to initiate medications that are already US FDA approved for the treatment of BD in adults. Atypical antipsychotics have demonstrated efficacy and are FDA-indicated for the treatment of mania (olanzapine, risperidone, quetiapine and aripiprazole as monotherapy and adjunctive therapy, and ziprasidone and asenapine as monotherapy), depression (olanzapine plus fluoxetine combination, and quetiapine as monotherapy) and maintenance therapy (olanzapine, aripiprazole and long-acting injectable risperidone as monotherapy, and quetiapine, ziprasidone and long-acting injectable risperidone as adjunctive therapy) for adults with BD.[10]

As a collective class of pharmacological agents, several lines of evidence support the safety and efficacy of atypical antipsychotics for treating paediatric BD.[12] Specifically, the second-generation antipsychotics risperidone, aripiprazole, olanzapine, quetiapine and ziprasidone all have multicentre, randomized, double-blind, placebo-controlled studies demonstrating efficacy as monotherapy in paediatric acute mania. As of 2009, risperidone, aripiprazole and quetiapine have been approved as monotherapy for the treatment of acute manic and mixed episodes in children and adolescents aged 10–17 years.[12] Olanzapine has been approved for a similar indication in adolescents aged 13–17 years.[12] Aripiprazole has also been approved for acute mania adjunct to lithium or valproate and for maintenance treatment in paediatric BD,[12] with maintenance efficacy extrapolated from adult data[13] and from comparisons of pharmacokinetic parameters between adults and children for aripiprazole. To date, there are no published placebo-controlled studies that are available for atypical antipsychotics for acute bipolar depression or maintenance treatment in children and adolescents, and as such, these topics are not discussed further in this review. Consensus pathways for the treatment of paediatric BD generally suggest starting with monotherapy and then progressing to a combined treatment from two different classes of medication for the treatment of acute mania in children.[9,14]

This paper provides a brief review of each of the atypical antipsychotics that have become

available for children and adolescents with acute manic or mixed states of mania and depression combined. The efficacy of an atypical antipsychotic is defined in terms of treatment response rates or remission of illness. Response rates are commonly reported as a change in a symptom score as determined by clinical assessments of mania from baseline to endpoint. The Young Mania Rating Scale (YMRS) is a commonly used validated instrument to determine the degree of manic symptomatology.[15] The response rate for the treatment of acute manic or mixed states is commonly defined as the proportion of patients with a ≥50% reduction in YMRS score from baseline to endpoint of the clinical trial. The remission rate is often defined as the proportion of patients with a YMRS score of <12 at endpoint.

After summarizing the efficacy of each antipsychotic, the most common adverse events associated with the medication are considered and dosing is discussed. In general, the incidence of extrapyramidal symptoms (EPS) or neuroleptic malignant syndrome is lower with atypical antipsychotics than with the conventional antipsychotics, but may still occur and should be monitored.[11] As a group, these medications may cause significant weight gain in youths, and subsequent metabolic problems such as an increased risk of developing type 2 diabetes mellitus and the metabolic syndrome.[11] Clinically significant treatment-emergent weight gain in most studies on atypical antipsychotics has been defined as a ≥7% increase in weight from baseline.

To assess treatment response and risk for adverse events, we also determined the number needed to treat (NNT) and the number needed to harm (NNH) at clinical outcome of each medication tested by randomized controlled design.[16] The NNT is the number of individuals who need to be treated with a specific agent to yield one additional good outcome compared with placebo, computed as $1/(p_{drug} - p_{placebo})$, where p_{drug} is the probability of response in the group assigned to the atypical antipsychotic, and $p_{placebo}$ is the probability of response in the placebo group at the endpoint of the study. The lower the NNT, the more effective the treatment is at yielding a good outcome. FDA-approved treatments for BD have single-digit NNTs for response compared with placebo, representing at least 10% superiority over placebo.

Conversely, the NNH indicates how many individuals need to be exposed to a risk factor to cause harm in one patient who would not otherwise have been harmed. NNH is computed as $1/(p_{drug} - p_{placebo})$, where p_{drug} is the probability of an adverse event with exposure to drug and $p_{placebo}$ is the probability of an adverse event with exposure to placebo at endpoint. The higher the NNH, the less likely are adverse events to occur. Clearly, the NNH ought to be higher than the NNT if there is to be a greater likelihood of good than harm. In most instances, double-digit NNHs are acceptable, representing no more than a 10% increase in risk compared with placebo.

NNTs and NNHs are commonly rounded up to the next whole number, but in this article are reported to the first decimal place. NNTs and NNHs are effect sizes and hence independent of statistical significance, and are thus most meaningful when there is a significant difference between active drug and placebo. In some articles, NNTs and NNHs are reported with 95% confidence intervals, with intervals that do not cross zero or include infinity representing significant

Table I. Treatment response for placebo-controlled trials of atypical antipsychotics used in paediatric mania

Medication	Young Mania Rating Scale response rate (%)		Number needed to treat (95% CI)	Reference
	drug	placebo		
Olanzapine	48	22	3.8 (2.4, 8.5)	17
Risperidone	61	28	3.0 (2.1, 5.7)	18
Quetiapine	61	37	4.2 (2.8, 8.5)	19
Aripiprazole	54	26	3.6 (2.5, 6.1)	20
Ziprasidone	62	35	3.7 (2.5, 7.0)	21

Table II. Rates of weight gain for available placebo-controlled trials of atypical antipsychotics used in paediatric mania

Medication	Event rate for clinically significant [≥7%] weight gain (%)		Number needed to harm (95% CI)	Reference
	drug	placebo		
Olanzapine	42	2	2.5 (2.0, 3.3)	17
Risperidone	14	5	11.1 (5.8, 120.7)	18
Quetiapine	12	0	8.2 (5.2, 18.9)	19
Aripiprazole	8	5	28.0 (10.3, ∞)	20
Ziprasidone	7	4	33.3 (10.9, ∞)	21

differences between active drug and placebo. These data are summarized in tables I and II.

As increasing evidence for the use of atypical antipsychotic medications in children and adolescents emerges, a critical evaluation of the efficacy and tolerability of these medications may help clinicians and patients make prudent decisions about proceeding with a particular treatment that may expose patients to adverse events while providing therapeutic benefits.[22] NNT and NNH data need to be integrated with individual patient factors and preferences to provide personalized qualitative evidence-based care. With these considerations in mind, dosing recommendations and guidelines for titration are also provided.

2. Olanzapine

Olanzapine was FDA approved for the treatment of mania in adults in 2004, and for the treatment of manic or mixed episodes of bipolar I disorder in adolescents aged 13 to 17 years in 2009. Olanzapine has a rapid onset of action for mixed and manic episodes.[23] A large, multisite, 3-week, double-blind, placebo-controlled study of olanzapine for 161 adolescents (mean age = 15 years) with manic or mixed episodes reported a significantly greater reduction in manic symptoms and higher rates of response and remission in patients taking olanzapine compared with those assigned to placebo.[17] In this study, participants were randomly assigned to receive either placebo or olanzapine at dosages of 2.5–5.0 mg/day, titrated in a response-dependent fashion up to 20 mg/day. The mean daily dose of olanzapine during the double-blind period was

10.7 mg (SD = 4.5). After a week of treatment, patients on olanzapine had an 18-point reduction in their YMRS score, whereas patients assigned to placebo reduced their YMRS score by 10 points (p = 0.001, effect size, d = 0.84). At endpoint, the group treated with olanzapine showed higher response (48% vs 22%, p = 0.002) and remission (35% vs 11%, p = 0.001) rates compared with placebo. Based on these findings, the NNT for response with olanzapine was 3.8 and for remission with olanzapine was 4.2.

Taking olanzapine was associated with greater mean weight gain (3.7 kg) compared with placebo (0.3 kg), with an incidence of clinically significant (≥7%) weight gain of 42% in patients taking olanzapine and 2% in placebo (p < 0.001, NNH = 2.5, 95% CI 2.0, 3.3). The olanzapine group also showed increases in prolactin relative to the placebo group, particularly among boys (females: 25.7% vs 0%, p = 0.007, NNH = 3.9, 95% CI 2.5, 8.9; males: 62.5% vs 5%, p < 0.001, NNH = 1.7, 95% CI 1.4, 2.5).[17] Thus, with olanzapine, the likelihood of harm (weight gain NNH of 2.5) offsets the likelihood of benefit (response and remission NNTs of 3.8 and 4.2, respectively).

Despite this unfavourable NNH : NNT ratio, olanzapine may be initiated at 2.5 mg/day, and titrated to a target dosage of 5–20 mg once daily or divided twice daily depending on the child's weight and treatment response. This recommendation is based on data from the above trial and our clinical experience with paediatric populations. Less longer-term data in paediatric BD patients is available, but a few open-label prospective studies have shown promising results. After completing the above 3-week trial,[17] 146 adolescents continued taking olanzapine in

an open-label fashion for up to 26 weeks.[24] At the end of this extended treatment period, study participants showed a 63% response rate, with ≥50% reduction in YMRS score and a Clinical Global Impressions – Bipolar Disorder (CGI-BP) severity score of ≤3. However, 69% of the adolescents had a 7% or greater increase in bodyweight and 40.5% of participants had abnormally high prolactin levels. Thus, metabolic adverse effects may limit the utility of olanzapine as an acute and maintenance agent for paediatric BD. However, it should be remembered that metabolic adverse effects and manic symptoms do not always weigh equally when considering risks and benefits of olanzapine treatment: the individual concerns of each patient should be taken into account by the clinician.

3. Risperidone

In 2007, risperidone became the first atypical antipsychotic to receive FDA approval as monotherapy for short-term treatment of acute manic or mixed BD episodes in youths aged between 10 and 17 years.[12] In a 3-week multicentre, randomized, double-blind, placebo-controlled trial in subjects aged 10–17 years with manic or mixed episodes, greater decreases in mean YMRS scores were observed in patients receiving risperidone 0.5–2.5 mg/day (mean modal daily dose 1.9 mg [n = 50]) or risperidone 3–6 mg/day (mean modal daily dose 4.7 mg [n = 61]) compared with those receiving placebo (n = 58).[18] At endpoint, YMRS response rates were 59% in the low-dose risperidone group, 63% in the high-dose group and 28% in the placebo group. Thus, the combined (low-dose and high-dose) risperidone group had a response rate of 61%, compared with 28% for placebo, yielding an NNT for response of 3.0 for risperidone.

Mean weight gain was about 2 kg with risperidone 0.5–2.5 mg/day, 1.5 kg with risperidone 3–6 mg/day and 0.65 kg with placebo. Clinically significant (≥7%) weight gain rates were 14% with risperidone and 5% with placebo,[18] yielding an NNH of 11.1. Rates of discontinuation of risperidone were 12% (13/111) versus 7% (4/58) with placebo. The most common adverse events resulting in discontinuations included somnolence (5%), nausea (3%), abdominal pain (2%) and vomiting (2%). In paediatric BD and schizophrenia trials, prolactin increases have been reported in 82–87% of patients receiving risperidone compared with 3–7% of those receiving placebo, yielding an NNH of 1.3.[25]

The recommended dosing of risperidone in children and adolescents with acute manic or mixed episodes is to start with 0.25 mg/day, and increase daily by 0.5–1 mg, with a target dosage of 2.5 mg/day once or divided either twice or three times daily.[12] The FDA recommends a 2.5 mg/day target as there was no evidence that dosages above 2.5 mg/day were more effective. As risperidone is commonly associated with weight gain and hyperprolactinaemia, physicians should consider monitoring prolactin levels prior to treatment and every 6 months thereafter.

4. Quetiapine

Quetiapine was approved by the FDA for the treatment of acute mania in adults in 2004, and was approved as monotherapy or an adjunct to lithium or divalproex for the acute treatment of manic episodes of BD in children and adolescents aged 10–17 years in 2009. A few controlled studies have found quetiapine effective for the treatment of paediatric mania. In a 3-week multicentre, randomized, double-blind, placebo-controlled trial of acute mania in subjects 10–17 years of age (n = 277), the YMRS response rate was higher for those receiving quetiapine (n = 188) than for those receiving placebo (n = 89) [61% vs 37%, p = 0.002], yielding an NNT of 4.2.[19]

Common adverse effects with quetiapine were somnolence (quetiapine 30%, placebo 10%, NNH = 5.0), sedation (quetiapine 25%, placebo 4.4%, NNH = 4.9) and dizziness (quetiapine 18.1%, placebo 2.2%, NNH = 6.3). Mean weight gain with placebo was 0.4 kg and for both quetiapine groups was 1.7 kg. The rates of clinically significant (≥7%) weight gain were 12.2% with quetiapine and 0% with placebo, resulting in an NNH for ≥7% weight gain of 8.2. In this trial, quetiapine was started at 50 mg at bedtime on day 1, increased to 400 mg/day in divided doses

by day 5 and to 600 mg/day in divided doses by day 7.

In addition, two smaller controlled studies suggest that quetiapine is a useful medication for the treatment of adolescent mania. In a double-blind, placebo-controlled, adjunctive study in children and adolescents with BD, DelBello and colleagues[26] reported that valproate and quetiapine reduced manic symptoms significantly more than valproate and placebo. In another double-blind study, this same group found that adolescent patients with BD receiving quetiapine monotherapy had faster resolution of their manic symptoms and higher rates of remission than those treated with valproate monotherapy, and quetiapine was well tolerated.[27]

The recommended dosing of quetiapine in youths with acute manic or mixed episodes is to start with 50 mg/day taken at bedtime, increased to 100 mg/day after 2 days, and then increased to a target dose of 300–600 mg after 2 additional days once or divided twice daily. Quetiapine is associated with sedation and orthostatic hypotension, presumably secondary to its affinity for histamine and α-adrenergic receptors, respectively. Weight gain in children receiving quetiapine appears to be slightly less than that in children treated with olanzapine or risperidone.[28]

5. Aripiprazole

Aripiprazole, a partial dopamine agonist, has also received FDA approval as monotherapy for the treatment of acute manic and mixed episodes in children and adolescents (age 10–17 years), as well as for maintenance treatment of BD and adjunctive therapy for major depression in children.[12] Aripiprazole is also approved for the treatment of schizophrenia in adolescents aged 13–17 years.

A 4-week, multicentre, randomized, double-blind, placebo-controlled trial studied adolescents (age 10–17 years) with acute manic or mixed episodes.[20] The YMRS response rate in 197 subjects receiving either 10 or 30 mg/day of aripiprazole was higher (pooled rate 54.2%) than in 99 subjects receiving placebo (26.1%). The

NNT for YMRS response to aripiprazole at endpoint was 3.6, and a significant decrease in YMRS was seen with aripiprazole at week 1 and thereafter.

Common adverse effects with aripiprazole were somnolence, EPS, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion and dizziness. Rates of somnolence (aripiprazole 22.9%, placebo 3.1%, NNH = 5.1), EPS (aripiprazole 19.8%, placebo 3.1%, NNH = 6.0), akathisia (aripiprazole 9.7%, placebo 2.1%, NNH = 13.2) and salivary hypersecretion (aripiprazole 5.6%, placebo 0%, NNH = 17.9) and clinically significant (≥7%) weight gain appeared to increase with aripiprazole dose (aripiprazole: 10 mg 4.0%, 30 mg 12.3%; placebo 4.6%; pooled NNH = 28). Mean weight gain was modest and statistically similar across groups (10 mg 0.55 kg, 30 mg 0.90 kg and placebo 0.54 kg). Adverse event discontinuation rates were 7% with aripiprazole and 2% with placebo.

The recommended dosing of aripiprazole in children and adolescents age 10–17 years with acute manic or mixed episodes is to start with 2 mg/day, increase to 5 mg/day after 2 days, and increase to the target dosage of 10 mg/day after 2 additional days, either once daily or divided twice daily.[12] Subsequent dose increases should be administered in 5 mg/day increments up to a 30 mg/day target once or divided twice daily.

6. Ziprasidone

Ziprasidone was approved by the FDA for the treatment of acute manic episodes in adults in 2006, but it has not been approved for use in paediatric mania. In a 4-week multicentre, randomized, double-blind, placebo-controlled trial in children and adolescents (age 10–17 years) with acute manic or mixed episodes, 149 subjects receiving ziprasidone (80–160 mg/day) had greater mean YMRS decreases compared with 88 subjects receiving placebo (–13.8 vs –8.6, respectively).[21] Response rates using a less stringent observed case analysis were 62% for the ziprasidone group and 35% for the placebo group, yielding an NNT for response to ziprasidone compared with placebo of 3.7. The most com-

mon adverse effects with ziprasidone were sedation (33%), somnolence (25%), headache (21%), nausea (13%), fatigue (13%) and dizziness (11%). Mean weight change was –0.6 kg and –0.2 kg for the ziprasidone and placebo groups, respectively. Clinically significant (≥7%) weight gain rates were 7% with ziprasidone and 4% with placebo, yielding an NNH of 33.3. There were no significant changes in mean body mass index (BMI), lipids, liver enzymes or glucose levels. One patient treated with ziprasidone had a QT prolongation to ≥460 msec.

Ziprasidone is among several atypical antipsychotics that block potassium currents[29] and prolong ventricular repolarization,[30,31] which may lead to prolonged QT intervals, torsades de pointes or other fatal arrhythmias.[32,33] It is recommended that prior to initiating treatment with ziprasidone, a careful personal history of congenital long QT syndrome be obtained, along with a family history of sudden cardiac death.[34] Ziprasidone should be avoided in individuals who are on other medications that have the propensity for prolonging the QT interval. Although there are currently no official recommendations for monitoring of the QT interval by electrocardiogram (ECG), it is recommended that an ECG be obtained at baseline and following attainment of ziprasidone target dosage.[35,36]

Paediatric populations may be given an initial daily dose of 20 mg, which may be titrated to 80–160 mg once or divided twice daily. Administration of ziprasidone may be complicated by the phenomenon of increased risk of akathisia at lower doses and the doubling of absorption when administered with food.

7. Clozapine

Clozapine lacks any randomized controlled trials to support its use in paediatric BD, and currently does not have FDA approval for the treatment of paediatric or adult mania. The data regarding the safety and efficacy of clozapine for paediatric BD are limited to a few case series.[37,38] Clozapine is not considered a first-line agent due to the lack of evidence of efficacy as well as its risk of agranulocytosis, which requires frequent blood draws for monitoring. Thus, clozapine is usually reserved for patients who are resistant to treatment with other agents.

Clozapine has a particularly challenging adverse effect profile, with the US prescribing information including boxed warnings regarding the risks of (i) agranulocytosis, (ii) seizures, (iii) myocarditis, (iv) other adverse cardiovascular and respiratory effects and (v) increased mortality (primarily cardiovascular or infectious) in elderly patients with dementia-related psychosis (an antipsychotic class warning). More frequently reported common adverse effects in younger populations include sialorrhoea, constipation, orthostatic hypotension, weight gain and sedation.

Clozapine may be initiated in children at 25 mg daily, and titrated up to 200–400 mg once or divided twice daily depending on the patient's weight and treatment response. It should also be noted that clozapine is metabolized primarily by the cytochrome P450 (CYP) 1A2, and smoking can cause an induction of its metabolism.

8. Guidelines for Safe Use of Atypical Antipsychotics in Paediatric Patients

When initiating treatment with an atypical antipsychotic in a child or adolescent, assessing personal and family histories of obesity, diabetes, dyslipidaemia and cardiovascular disease is essential.[39] Furthermore, clinicians should monitor blood pressure, fasting lipids and glucose at the initial appointment, 3 months after the initial appointment and then annually.[10] A BMI should be calculated at baseline and every 3 months thereafter.[39] If there is relative weight gain of 5% compared with baseline weight during the first 3 months of treatment, consideration should be given to discontinuing or switching to another agent. Clinicians should also have discussions with patients and their families about their lifestyle and dietary measures, and seek nutritional advice if needed.[39] Additionally, oral antihyperglycaemics such as metformin may be effective in reducing the risk of weight gain and metabolic dysfunction in paediatric patients on atypical antipsychotics.[40] As the NNH for clinically significant weight gain varies across agents

(olanzapine 2.5, quetiapine 8.2, risperidone 11.1, aripiprazole 13.0, ziprasidone 33.3), the risk of this adverse effect needs to be considered when selecting a specific atypical antipsychotic.

9. Use of Atypical Antipsychotics in Children and Adolescents at Familial Risk for BD

Children and adolescents of parents with BD may have an increased risk for developing BD themselves. Effective early intervention strategies for children and adolescents with such familial risk factors could delay the progression of already manifesting mood disorders.[41] One early intervention single-blind study used quetiapine for children and adolescents with non-bipolar I mood disorders and a first-degree relative (parent or sibling) with bipolar I disorder.[42] This study used the Clinical Global Impression (CGI) and the Childhood Depression Rating Scale-Revised (CDRS-R) in addition to the YMRS to demonstrate the effectiveness and tolerability of quetiapine (mean + endpoint dosage = 460 + 88 mg/day) in this familially at-risk population. Additional longitudinal studies are needed to determine whether atypical antipsychotics are effective for treating mood symptoms in those with a familial risk for BD, and if they prevent or delay the onset of full manic episodes in this high-risk population.[43]

10. Conclusion

Atypical antipsychotics have proven to be effective in the treatment of acute mania and mixed states in children and adolescents with BD. NNTs for response to mania range between approximately 3 and 5, and appear to carry a similar pattern to those seen in studies of adults with BD.[44] These data collectively demonstrate, by randomized controlled design, that atypical antipsychotics have efficacy for the treatment of manic or mixed symptoms in youths with BD. NNHs for weight gain vary more, between approximately 3 and 33, and thus ought to be considered when selecting individual agents. Indeed, there were other adverse events such as sedation,

hyperprolactinaemia and EPS that were present, and most of the studies reported were short-term trials. Efficacy must be balanced with the safety and tolerability of an agent to aid in optimizing treatment selection. Additional studies are necessary to determine the long-term efficacy and tolerability of these medications as well as their use in other mood states, such as bipolar depression, and co-morbid conditions such as anxiety and attention deficit with hyperactivity. Future longitudinal studies are needed to build upon the current empirical evidence for the treatment of children and adolescents with, and at risk for, BD.

Acknowledgements

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