Development and Psychopathology **18** (2006), 1231–1246
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Printed in the United States of America
DOI: 10.1017/S0954579406060597

Pharmacological interventions for bipolar youth: Developmental considerations

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Abstract

Despite the high prevalence rate, there have been relatively few controlled studies to systematically examine pharmacological treatments for children and adolescents with bipolar disorder. We review the differences in clinical characteristics between youth and adults with bipolar disorder and the extant literature of pharmacological treatments for children and adolescents with bipolar disorder, as well as discuss the effectiveness of pharmacological interventions for treating children and adolescents who are at familial risk for developing bipolar disorder. Although the number of controlled studies of youth with manic and mixed episodes is rapidly growing, there are few studies examining treatments for depression and the prevention of recurrent affective episodes in this population. Although children and adolescents with bipolar disorder commonly present with co-occurring psychiatric disorders, such as attention-deficit/hyperactivity disorder, there are limited data to guide the treatment of these patients. Recently, studies have begun to characterize prodromal manifestations of bipolar disorder and identify early intervention strategies for treating children and adolescents with an elevated risk for developing bipolar disorder.

Pediatric bipolar disorder (BPD) is a common psychiatric disorder that is often associated with significant morbidity and mortality (Geller & Luby, 1997; Lewinsohn, Klein, & Seeley, 1995). The prevalence of BPD in a community sample of adolescents is estimated to be about 1% (Lewinsohn et al., 1995). Prior studies suggest that bipolar youth have impaired family and peer relationships (Geller, Bolhofner, et al., 2000), impaired academic performance with high rates of school failure and dropout (Lofthouse & Fristad, 2004), high rates of substance use disorders (Wilens et al., 2004), and elevated rates of suicide attempts and completions (Goldstein et al., 2005; Lewinsohn, Klein, & Seeley, 2000). Despite the significant impairment that is often associated with this illness, there have been relatively few studies examining pharmacological intervention for bipolar youth. Moreover, developmental differences between children and adolescents versus adults with bipolar disorder add to the complexity of treating this population. Specifically, children and adolescents with bipolar disorder commonly present with symptoms of a major depressive episode or attention-deficit/hyperactivity disorder (ADHD), and therefore, are often treated with medications that can potentially exacerbate illness course, such as antidepressants and psychostimulants.

In this article we will review the phenomenological differences between children and adolescents versus adults with bipolar disorder that often complicate the treatment of bipolar youth. In addition, we will examine pharmacological treatment studies of children and adolescents with bipolar disorder and discuss preliminary data examining the effectiveness of pharmacologic interventions for treating children and adolescents who are at familial risk for bipolar disorder.

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https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press

Developmental Differences in Phenomenology

Children and adolescents with BPD present differently than adults with BPD. However, whether these differences are due to developmental differences in symptom expression or difference in underlying etiologies of pediatric-versus adult-onset bipolar disorder remains unclear (Bowring & Kovacs, 1992; Wozniak, Biederman, & Richards, 2001). Symptoms of bipolar disorder in children and adolescents may also be difficult to establish because of the variability of symptom expression depending upon the context and phase of the illness and the mood and behavioral effects of psychotropic medications that the patient may be prescribed.

Several recent studies have highlighted developmental differences in the phenomenology and clinical course between children and adolescents versus adults with BPD (Geller, Tillman, Craney, & Bolhofner, 2004; Geller, Zimerman, et al., 2000; Wozniak & Biederman, 1997). Typically, children and adolescents with BPD have severe mood dysregulation characterized by four to eight severe "mood swings" per day (Geller et al., 2004; Tillman & Geller, 2003). This affective dysregulation often leads to disruptive and aggressive behaviors (Isaac, 1992, 1995; Wozniak et al., 1995). In addition, children and adolescents with bipolar disorder commonly present with mixed (co-occurring mania and depression) episodes and psychotic symptoms (Tillman & Geller, 2003).

Similar to adults with BPD, children and adolescent frequently have co-occurring psychiatric disorders that complicate their diagnosis and treatment response. ADHD, anxiety disorders, oppositional defiant disorder, and conduct disorder (Kovacs & Pollock, 1995; West, McElroy, Strakowski, Keck, & McConville, 1995; Wozniak et al., 1995) are among the most frequently diagnosed comorbid disorders in bipolar youth. ADHD is ubiquitous in prepubertal bipolar youth, and is diagnosed in approximately half of bipolar adolescents (Geller, Cooper, Sun, et al., 1998; Wozniak et al., 1995). In addition, Wilens and colleagues (2004) have demonstrated that adolescents with BPD are five times more likely to develop a substance abuse disorder than non-BPD adolescents. These co-occurring diagnoses are important to consider in determining the most effective treatment options for an individual diagnosed with childhood or adolescent bipolar disorder. The recent treatment guidelines for children and adolescents with bipolar disorder by Kowatch et al. (2005) recommended that it was important to first stabilize a patient's mood with mood stabilizers and or atypical antipsychotics, and then treat whatever comorbid disorders that remain. In the next sections the evidence for using mood stabilizers and atypical antipsychotics for bipolar mania and depression is summarized.

Mood Stabilizers

Lithium

Lithium is the oldest mood stabilizer, and has significant data supporting its use for bipolar disorder in adults (Cade, 1949). In addition, lithium is the only medication approved by the United States Food and Drug Administration (FDA) for use in the treatment of mania in adolescents (ages 12–18 years) with bipolar disorder. Although several controlled studies have demonstrated the efficacy of lithium in the treatment and prevention of manic episodes in adults (McElroy & Keck, 2000), to date, there have been no prospective placebo-controlled studies of lithium in *manic* youth with bipolar disorder. However, there have been six controlled trials of lithium in bipolar children and adolescents. Of these six studies, four (Delong & Nieman, 1983; Gram & Rafaelsen, 1972; Lena, 1979; McKnew et al., 1981) used a cross-over design, which is not ideal for assessing outcome in a sample that has an cyclical illness. The average number of subjects in each of these studies was 18 and response rates ranged from 33 to 80%, reflecting the heterogeneity of the sample and the differences among study designs.

There have been two placebo-controlled investigations of lithium in children and adolescents with bipolar disorder. In the first study, Geller, Cooper, Sun, et al. (1988) found that after 6 weeks of treatment, bipolar adolescents with substance use disorder who were

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treated with lithium showed a statistically and clinically significant improvement in global assessment of functioning and a greater decrease in percent positive toxicology screens compared with those treated with placebo (46 vs. 8% response rates). Although this study demonstrated the efficacy of lithium carbonate for the treatment of bipolar adolescents with comorbid substance use disorders, the specific effects of lithium on mood symptoms was not assessed.

In the second placebo-controlled study of lithium, Kafantaris et al. (2004) reported that lithium appeared no more effective than placebo for the continuation phase of treatment after patients were stabilized with open-label lithium. However, the discontinuation phase of this study was only 2 weeks, which was probably not enough time to detect a difference between the group that remained on lithium and the group randomized to placebo. In general, several open-label studies suggest that approximately 40 to 50% of manic children and adolescents with bipolar disorder will respond to lithium monotherapy, which is not a very high response rate (Findling, McNamara, et al., 2003; Kowatch et al., 2000; Youngerman & Canino, 1978). The majority of children and adolescents with bipolar disorder require three to four different psychotropic medications to achieve remission and a good level of functioning.

There have been only two prospective studies examining treatments for depression associated with bipolar disorder in youth. Recently, Patel et al. (2006), evaluated the use of lithium for bipolar depression in adolescents and reported response and remission rates (defined by a ≥50% reduction in the Children's Depression Rating Scale—Revised [CDRS-R] score from baseline to endpoint and a CDRS-R score ≤28 and a Clinical Global Impression Improvement score of 1 or 2) were 48 and 30%, respectively. Although these patient's depressive symptoms improved with lithium treatment their mean CDRS-R score at endpoint was 38.5, indicating continued depressive symptoms.

Serum lithium levels in the range of 0.8 to 1.2 meq/L are typically necessary for mood stabilization, although these levels are based on studies of adults with bipolar disorder. Indeed, one study found that using lithium 7 magnetic resonance spectroscopy children and adolescents had lower serum to brain concentrations than adults, suggesting that children and adolescents may need higher serum lithium levels than adults to make certain that brain lithium concentrations reach therapeutic level (Moore et al., 2002). Common side effects of lithium that may be particularly problematic for children and adolescents include nausea, polyuria, polydipsia, tremor, acne, and weight gain. In addition, the following medications may increase serum lithium levels: antibiotics (e.g., ampicillin and tetracycline), nonsteroidal antiinflammatories (e.g., ibuprofen), antipsychotic agents, propanolol, and serotonin-selective reuptake inhibitors (SSRIs, e.g., fluoxetine; Ciraulo, Shader, Greenblatt, & Creelman, 1995).

Valproate

There have been several case reports and open-prospective trials suggesting the effectiveness of valproate for the treatment of children and adolescents with bipolar disorders (Deltito, Levitan, Damore, Hajal, & Zambenedetti, 1998; Kastner, 1992; Kastner, Friedman, Plummer, Ruiz, & Henning, 1990; Papatheodorou & Kutcher, 1993; Papatheodorou, Kutcher, Katic, & Szalai, 1995; West & McElroy, 1995; West et al., 1994; Whittier, West, Galli, & Raute, 1995). In a controlled 6 to 8 week study, Kowatch and colleagues (2000) directly compared the effectiveness of lithium, valproate, and carbamazepine for manic, hypomanic, or mixed episodes associated with bipolar disorder, Type I or II. Using a ≥50% change from baseline to endpoint in the Young Mania Rating Scale (YMRS) scores to define response, the response rates were 38, 38, and 53% for carbamazepine, lithium, and divalproex, respectively ($\chi^2 = 0.85$, $p = .60$). Each of the three mood stabilizers was well tolerated in this study (Kowatch et al., 2000). Wagner and colleagues (2002) published the results of an open-label study of valproate in 40 children and adolescents (ages 7–19 years) with bipolar disorder. Participants who improved in the open-label study were supposed to partici-

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pate in a discontinuation study following the open-label phase, during which they would be randomized to either placebo or valproate, but too few subjects were enrolled in the double-blind period to provide meaningful results. In their initial open-label phase, subjects were given a starting dosage of divalproex of 15 mg/kg/day. The mean final dosage was 17 mg/kg/day. Twenty-two subjects (55%) showed ≥50% in Mania Rating Scale scores during the open phase of treatment, suggesting that approximately half of manic bipolar youth will respond to divalproex. The majority of subjects in both of these open, prospective studies demonstrated clinically significant decreases in manic symptoms while treated with valproate, as indicated by a ≥50% decrease in YMRS scores, which corresponds to a large effect size.

Common side effects of valproate in children and adolescents include nausea and vomiting, increased appetite, weight gain, sedation, thrombocytopenia, hair loss, and tremor. Valproate is metabolized in the liver by cytochrome P450 enzymes and has interactions with several medications that also are metabolized by this system. Medications that will increase valproate levels include erythromycin, SSRIs, cimetidine, and salicylates. Valproate may increase the levels of phenobarbital, primidone, carbamazepine, phenytoin, tricyclics, and lamotrigine. Valproate should be administered cautiously and serum levels and liver functions monitored carefully in patients with significant liver dysfunction. Fetal exposure to valproate is associated with an increased rate of neural tube defects (Ketter, Wang, Nowakowska, & Marsh, 2004).

There have been recent concerns about the possible association between valproate and polycystic ovarian syndrome (PCOS). PCOS is an endocrine disorder characterized by ovulatory dysfunction and hyperandrogenism, affecting between 3 and 5% of women who are not taking psychotropic medications (Rasgon, 2004). Common symptoms of PCOS include irregular or absent menstruation, lack of ovulation, weight gain, hirsutism, and/or acne. The initial reports of the association between PCOS and divalproex exposure were in women with epilepsy. The association was particularly strong if their exposure was during adolescence (Isojarvi, Laatikainen, Pakarinen, Juntunen, & Myllyla, 1993). In a recent report, an increased (7.5 times) risk of new-onset oligoamenorrhea with hyperandrogenism was also found in bipolar women who were exposed to valproate (Joffe et al., 2006). The developmental consequences of hyperandrogenism at this time are unknown, but pubertal females treated with valproate should have a baseline assessment of menstrual cycle patterns and have continued monitored for menstrual irregularities, weight gain, hirsutism, and/or acne that may develop during valproate treatment. If symptoms of PCOS develop, referral to an endocrinologist should be considered to determine if PCOS is present and the risk of continued treatment with valproate.

Carbamazepine

Carbamazepine is an anticonvulsant agent structurally similar to imipramine that was first introduced in the United States in 1968. There are two, recent controlled studies of a long-acting preparation of carbamazepine, Equetro, in adults with BPD that demonstrated efficacy for carbamazepine as monotherapy for mania in adults (Weisler et al., 2006). There have been no controlled studies of carbamazepine for the treatment of children and adolescents with bipolar disorder, and the majority of reports in the literature concern its use in children and adolescents with ADHD or conduct disorder (Cueva et al., 1996; Evans, Clay, & Gualtieri, 1987; Kafantaris et al., 1992; Puente, 1975).

Carbamazepine is metabolized by the P450 hepatic system to an active metabolite, carabamazepine-10,11-epoxide. Carbamazepine induces its own metabolism and this "autoinduction" is complete 3 to 5 weeks after achieving a fixed dose. Common side effects of carbamazepine in children and adolescents include sedation, ataxia, dizziness, blurred vision, nausea, and vomiting. Carbamazepine has many clinically significant drug interactions in children and adolescents because of its stimulation of the hepatic P450 isoenzyme system. Carbamazepine may decrease levels of the medications including oral contracep-

https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press

tives and lamotrigine (Ciraulo et al., 1995). Dosing carbamazepine in combination with sodium divalproex may be challenging because the CYP450 drug interaction with these two agents. Side effects of carbamazepine include developing aplastic anemia and severe dermatological reactions, such as Stevens-Johnson's syndrome, hyponatremia, nausea, and sedation. Carbamazepine is therefore less commonly used in children and adolescents with bipolar disorder (O'Donovan, Kusumakar, Graves, & Bird, 2002).

Novel antiepileptic agents

There have been several new antiepileptic drugs (AEDs) that have been developed for the treatment of epilepsy that may be useful for the treatment of bipolar disorder, although the data are presently limited regarding the efficacy and tolerability of these agents for the treatment of PBD. In addition, there have been several negative trials of these agents in manic or mixed adults (Bowden & Karren, 2006).

Lamotrigine (Lamictal) has a novel mechanism of action by blocking voltage-sensitive sodium channels, and secondarily inhibiting the release of excitatory neurotransmitters, particularly glutamate and aspartate (Ketter, Wang, Becker, Nowakowska, & Yang, 2003). Lamotrigine also inhibits serotonin reuptake, suggesting it might possess antidepressant properties. In 2003, the FDA approved lamotrigine for the long-term maintenance treatment of bipolar type I disorder in adults. Several prospective studies in adults with BPD suggest that lamotrigine may be beneficial for the treatment of mood (especially depressive) symptoms in bipolar disorder (Bowden et al., 2003; Calabrese et al., 1999). Chang, Saxena, and Howe (2006) recently published an 8-week, open-label trial of lamotrigine alone or as adjunctive therapy for the treatment of 20 adolescents ages 12–17 years (mean age = 15.8 years) with bipolar disorders, who were experiencing a depressive or mixed episode. The mean final dose was 131.6 mg/day, and 84% of these subjects were rated as much or very much improved on the CGI. Larger, placebo-controlled studies of lamotrigine in bipolar youth are needed.

Lamotrigine is primarily eliminated by hepatic metabolism through glucuronidation processes. The glucuronidation of lamotrigine is inhibited by valproic acid, and is induced by carbamazepine. The addition of carbamazepine to lamotrigine decreases lamotrigine blood levels by 50 and 29%, respectively. Concomitant treatment with valproic acid increases lamotrigine blood levels, and therefore, it is advisable to use lower lamotrigine doses and proceed very cautiously when coadministering these medications. In addition, when coadministered with oral contraceptives patients may require increased lamotrigine doses because estrogen induced the metabolism of lamotrigine. However, postpartum or following discontinuation of oral contraceptives doses should be decreased because lamotrigine levels may double for a given dose.

The most common side effects of lamotrigine are dizziness, tremor, somnolence, nausea, and headache. Rashes develop in 12% of patients and typically within the first 8 weeks of lamotrigine therapy. Rarely, severe cutaneous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been described (Calabrese et al., 2002). The risk of developing a serious rash is greater in children and adolescents less than 16 years old compared with adults where the incidence is approximately 0.1% (Messenheimer & Guberman, 2000). Patients taking concomitant valproate are also at increased risk for developing a rash, because valproate elevates lamotrigine levels. Slow titration of lamotrigine is recommended, and is associated with a lower risk of having a rash. Case reports of lupus, leukopenia, agranulocytosis, hepatic failure, and multiple organ failure associated with lamotrigine treatment have been reported. However, lamotrigine has been well tolerated as long-term treatment in pediatric patients with epilepsy.

Gabapentin (Neurontin) is structurally similar to GABA, increases GABA release from glia, and may modulate sodium channels. Gabapentin is not metabolized or protein bound, and does not alter hepatic enzymes or interact with other anticonvulsants. However, the bioavailability of gabapentin is decreased

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by 20% with concomitant use of aluminum/magnesium hydroxide antacids. Double-blind controlled studies of gabapentin as adjunctive therapy to lithium or valproate and as monotherapy suggest it is no more effective than placebo for the treatment of mania in adults (Pande, Crockatt, Janney, Werth, & Tsaroucha, 2000); however, gabapentin may be useful in combination with other mood stabilizing agents for the treatment of anxiety disorders in adults with bipolar disorder (Keck, Strawn, & McElroy, 2006). Gabapentin has a relatively benign side effect profile. The most common side effects in studies involving bipolar patients are sedation, dizziness, tremor, headache, ataxia, fatigue, and weight gain. Gabapentin has rarely been associated with rashes, thyroiditis, sexual dysfunction, and renal impairment.

Topiramate (Topamax) is a sulfamate-substituted monosaccharide, with several potential mechanisms of action, including blockade of voltage-gated sodium channels, antagonism of the kainate/AMPA subtype of glutamate receptor, enhancement of GABA activity, and carbonic anhydrase inhibition. Topiramate is a weak inducer of cytochrome P450 enzymes, and therefore, is potentially associated with a risk of oral contraceptive failure (particularly, low-dose estrogen oral contraceptives). Preliminary data from case reports and open studies suggest that topiramate has antimanic properties when used as adjunctive treatment and as monotherapy in bipolar children and adolescents (Barzman et al., 2005; DelBello, Kowatch, et al., 2002a). There was a double-blind placebo-controlled study of topiramate for children and adolescents with manic or mixed episodes associated with bipolar disorder (ages 6–17 years, $n = 56$; Delbello et al., 2005) that was discontinued early after the adult mania trials with topiramate failed to show efficacy. Efficacy endpoints in this study included the YMRS. Reduction in the mean YMRS score from baseline to final visit using the last observation carried forward method was not statistically different between the topiramate group (-9.7 ± 9.65) and the placebo group (-4.7 ± 9.79), $F\ (1, 48) = 2.12$, $p = .152$. The only statistically significant difference between treatment groups that was identified was the difference between slopes of the linear mean profiles of the YMRS ($p = .003$) using a repeated measures regression, which was not the primary outcome measure. This study was stopped early, which precludes any definite conclusions about the efficacy of this agent for the treatment of mania in children and adolescents.

Side effects of topiramate include, sedation, fatigue, parasthesias, impaired concentration, and psychomotor slowing. In contrast to other AEDs and antipsychotics used to treat bipolar disorder, topiramate is associated with anorexia and weight loss. Body weight reduction seems to be dose related, and is more common in patients with larger body mass indices. Word-finding difficulties have been reported in up to one-third of adult patients treated with topiramate, and this has also been reported to occur in children. Cognitive disturbances might be worse in patients treated with concomitant divalproex.

Oxcarbazepine (Trileptal), the 10-keto analogue of carbamazepine, is biotransformed by hydroxylation to its active metabolite 10,11-dihydro-10-hydroxycarbamazepine, which is the primary active metabolite and accounts for its antiseizure properties. Recently, Wagner and colleagues (2006) reported the results of a multicentered, randomized double-blind placebo controlled study. In that study, 116 youth with bipolar disorder (mean age 11.1 ± 2.9 years) were randomized to receive either oxcarbazepine or placebo. The difference in the primary outcome variable, change in YMRS mean scores, between the treatment groups was not statistically or clinically significant, and therefore, there is little evidence to support the use of oxcarbazepine for the treatment of children and adolescents with bipolar disorder. Zonisamide (Zonegran) is a sulfonamide derivative antiepileptic that has several potential mechanisms of action including blockade of voltage-sensitive sodium channels and calcium currents, modulation of GABAergic and dopaminergic systems, carbonic anhydrase inhibition, and free-radical scavenging. Zonisamide is protein bound (40–60%) but does not appear to affect the protein binding of other drugs. Concurrent administration with enzyme-inducing anticonvulsants

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such as carbamazepine stimulate zonisamide metabolism and decrease serum zonisamide levels at steady state. Open-label studies suggest that zonisamide may be useful for the treatment of adults with bipolar disorder (McElroy et al., 2005); however, there have been no studies examining zonisamide for the treatment of children and adolescent with bipolar disorder. Common side effects of zonisamide in patients with epilepsy include nephrolithiasis, drowsiness, ataxia, and loss of appetite. Rare but serious side effects include severe rashes (i.e., Stevens–Johnson syndrome and toxic epidermal necrolysis) as well as hematologic and immunological abnormalities, such as aplastic anemia or agranuclocytosis, immunoglobulin A and G2 deficiency, and hyperthermia in pediatric patients.

Atypical Antipsychotics

Case series, retrospective chart reviews, open-label, and controlled studies suggest that the atypical antipsychotic medications result in greater response rates for the treatment of adolescent mania than are found in comparable studies of lithium and antiepileptic agents, and in general, are well tolerated (Findling & McNamara, 2004; Kowatch & DelBello, 2006; Perlis, Welge, Vornik, Hirschfeld, & Keck, 2006). All of the atypical antipsychotics have received FDA approval for the treatment of mania associated with bipolar disorder in adults, and olanzapine and aripiprazole have received FDA approval as maintenance treatment for adults with bipolar disorder. The atypical antipsychotics are more advantageous compared with more conventional neuroleptics because they are less frequently associated with extrapyramidal symptoms.

There have been several recent reports suggesting that atypical antipsychotics including clozapine (Kowatch et al., 1995), risperidone (Frazier et al., 1999), olanzapine (Chang & Ketter, 2000; Khouzam & El-Gabalawi, 2000; Soutullo, Sorter, Foster, McElroy, & Keck, 1999), quetiapine (DelBello, Schwiers, Rosenberg, Strakowski, & Stephen, 2002b), and aripiprazole (Barzman et al., 2004) are effective for the treatment of PBD. In a retrospective case series of children and adolescents who were severely ill (50% with bipolar disorder), Kowatch and colleagues (1995) found that CGI severity ratings significantly improved from baseline to endpoint, and that patients experienced minimal side effects following treatment with clozapine. However, side effects to clozapine that have been reported in studies of adults include seizures and agranulocytosis (Kowatch & DelBello, 2005).

There have been two studies of risperidone for the treatment of youth with bipolar disorder. In the first, Frazier and colleagues (1999) performed a retrospective chart review evaluating risperidone as adjunctive treatment for pediatric mania ($N = 28$). Subjects received a mean dose of 1.7 ± 1.3 mg over an average period of 6.1 ± 8.5 months. Using a CGI Improvement score of ≤ 2 to define response, 82% demonstrated response in both manic and aggressive symptoms, 69% in psychotic symptoms, but only 8% in ADHD symptoms. In a more recent open-label prospective study, Biederman, Mick, Wozniak, et al. (2005) conducted an 8-week, open-label, prospective study of risperidone monotherapy (1.25 ± 1.5 mg/day) for 30 bipolar youths (manic, mixed, or hypomanic; 6–17 years of age). They reported that 70% responded, as defined by a CGI-Improvement score ≤ 2, that these subjects' weights increased significantly from baseline (2.1 ± 2.0 kg), and there was a fourfold increase in prolactin levels from baseline. Side effects that are commonly reported with risperidone include extrapyramidal symptoms, weight gain, and prolactin elevation.

Tohen et al. (2005) recently reported the results of a large double-blind placebo controlled study of olanzapine that included 159 children and adolescents (ages 10–17 years) with bipolar disorder who were randomized to placebo or olanzapine (1:2 ratio) for 3 weeks. Mean daily dose of olanzapine was 9 mg during this study. There was a statistically significant greater reduction in manic symptoms in the olanzapine group compared to the placebo group. However, 42% of the children and adolescents gained $\geq 7\%$ of their baseline body weight, which is a large gain in a short period of time. Other side effects of olanzapine included lipid profile abnormalities and elevated prolactin levels.

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Biederman, Mick, Hammerness, et al. (2005) compared 8 weeks of risperidone versus olanzapine monotherapy for the treatment of preschoolers with bipolar disorder. Risperidone was initiated at an open-label dose of 0.25 mg/day, increased weekly according to response and tolerability to a maximum does of 2.0 mg/day. Olanzapine was initiated at 1.25 mg/day and increased to no more than 10 mg/day. The authors reported a decrease in YMRS score of 18.3 ± 11.9 ($p < .001$) in risperidone-treated subjects and of 12.1 ± 10.4 ($p < .001$) in olanzapine-treated subjects. There was not a significant difference between groups in their treatment response, but the study sample size limited the ability to detect statistically significant treatment group difference in response.

There are two controlled studies that suggest the efficacy of quetiapine for adolescent mania (DelBello et al., 2006; DelBello, Schwiers, et al., 2002b). In the first double-blind placebo-controlled study of quetiapine in adolescents, DelBello et al. (2002a) examined the efficacy, safety, and tolerability of quetiapine as an adjunct to divalproex for acute mania in adolescents with bipolar disorder. In this study, 30 manic or mixed bipolar I adolescents (12–18 years) received an initial divalproex dose of 20 mg/kg and were randomized to 6 weeks of combination therapy with quetiapine, which was titrated to 450 mg/day ($n = 15$), or placebo ($n = 15$). Primary efficacy measures were change from baseline to endpoint in YMRS score and YMRS response rate. Safety and tolerability were assessed weekly. The divalproex plus quetiapine group demonstrated a statistically significant greater reduction in manic symptoms than the divalproex plus placebo group ($p = .03$). Moreover, YMRS response rate was significantly greater in the divalproex plus quetiapine group than in the divalproex plus placebo group (87 vs. 53%, $p = .05$). No significant group differences from baseline to endpoint in safety measures were noted. These data indicate that the combination of a mood stabilizer and an atypical antipsychotic agent may be more effective than mood stabilizer alone for the treatment of mania in bipolar youth. In a larger, follow-up study, DelBello and colleagues (2006) randomized 50 adolescents (ages 12–18 years) with bipolar I disorder, manic or mixed episode to quetiapine (400–600 mg/day), or divalproex (serum level = 80–120 μg/mL) for 28 days in a double-blind study, and found that patients receiving quetiapine had faster resolution of their manic symptoms and higher rates of remission than those treated with divalproex. In addition, both medications were well tolerated without excessive weight gain.

There are currently few controlled studies to support the use of the newer atypical antipsychotics (aripiprazole and ziprasidone) for youth with bipolar disorder. Two retrospective case series reported very similar results, suggesting that approximately 70% of children and adolescents with bipolar disorders will respond to aripiprazole (Barzman et al., 2004; Biederman, 2003). However, one study reported that approximately one-quarter of patients treated with aripiprazole experience akathisia (Barzman et al., 2004).

Ziprasidone has the advantage of being associated with the least amount of weight gain among the atypical antipsychotics in adults (Correll et al., 2006). In a recently completed dose finding 3-week open-label study of ziprasidone for adolescents with psychosis ($N = 46/63$ with bipolar disorder), patients were randomized to receive 40 mg twich a day (low-dose group, $n = 23$) or 80 mg twich a day (high-dose group, $n = 40$) of ziprasidone titrated over approximately 10 days (Versavel et al., 2005). In the patients with bipolar disorder, there was a mean reduction in YMRS score of 17.2 (8.2) for completers in the low-dose group and 13.1 (8.9) for completers in the high-dose group. The most common side effects in this study included sedation, nausea, headaches, and dizziness. The most important fact is that the QT correction (QTc) change over the course of 3 weeks at the maximum serum concentration of ziprasidone was 1.3 ms for the low-dose group (80 mg/day) and 11.2 ms for the high-dose group (160 mg/day), indicating that ziprasidone does not cause significant QTc prolongation at these dosages.

Together, the findings from these studies suggest that similar to adults, the atypical antipsychotics are more powerful pharmacologi-

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cal interventions for adolescent mania than lithium or the antiepileptic agents like valproate. However, additional studies are needed evaluating the efficacy of atypical antipsychotics for depression associated with adolescent bipolar disorder, as well as for maintenance treatments. Furthermore, controlled studies assessing the metabolic consequences and possible treatment strategies for the weight gain and metabolic abnormalities associated with atypical antipsychotic are necessary.

Combination Treatment Strategies: Developmental Considerations

Kafantaris, Coletti, Dicker, Padula, and Kane (2001) evaluated acutely manic adolescents with psychotic features following treatment with lithium and an adjunctive antipsychotic to assess whether antipsychotics are necessary for psychotic mania in adolescents. Antipsychotics were gradually tapered and discontinued after 4 weeks of therapeutic lithium levels in patients whose psychotic symptoms resolved, and these patients were maintained with lithium monotherapy for up to 4 weeks. Significant improvement was seen in 64% of the sample, with psychotic features after 4 weeks of combination treatment. However, 43% did not maintained their response after discontinuation of the antipsychotic medication, suggesting that greater than 4 weeks of antipsychotic treatment is required for some adolescents with psychotic mania. Variables associated with successful discontinuation of antipsychotic medication in this sample were first episode, shorter duration of psychosis, and the presence of thought disorder at baseline

Although recent data suggest that the combination of mood stabilizers and atypical antipsychotics is more effective than mood stabilizer alone for adolescent mania (DelBello et al., 2002b), a recent 6-month open-trial compared the efficacy of two combination therapies for manic or mixed episodes of PBD. This study examined divalproex and risperidone versus lithium and risperidone in 37 subjects ages 5–18 years with a mixed or manic episode (Pavuluri et al., 2004). Effect sizes based on change in YMRS scores from baseline to endpoint were 4.36 for the divalproex and risperidone group and 2.82 for the lithium and risperidone group. Response rates based on a $\geq$50% decrease from baseline in YMRS score were 80% for the divalproex and risperidone group and 82.4% for the lithium and risperidone group, and both combination treatments were well tolerated, suggesting that either treatment strategy may be used for manic adolescents.

Bipolar Depression: Developmental Perspectives

Adolescents with bipolar disorder whose index episode is major depression are more likely to experience a poorer outcome compared with those with an index episode of mania or mixed mania (Strober, Morrell, Lampert, & Burroughs, 1990). Despite the severe morbidity and mortality associated with bipolar depression, there are limited data regarding the treatment of depression in children and adolescents with bipolar disorder.

Treatment of bipolar depression can be complicated because of the often necessary use of combinations of medication, including antidepressants, which may induce mania, hypomania, or rapid cycling while treating depressive symptoms (Compton & Nemeroff, 2000). A retrospective study assessing treatment of depressed children and adolescents with bipolar disorder suggests that SSRIs may be effective for acute bipolar depression, but these agents may be associated with mood destabilization and exacerbation of manic symptoms (Biederman, Mick, Spencer, Wilens, & Faraone, 2000). Specifically, in this study depressive symptoms were 6.7 times more likely to improve when subjects received an SSRI. However, SSRIs were associated with a greater probability of relapse of manic symptomatology (relative risk = 3.0). In patients with active manic symptoms, the concomitant use of SSRIs with mood stabilizer treatment did not significantly inhibit the improvement of manic symptoms associated with mood stabilizer treatment, suggesting that further controlled studies of antidepressants in combination with mood stabilizers or atypical antipsychotics are needed. Antidepressant medications should be used with caution in chil-

https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press

dren and adolescents with bipolar disorder because of the potential risk for increased mood instability and for the emergence of suicidal ideation.

As previously described, there have been two recent prospective open-label studies assessing lithium and lamotrigine for bipolar depression in adolescents (Chang et al., 2006; Patel et al., 2006). Methodological differences between the studies make it difficult to compare the results between theses studies. Specifically, Chang et al. (2006) included adolescents with depression or mixed episodes and bipolar disorder, Type I or II, and lamotrigine was used as monotherapy or adjunctive to other medication. In contrast, Patel et al. (2006), included only adolescents with bipolar disorder, type I, depressed, and lithium was used as monotherapy. Nonetheless, these studies suggest that both medications may be useful for depression associated with bipolar disorder in adolescents. Recent placebo-controlled studies suggest that atypical antipsychotics, specifically, quetiapine and olanzapine, are useful for the treatment of depression in bipolar adults (Calabrese et al., 2005).

Maintenance Treatment: Developmental Perspective

There are no placebo-controlled maintenance studies for children and adolescents with bipolar disorder. In fact, there has been only one controlled, maintenance study. In addition to the treatment of acute affective episodes, lithium may also be useful for the prevention of recurrent affective episodes in children and adolescents with bipolar disorder. In one of the only maintenance treatment studies for PBD, Strober et al. (1990) prospectively evaluated 37 adolescents whose mood had been stabilized with lithium while hospitalized. After 18 months of follow-up, 35% of these patients discontinued lithium, and 92% of those who discontinued subsequently relapsed compared to 38% of those who were lithium compliant, supporting the potential utility of lithium for maintenance treatment for bipolar disorder in adolescents.

The aim of the only controlled study (Findling et al., 2005) to examine maintenance treatment for bipolar youth (ages 5–17 years) was to determine whether divalproex was superior to lithium in bipolar youth who had been stabilized on the combination of lithium and divalproex. Patients meeting remission criteria were then randomized in a double-blind fashion to treatment with either lithium ($N = 30$) or divalproex ($N = 30$) for up to 76 weeks. Study participation ended if the subject required additional clinical intervention or if the subject did not adhere to study procedures. The treatment groups did not differ in survival time until emerging symptoms of relapse ($p = .55$) or survival time until discontinuation for any reason ($p = .72$), suggesting that divalproex was not found to be superior to lithium as maintenance treatment in youths who were initially stabilized on the combination of lithium and divalproex. Of note, only 10% of patients in each group did not require intervention during their study participation, suggesting that more effective treatment options are needed.

Findling and colleagues (2006) recently published the results of an open trial of lithium combined with divalproex combination. In this study, 38 subjects (mean age 10.5 years) who had initially responded to lithium combined with divalproex, but relapsed during monotherapy with either medication, were treated with lithium and divalproex as outpatients for 8 weeks. Eighty-nine percent of subjects responded to restabilization. Based on these findings, the authors concluded that youths who had initially responded to a combination of lithium with divalproex may be effectively restabilized on this combination if they relapse during maintenance monotherapy with either medication. In general, it is recommended that patients with bipolar disorder continue at least one medication as maintenance treatment; however, combination medications are often necessary (Kowatch et al., 2005).

Co-occurring Psychiatric Disorders: Developmental Considerations

Children and adolescents with bipolar disorder commonly present with co-occurring psychiatric disorders (Pavuluri, Birmaher, &

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Naylor, 2005), the most common of which is ADHD. Treatment of children with BPD and co-occurring ADHD require mood stabilization with a traditional mood stabilizer or an atypical antipsychotic as a necessary prerequisite prior to initiating stimulant medications (Biederman et al., 1999); however, controlled studies are lacking to support this common clinical practice. However, a recent randomized controlled trial of 40 bipolar children and adolescents with ADHD demonstrated that low-dose mixed-salts amphetamine are effective and well tolerated for the treatment of comorbid ADHD symptoms following mood stabilization with divalproex (Scheffer, Kowatch, Carmody, & Rush, 2005). Sustained release psychostimulants may be more effective at reducing rebound symptoms in bipolar children and adolescents.

Up to 40% of bipolar adolescents have co-occurring substance use disorders (Wilens et al., 2004). Despite this high co-occurrence there has been only one small, older treatment study of bipolar adolescents with substance use disorders that suggested lithium may be more effective than placebo in reducing substance abuse in adolescent with BPD (Geller, Cooper, Sun, et al., 1998).

Results from recent studies suggest that topiramate is useful for the treatment of disorders related to poor impulse control in adults, including alcohol dependence (Johnson et al., 2003), binge eating (McElroy et al., 2003, 2004) and bulimia nervosa (Hoopes et al., 2003).

As discussed above, PBD commonly co-occurs with disorders of impulse control, specifically ADHD, disruptive behavior disorders, and substance use disorders, and therefore, children and adolescents with bipolar disorder may respond differently than adults to specific treatments. Therefore, topiramate may be useful as adjunctive treatment for bipolar youth with co-occurring disorders that commonly present with impulse dyscontrol. Alternatively, children and adolescents who are earlier in their illness course may respond better than older patients, who typically have a history of multiple treatment failures. Specifically, the relationship between acute affective episodes and cellular stress has been well documented (Carlson, Singh, Zarate, Drevets, & Manji, 2006; Chen & Manji, 2006; Einat & Manji, 2006; Zarate, Singh, & Manji, 2006). Stress induced cortisol elevation results in excessive neuronal glutamate release that typically occurs early following stress (onset of illness). Therefore, bipolar youth who are closer to illness onset may be more likely than adults, who are further along in illness course, to respond to medications that block acute glutamatergic neurotoxicity. Indeed, topiramate, inhibits the excitatory effects of glutamatergic receptors. Nonetheless, these findings highlight the importance of evaluating new treatment options for bipolar disorder in age-specific, controlled trials.

Early Intervention

The most common age of onset of bipolar disorder is during adolescence (Perlis et al., 2004). Therefore, children and adolescents are the ideal populations in which to identify those at risk for developing bipolar disorder prior to illness onset and establish effective early-intervention or prevention strategies. Although children and adolescents of parents with bipolar disorder have an increased risk for developing bipolar disorder, prodromal manifestations of bipolar disorder have not been consistently identified (DelBello & Geller, 2001). To determine prodromal manifestations of bipolar disorder longitudinal studies are needed to establish who will develop bipolar disorder. Therefore, based on data that suggest child offspring of bipolar parents have an elevated risk for developing ADHD and other mood disorders (e.g., major depressive disorder and cyclothymia), investigators have begun to examine whether early-intervention treatment with mood stabilizers or atypical antipsychotics are effective.

In a small, double-blind controlled study, Geller, Cooper, Zimerman, et al. (1998) determined that lithium was no more effective than placebo for the treatment of adolescents with major depressive disorder and a familial risk for bipolar disorder. There have been several recent investigations of divalproex for the treatment of mood symptoms in children at familial risk for bipolar disorder. Chang et al. (2003)

https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press

found a significant reduction in mood symptoms and improvement in overall functioning following treatment with divalproex in 23 children who did not have bipolar I disorder but who were diagnosed with mood symptoms/syndromes and who had a parent with bipolar disorder. Similarly, Findling, Calabrese, and Youngstrom (2003) reported that children with mood symptoms and a multigenerational family history of bipolar disorder had a significant reduction in mood symptoms when treated with divalproex compared with placebo; however, there was no statistically significant group difference in those without a multigenerational family history.

In a recently completed 12-week study (M. A. DelBello, personal communication, 2006), adolescents ($N = 20$, mean age = 14.7 years; 40% female, 90% Caucasian) with a mood disorder other than bipolar I disorder and a parent with bipolar disorder were initiated on 100 mg quetiapine and titrated to 400 mg by Day 4 (mean = 460 mg/day). Eleven of the adolescents were diagnosed with bipolar disorder not otherswise specified, three with dysthymia, three with bipolar II disorder, two with cyclothymia, and one with major depressive disorder. The mean YMRS and CDRS-R scores were significantly decreased from baseline measures at all time points (all $p < .001$). The most common side effects were somnolence, headache, musculoskeletal pain, and dyspepsia. There findings suggest that quetiapine may be useful for the treatment of early manifestations of bipolar I disorder in those at familial risk; however, placebo-controlled studies are needed. In addition, whether these adolescents would have progressed to develop bipolar I disorder remains unknown.

Conclusions

Because of the high rate of co-occurring disorders, the shorter illness duration, and the greater susceptibility to side effects compared with bipolar adults, age-specific efficacy and tolerability studies are needed to determine optimal medication treatments for bipolar youth. Although several studies suggest that there are effective and well-tolerated treatment options for manic or mixed episodes associated with bipolar disorder, there are very few pharmacological intervention studies for depression associated with PBD. Furthermore, maintenance treatment strategies for bipolar youth have yet to be established. Establishing evidence-based treatments for commonly co-occurring psychiatric disorders in children and adolescents with bipolar disorder is another area of investigation that needs additional study. Studies that identify putative risk factors for the development of bipolar disorder in high-risk children with first-degree relatives with bipolar disorder are also clearly needed. Nonetheless, over the past decade there has been considerable progress in developing rationale treatment strategies for children and adolescents with bipolar disorder.

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https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press

Paper presented at the American College of Neuropharmacology, Waikoloa, Hawaii.

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https://doi.org/10.1017/S0954579406060597 Published online by Cambridge University Press