

Pediatric Bipolar Disorder: Evidence-Based Psychopharmacological Treatments

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TOPIC: Pediatric bipolar disorder can cause severe disturbances in global functioning. Diagnosing pediatric bipolar disorder is challenging due to the range of symptom expression, developmental differences as compared to adults, presence of comorbid disorders, and developing diagnostic criteria. Treating this disorder can be equally challenging due to frequent symptom relapse and the dearth of research until recently on effective psychopharmacological interventions that guide clinical prescribing practices.

PURPOSE: This paper will help child psychiatric nurses have a better understanding of the unique presentation of pediatric bipolar disorder to facilitate selection of appropriate medication treatment options, taking into account symptom presentation, presence of comorbid diagnosis, drug efficacy, adverse effects, and drug-drug interactions based on research findings.

SOURCES: Literature specific to assessment and psychopharmacological treatment of pediatric bipolar disorder was reviewed.

CONCLUSIONS: Screening of youth with mood spectrum problems for bipolar disorder should occur in every diagnostic assessment and should be ongoing due to range of mood symptoms and the cyclical and episodic nature of this disorder. Youth with bipolar disorder may manifest symptoms and course that differ from adults. Additionally, co-occurring disorders are common in this population, which can complicate medication selection.

Psychopharmacological treatment with the use of specific mood stabilizers and/or atypical antipsychotic medications is warranted depending on symptom presentation; however, monotherapy with mood stabilizers has not demonstrated effectiveness in long-term remission of pediatric bipolar symptoms. Recent research indicates that a combined treatment with two mood stabilizers or a mood stabilizer and an antipsychotic holds promising results for pediatric bipolar I, for youth with acute manic symptoms plus psychosis, and for long-term remission of symptoms.

Search terms: Pediatric bipolar disorder, psychopharmacological management

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Introduction

Increasingly, child and adolescent advanced practice nurses are being required to evaluate and treat children with bipolar disorder. Whereas the research data have been sparse, diagnostic and treatment standards are rapidly changing. Guidelines for assessment and treatment of this disorder are necessary to provide clinicians with the knowledge to successfully diagnose and treat these clients. This article will review the current epidemiology, diagnostic criteria, and rating scales used in the diagnosis of pediatric bipolar disorder. Research on the comorbidities with pediatric bipolar disorder, genetic findings, neuroanatomy, neurobiology, and psychopharmacological treatments will be presented.

Bipolar disorder, once not recognized in children and adolescents, has been increasingly studied over the past 10 years. Comprehensive reviews of literature on the diagnostic issues related to pediatric bipolar disorder are available by Pavuluri, Birmaher, and Naylor (2005), and Kowatch and DeBello (2006). In addition, DuVal (2005) and Hamrin and Bailey (2001) have published case studies reviewing the diagnosis of children with pediatric bipolar disorder. This article will provide a brief overview of the current knowledge of the diagnostic issues involved in pediatric bipolar disorder with a focus on the research on psychopharmacological treatments and provide psychopharmacological management recommendations for treatment of this disorder. This paper will not cover the psychosocial interventions for pediatric bipolar disorder.

Pediatric bipolar disorder can cause severe disturbances in global functioning for children and their families. Children with bipolar disorder struggle with academic success and interpersonal relationships, and

Table 1. DSM–IV–TR Classification and Definitions for Mood Disorders

Bipolar I	Manic or mixed episodes with or without depression
Bipolar II	Major depression with hypomania
Bipolar disorder-not otherwise specified (NOS)	Criteria not met for bipolar I, bipolar II, cyclothymia or have too few manic symptoms
Mixed episodes	Manic and depressive symptoms lasting at least 1 week
Mania	An abnormally and persistently elevated, expansive, or irritable mood, lasting at least a week
Hypomania	A persistently elevated, expansive, or irritable mood, lasting at least 4 days, that is clearly different from the usual nondepressed mood
Cyclothymia	Chronic fluctuating mood disturbances hypomania and minor depressive symptoms
Rapid cycling	Four or more episodes per year
Ultrarapid cycling	Five to 364 episodes per year
Ultradian cycling	Mania is present for more than 4 hr/day

they are at a much greater risk for substance abuse, legal difficulties, increased suicidal behavior, and hospitalizations. Nearly 20% of adult patients with bipolar disorder reported symptoms prior to age 19 (Mohr, 2001). Further evidence of early onset is supported by Kogan et al. (2004), who reported on the first consecutive 1,000 adult bipolar disorder patients enrolled in the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder study. They found that 27.7% of the adult subjects in this study experienced prepubertal onset (under 13 years of age), and 37.6% experienced adolescent onset (defined as 13–18 years). These findings confirm that child psychiatric nurse practitioners are in an important clinical position to recognize and treat childhood bipolar disorder.

Pediatric bipolar disorder is a complex mood disorder with a myriad of features (Table 1), some of which are similar to those of adult bipolar disorder. It occurs in approximately 1 to 1.5% of the pediatric general population (Kashani et al., 1987; Lewinsohn, Klein, & Seeley, 1995); however, in psychiatric clinical settings the prevalence rate ranges from 17 to 30% in pediatric populations (Youngstrom & Duax, 2005). Symptom presentation differs between children and adults. The grandiosity observed in adults usually includes hallmark behaviors including excessive spending,

inflated self-esteem, and inappropriate attire. Grandiosity and euphoria in children usually present with such behaviors as argumentativeness, bossiness, excessive giddiness, and attitudes of superiority, such as they are stronger or smarter than others including adults, that is different from their baseline functioning. More commonly, symptoms of irritability, rage, “affective storms,” and aggression are prominent. However, aggression with this disorder is less organized and more reactive and impulsive (Biederman et al., 1996). Additionally, these youths are often described as out of control and destructive, and demonstrate severe impairment in social and academic functioning (Geller, Cooper, et al., 1998). Another difference between children and adults is that children may not have clear symptom-free periods of euthymia like adults, demonstrating more time spent with syndromal and subsyndromal symptoms of mania and depression, and children have more frequent polarity switches than adults (Birmaher et al., 2006; Geller, Tillman Craney, & Bolhofner, 2004). (See Table 2 for *Diagnostic and Statistical Manual [DSM]* symptomatology).

Other symptoms nurse practitioners should assess for include increased talkativeness, decreased need for sleep, emotional over-reactivity, distractibility, racing thoughts, flight of ideas, poor judgment, pressured speech, unusual energy, increased goal-directed activity,

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Table 2. Lithium

Adverse effects	Toxicity
Diarrhea	Diarrhea
Nausea	Vomiting
Hypothyroidism	Ataxia
Sedation	Confusion
Headaches	Hyper-reflexia
Tremor	Dysarthria
Polyuria	Drowsiness
Polydipsia	
Acne	
Weight gain	

and excessive involvement in pleasurable or risky activities that may have painful consequences (American Psychiatric Association, 2000). Wozniak et al. (1995) found that pediatric onset bipolar disorder was characterized by higher rates of depression, psychosis, a positive family history of mania, and poor global functioning. The course of illness for patients with an age of onset prior to age 17 was associated with increased frequency of mood switches, worsening course of illness, and a history of early abuse (physical, verbal, or sexual) (Suppes et al., 2001).

Also, children with bipolar disorder usually have a chronic and resistant course that requires long-term intervention.

A prodromal depressive presentation, which often manifests as the first presenting symptom, can lead to greater risk for suicidal behavior and manic states. Dalton, Cate-Carter, Mundo, Parikh, and Kennedy (2003) found that 25% of children and adults with bipolar disorder attempt suicide, especially during a depressive episode. Goldstein et al. (2005) found similar statistics when evaluating 405 children and adolescents ages 7–17 with bipolar disorder. Their findings were that one-third of youth (33%) with bipolar disorder had a lifetime history of a suicide attempt. Attempters were older than nonattempters, and they were more likely to have mixed episodes and psychotic

features. In addition, attempters were more likely to have comorbid substance use, panic disorder, nonsuicidal self-injurious behaviors, family history of suicide attempts, history of hospitalizations, and history of physical and sexual abuse than nonattempters.

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Conversion from major depressive disorder to bipolar disorder should be carefully evaluated. Geller, Craney, et al. (2001) followed 72 children with depression from prepubertal age to adulthood. Forty-eight percent developed bipolar disorder by a mean age of 20.7 years. In evaluating the neurocognitive functioning of children with bipolar disorder, Pavuluri et al. (2006) evaluated 28 unmedicated and 28 medicated children with bipolar disorder, as well as 28 healthy controls. Subjects with bipolar disorder, regardless of medication status, showed impairments in domains of attention, executive functioning, working memory, and verbal learning compared to healthy controls. Bipolar youths who also had comorbid attention deficit/hyperactivity disorder (ADHD) performed worse on tasks assessing attention and executive functioning than patients with bipolar disorder alone. McClure et al. (2005) compared 40 youth with pediatric bipolar disorder to 22 controls without bipolar disorder. This study found that youth with bipolar disorder had deficits in pragmatic judgment of language and facial expression recognition, and performed poorly on tasks requiring flexibility when compared to control subjects.

Geller, Craney, et al. (2001) and Geller et al. (2002) completed a 1- to 2-year longitudinal study of 93 adolescents with bipolar disorder evaluating recovery and relapse rates. Only 47% of these adolescents received antimanic medication during the time of the study. The adolescents with bipolar disorder at year 1 showed a 37% recovery rate, and a 38% relapse rate after recovery. At year 2, the researchers found that the mean time between relapse and recovery was 28.6 weeks. The 2-year recovery and relapse rates were 65 and 55.2%, respectively. The researchers also found that low maternal warmth correlated positively with relapsed subjects. Birmaher et al. (2006) conducted a longitudinal study evaluating the course of bipolar spectrum disorder in 263 children and adolescents with the diagnosis of bipolar I, bipolar II, and bipolar NOS (not otherwise specified) over the course of 2 years. Seventy percent of the subjects with bipolar disorder recovered from their index episode, and 50% had at least one syndromal recurrence, particularly depressive episodes. Furthermore, early-onset bipolar disorder, bipolar NOS, long duration of mood symptoms, low socioeconomic status, and psychosis were associated with poorer outcomes and rapid mood changes. Secondary analysis comparing bipolar I youths with bipolar I adults showed that youths had longer symptom duration, more mixed cycling episodes, and more frequent polarity switches. The study did not comment on what type of treatments or psychopharmacology the children received during their enrollment in the study. Other researchers have also found that children with bipolar disorder have long-duration episodes of rapid cycling and mixed mania with fluctuations of mood occurring daily (Findling et al., 2001; Geller, Williams, et al., 1998; Geller et al., 2004).

This data encourage clinicians to frequently evaluate the type and frequency of symptoms, intensity, number of *DSM-IV* symptoms, polarity switches, and duration and recurrence of symptoms. McClellan (2005) and Carlson and Kelly (1998) highlight that clinicians must also take into account the child's temperament, attachment, parent-child relationships, parenting styles, child's

response to limit setting, comorbid conditions, cognition, and other moderating and mediating factors, including trauma, when making a bipolar diagnosis.

Because of the variations in presentation, there are many challenges in categorizing the symptoms unique to the pediatric presentation of bipolar disorder, including symptoms of mania or hypomania, depression, irritability, and cycling and length of episodes. To clarify the diagnostic criteria, Leibenluft, Charney, Towbin, Banqoo, & Pine (2003) suggest a phenotypic system of juvenile mania that will help clarify the diagnostic criteria: The "narrow" phenotype would include patients who meet the full *DSM-IV* symptom and duration criteria for hypomania or mania and also have hallmark symptoms of elevated mood or grandiosity. The "intermediate" phenotype would include hypomania or mania not otherwise specified. Clear episodes and hallmark symptoms must be present and the duration would be between 1 and 3 days. Irritable hypomania or mania is present in which the patient has demarcated episodes with irritable but not elevated mood. Lastly, the broad phenotype would include patients who exhibit chronic, nonepisodic illness that does not include the hallmark symptoms of mania but instead presents with symptoms of severe irritability and hyperarousal.

Comorbidity

According to Biederman et al. (2004), ADHD is present in 60 to 90% of bipolar patients. Three common overlapping symptoms in both diagnoses include excessive talking, increased activity, and distractibility; however, in bipolar disorder these symptoms are not likely to be present every day, unlike ADHD. In making a differential diagnosis, it is important to note that children with ADHD alone do not have persistent mood instability with explosive outbursts as seen in bipolar disorder. Additionally, children with bipolar disorder display three common symptoms not usually observed in children with ADHD: elevated mood, grandiosity, and flight of ideas (Geller et al., 2002).

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Tillman et al. (2003) observed that ADHD usually precedes bipolar symptoms, and recommend that children with ADHD need to be carefully screened for symptoms of pediatric bipolar disorder. They also found that the diagnosis of oppositional defiant disorder and conduct disorder were made after the diagnosis of bipolar disorder. Kovacs and Pollack (1995) found a 69% rate of conduct disorder in children with bipolar disorder in their study. Other comorbid conditions include substance abuse, depression, anxiety disorders, Tourette syndrome, bulimia nervosa, and pervasive developmental disorders (Birmaher et al., 2002; Lewinsohn et al., 1995; West et al., 1996; Wozniak et al., 1997, 1999, 2001). Furthermore, when bipolar disorder is present in adolescence, it can be predictive of an increase in antisocial and borderline personality symptoms (Lewinsohn, Klein, & Seeley, 2000). Distinguishing between bipolar disorder and other disorders, such as oppositional defiant disorder, conduct disorder, anxiety, major depression, and borderline personality disorder, requires careful assessment of these youths over a longer period of time with more frequent contacts to establish the cyclical nature (although the cycles can be atypical from those of adults) of the bipolar disorder versus the more persistent symptoms present in the other diagnoses. Also, these disorders can coexist, which requires careful treatment strategies.

Because many of the youth identified in the research as having bipolar disorder have trauma histories, it would be important also to evaluate for comorbid post-traumatic stress disorder.

Genetics

Offspring of parents with bipolar disorder were at 2.7 times higher risk for developing a psychiatric disorder and fourfold higher risk (14–50%) for developing a mood disorder as compared to children of parents without psychiatric illness (Chang, Steiner, & Ketter, 2000).

Furthermore, early onset bipolar disorder is associated with children who have a proportionately higher

genetic load for the disorder (Neuman, Geller, Rice, & Todd, 1997). Additionally, in a study of monozygotic twins with bipolar disorder, Potash and DePaulo (2000) observed a 60% concordance rate.

Neuroanatomy

The affective circuitry, including the dorsolateral prefrontal cortex, the orbitofrontal cortex, amygdalae, the cingulate gyrus, and the limbic system, have all been implicated in bipolar disorder. Dickstein et al. (2005) evaluated magnetic resonance images in 20 children with bipolar disorder and 20 youths without psychiatric disorders. Results showed that youth with pediatric bipolar disorder had gray matter reductions in the left amygdala and in the left dorsolateral prefrontal cortex as compared to controls. No differences in hippocampal volumes were detected, unlike the results from Frazier et al. (2005), who noted that a smaller hippocampal volume was seen in 43 subjects with bipolar disorder. Other researchers (Blumberg et al., 2005; Chang et al., 2005) found decreased amygdala volumes when evaluating high-resolution magnetic resonance images (MRIs) in 20 and 18 youths, respectively, with bipolar disorder compared to healthy controls. The MRI results in the youths with bipolar disorder showed a consistent reduction in gray matter volume in both the left and right amygdalae. Furthermore, subjects who had been treated in the past with either lithium or valproic acid had more gray matter volume in the amygdala than subjects never receiving medication (Chang et al., 2005). Rich et al. (2006) also evaluated the amygdala function in pediatric bipolar disorder. Twenty-two youth with bipolar disorder were compared to 21 healthy controls using functional MRI tests when subjects were directed to label emotional aspects of faces versus nonemotional aspects of faces. Bipolar patients perceived greater hostility in neutral faces and had greater activation in the left amygdala, accumbens, putamen and ventral prefrontal cortex when rating their fear of faces compared to controls. Kaur et al. (2005) compared

16 youth with bipolar disorder (mean age of 15.5 years) to 21 matched healthy comparison subjects to examine the cingulate cortex. They found that children with bipolar disorder had significantly smaller mean volumes compared to healthy subjects in the left anterior cingulate, left posterior cingulate, and right posterior cingulate.

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Neurobiology

While genetic studies support a hefty piece of the bipolar etiology, the exact pathophysiology of this highly complex disorder is still unclear (Kapczinski, Frey, & Zannatto, 2004). Research in the areas of neurotransmitters, signaling pathways and protein systems provide an important window into the bipolar etiology.

The role of the monoamines (dopamine, serotonin, and norepinephrine) is of great importance. The aforementioned limbic, striatal, and prefrontal circuitry, which have been the focus of MRI research and are responsible for mood regulation, are richly supplied by these neurotransmitters. Furthermore, psychopharmacological success supports a pathological process in these pathways and receptor sites (Payne, Quiroz, Gould, Zarate, & Manji, 2004). Additionally, preliminary findings suggest that changes in the binding site on the gamma-amino butyric acid (GABA) receptor may be affected (Dean, 2004).

Cyclic adenosine monophosphate (cAMP), a “messenger” in the neurotransmitter pathways, has been researched as a possible factor in the etiology of bipolar disorder. In postmortem studies, Chang, Li, and Warsh (2003) found lower levels of cAMP in brain regions from patients with bipolar affective disorder as compared to controls. The G-protein complex binds dopamine and serotonin to their respective site receptors. These monoamines regulate, in part, behavior and mood. Several studies have linked a disturbance in G-protein levels in patients with bipolar disorder, although the relationship remains unclear (Emamghoreishi et al., 2000; Friedman & Wang, 1996; Spleiss et al., 1998).

The neurobiologic processes involved in the etiology of bipolar disorder are unlikely to be linear. Further systematic studies on the neurotransmitter systems of the central nervous system, as well as the interaction between receptors, G-proteins, cAMP kinases, and signal-transduction pathways, are required to better understand the pathophysiology of bipolar disorder (Dean, 2004).

Rating Scales

The Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) was designed for adults but demonstrated validity in studies involving 612 children and adolescents with bipolar disorder (Youngstrom, Danielson, Findling, Gracious, & Calabrese, 2002; Youngstrom, Gracious, Danielson, Findling, & Calabrese, 2003). Furthermore, a child-specific rating scale, the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS), was recently developed as a revision of the KSADS and administered to 93 youths with bipolar disorder (Geller, Zimmerman, et al., 2001). This scale shows good concurrent validity with a 97% agreement when used by an “expert” clinical interviewer (Wozniak et al., 2003). This revision of the KSADS showed that children who have mania and bipolar I disorder present differently than adults with episodes that are longer,

mixed in nature, and follow a more chronic course. The Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime version (Kaufman et al., 1997) is another screening instrument used in detection of mood spectrum disorders, including bipolar disorder symptoms and schizophrenia in children. Another tool available for specifically screening children and adolescents for bipolar disorder is the short form of the General Behavior Inventory (GBI) (Youngstrom, Findling, Danielson, & Calabrese, 2001). The form also has a parent version.

In a comparative study, Youngstrom and colleagues (2004) measured the diagnostic ability of six different screening instruments for pediatric bipolar disorder. They included the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS) (Kaufman et al., 1997), the Child Behavior Checklist (Achenbach, 1991a), the Parent version of Young Mania Rating Scale (Gracious, Youngstrom, Findling, & Calabrese, 2002), and Parent—General Behavior Inventory (P-GBI) (Youngstrom et al., 2001). In a sample of 642 youths, ages 5 to 17, the researchers found that the Parent—Young Mania Rating Scale, the Parent General Behavior Inventory, and the Parent version of—Child Behavior Checklist demonstrated the best probability of detecting a pediatric bipolar diagnosis. In addition, parent ratings were more useful than teacher report (Achenbach, 1991b) or the adolescent self-report (Achenbach, 1991c) measures in determining a diagnosis of pediatric bipolar disorder.

Psychopharmacological Treatments

Psychopharmacology is the first-line treatment for pediatric bipolar disorder. This section will review the current psychopharmacological agents used in treating pediatric bipolar disorder, review available research studies, and provide the reader with clinical applications, including the drug's effectiveness, adverse effects, drug-drug interactions, as well as medication recommendations for achieving long-term remission of symptoms. This psychopharmacological search is

limited to studies done in the pediatric population. Open label and double-blind placebo-controlled studies were included. Individual case reports were referred to in this review. MedLine and the Cumulative Index for Nursing and Allied Health Literature (CINAHL) were the selected databases. Snowballing techniques were used to find other studies.

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Lithium

Lithium has been a medication treatment used in adult bipolar disorder for over 50 years. It is recommended for bipolar disorder with symptoms of euphoric mania. It is the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania and bipolar disorder in adolescents, specifically, ages 12–18 years. Lithium is thought to exert multiple neurotransmitter effects, including enhancing serotonergic transmission, increasing norepinephrine synthesis, blocking postsynaptic dopamine, and increasing GABA activity (Bschor et al., 2003). It is likely to produce alterations in ion channels of cell membranes and affect the intracellular signaling processes (Manji & Lenox, 1999).

Research

Geller, Williams, et al. (1998) evaluated 25 youth with bipolar disorder and comorbid substance dependence in a 6-week double-blind randomized placebo-controlled trial. The response rate for lithium was 46% compared to 8% response rate in the placebo-control group. The primary outcome measure was the Children's Global Assessment Scale. However, when assessing

the improvement using the KSADS, using a one-tailed fisher test, there was no significant difference between active and placebo groups. Kafantaris, Coletti, Dicker, Padula, & Kane (2003) evaluated 100 acutely manic bipolar adolescents with lithium in an open-label study. Additionally, half of the subjects were also treated with an antipsychotic for presence of psychotic symptoms. At week 4 of treatment, 63 patients on lithium were categorized as responders and 26 achieved remission of symptoms. The primary outcome measures were the Young Mania Rating Scale and the Clinical Global Impression Scale. The researchers concluded that lithium was effective for acute stabilization of manic symptoms and that adjunctive use of an antipsychotic improved the patient's symptoms. Strober et al. (1998) found that children who had comorbid ADHD with mania, and prepubertal onset of the disorder, predicted a poorer response to acute lithium therapy.

Clinical Implications

Whereas lithium continues to be the only FDA-approved medication for 12- to 18-year-olds with bipolar disorder, it requires diligent monitoring. It takes children approximately 1 week to achieve a steady state. Baseline blood work should include a lithium level, as well as a creatinine concentration, thyroid function tests, and a complete blood count, and should be repeated every 6 months. Lithium's small therapeutic window is between 0.8 and 1.2 mmol/L. To achieve an accurate lithium level, blood should be drawn 12 hr after a dose. The usual starting dose is 300 mg/day titrated up every 3–5 days until the level is within a therapeutic range. Patients should be educated regarding adequate fluid intake and the use of a reliable contraception method because of lithium's potential to cause birth defects. Adverse effects and lithium toxicity are described in Table 2. Several drugs have been found to increase lithium levels, including carbamazepine, nonsteroidal anti-inflammatory drugs, tetracyclines, and thiazide diuretics (Scahill, Farkas, & Hamrin, 2001). Theophyl-

line and caffeine promote lithium excretion, resulting in lower serum levels of lithium at the same oral dose (Pies, 1998). Clinicians should discuss these potential interactions with patients and families.

Anticonvulsants

Anticonvulsants work by prolonging the inactivation of voltage-sensitive sodium and calcium channels. This, in turn, decreases the release of catecholamines, which neutralize neurotransmitters such as dopamine, serotonin, and norepinephrine. Anticonvulsants also increase the inhibitory neurotransmitter GABA (White, 2003).

Research

In a randomized nonblind, open trial, 42 youth with bipolar I and II in a mixed or manic state were randomized to carbamazepine, lithium, or divalproex sodium for 6 weeks (Kowatch et al., 2000). Responders were categorized if they experienced a greater than 50% improvement on the YMRS, and achieved a rating of "much improved" or "very much improved" on the Clinical Global Impression Improvement scale (CGI-I). Results demonstrated a 38% response rate for carbamazepine and lithium, respectively, and a 53% response rate for divalproex sodium.

In a retrospective chart review, carbamazepine was compared to lithium and divalproex sodium in 44 pre-adolescents with bipolar disorder (Davanzo et al., 2003). Patients were excluded if they needed adjunctive antipsychotic medications in addition to their mood stabilizer. Lithium and divalproex sodium were statistically superior to carbamazepine at week 2. The CGI was the primary measure. There was a 34% response rate to carbamazepine compared to a 42% response rate to lithium and 46% response rate to divalproex sodium.

Wagner et al. (2002) evaluated 40 youth with manic, hypomanic, or mixed episodes in an 8-week open-label trial for divalproex sodium. Sixty-one percent of the

subjects experienced a 50% reduction in symptoms on the YMRS; however, most subjects did not achieve full remission at the study's endpoint. Pavuluri, Henry, Carbray, Naylor, and Janicak (2005) evaluated divalproex sodium for pediatric mixed mania in a 6-month open-label prospective study. The outcome measure was the YMRS. The response rate was 73.5%, indicating a greater than 50% change from baseline at the end of the study. Seventeen patients were on adjunctive risperidone, 5 patients were on adjunctive trazadone, and 13 patients were on adjunctive methylphenidate. Adverse effects were weight gain with a mean increase of 5.6 kg, and six subjects had abnormally elevated alanine transferase levels. Other side effects were sedation, increased appetite, and cognitive dulling. Calabrese et al. (2005) conducted a 20-month double-blind maintenance trial of lithium versus divalproex sodium in 60 rapid cycling bipolar youth. The Hamilton Depression Scale and the YMRS were the primary measures. Of the 254 patients originally enrolled in the open-label acute stabilization phase, 76% discontinued owing to poor adherence, nonresponse (74% had continued depression and 26 remained manic), or intolerable side effects. Of the 60 patients randomly assigned to the double-blind maintenance monotherapy, 53% relapsed (59% with depression and 41% with manic symptoms). Twenty-two subjects completed the study. Ten percent had intolerable side effects and 10% were poorly adherent. The rates of relapse were 56% for lithium and 50% for divalproex.

Whereas there were no significant differences in duration until relapse, the researchers concluded that rapid cycling with refractory depression was a predictor of poor outcome to treatment. Furthermore, one drug was not more effective than the other in the long-term management of rapid cycling bipolar disorder.

MacMillan et al. (2006) conducted a chart review comparing divalproex sodium with oxcarbazepine in 31 youth with aggressive behaviors and bipolar disorder for 4 months. The Clinical Global Impressions—Severity (CGI-S) and CGI aggression scale were the primary measures. There were significantly greater

reduction in CGI-S and CGI-Ag-S scores with divalproex compared with oxcarbazepine at 4 months. Patients on oxcarbazepine had higher rates of discontinuation as a result of worsening aggression.

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Findling et al. (2005) evaluated 139 youth with bipolar disorder I or II in a double-blind randomized controlled trial comparing lithium to divalproex sodium on the primary outcome measures of time to relapse and time to premature discontinuation. The study was not placebo controlled. The children were started on combined lithium and divalproex sodium for 10 weeks, and then 60 youth were randomized to monotherapy of either lithium or divalproex for 76 weeks. Divalproex was not superior to lithium as maintenance treatment, and both groups needed a second medication at week 14 for stabilization. Approximately 40% of the patients were on either drug at 100 days, and both groups demonstrated a worsening of manic and depressive symptoms over time. More than half of the patients discontinued the study as a result of recurrence of hypomanic or manic symptoms. Side effects for emesis and enuresis were worse for lithium compared to divalproex sodium. Only 10% of both groups stayed on the drug for the entire 76 weeks.

There are two placebo-controlled trials involving anticonvulsants that demonstrated that the drug was

not more effective than placebo. Both studies used the YMRS as the primary measure. In the first study, oxcarbazepine, a 10-keto analog of carbamazepine, was evaluated in 116 children and adolescents with bipolar I disorder in a randomized double-blind placebo-controlled trial. Scores for oxcarbazepine did not significantly improve (Wagner et al., 2006). This is the second study to demonstrate the lack of effectiveness of oxcarbazepine in pediatric bipolar disorder. Second, topiramate, a novel broad spectrum anticonvulsant, was evaluated in a double-blind placebo-controlled study with 56 children and adolescents with bipolar disorder type I for 28 days (Delbello et al., 2005). Topiramate was not statically different from placebo; however, the pediatric study was discontinued early after topiramate trials in adult studies did not demonstrate efficacy in treating bipolar disorder.

Topiramate did demonstrate improvements in CGI-S scores as an adjunctive treatment in two retrospective chart reviewed studies involving 25 youth in each study (Barzman et al., 2005; Delbello et al., 2002). These data should be viewed with caution as these studies were not placebo controlled or prospective, and topiramate monotherapy did not demonstrate efficacy with adults or children.

Lamotrigine, an effective treatment for treatment-refractory adult bipolar disorder (Nierenberg et al., 2006), received a black-box warning for those under age 16 owing to potential of increased incidence of Steven-Johnson's rash in youth. Whereas lamotrigine has been associated with being weight neutral or causing weight loss in adults with and without obesity (Bowden et al., 2006), it can have other adverse effects including dizziness, fatigue, headache, blurred vision, impaired memory. Lamotrigine was reported to demonstrate effectiveness in Carandang, Maxwell, Robbins, and Oesterheld's (2003) adolescent bipolar case study, particularly for depressive symptoms in adolescent bipolar disorder. This drug may hold promise for adolescents with rapid cycling and frequent depressive relapses, however, further randomized controlled trials are indicated for lamotrigine.

Clinical Implications

Baseline laboratory values should include serum blood levels, CBC values, liver function tests and weigh. These items should be monitored throughout treatment. Side effects of anticonvulsants include weight gain, nausea, sedation, dizziness, tremor, headache, visual disturbances, blood dyscrasias, elevated thyrotropin levels and alopecia. Divalproex sodium has been linked to the development of polycystic ovarian syndrome in women (Joffe et al., 2006). Advanced practice nurses need to provide adolescent females and their families with informed consent, including warnings about menstrual irregularities, hirsutism, acne, male pattern hair loss, and elevated testosterone before starting divalproex sodium. Carbamazepine has also been associated with a small number of cases of Stevens-Johnson's rash. Oral contraceptives may become ineffective with carbamazepine.

Antipsychotics

Atypical antipsychotics combine dopaminergic and serotonergic properties to provide mood stabilization. The studies evaluating monotherapy using the atypical antipsychotics are either open label or chart reviews.

Research

Frazier et al. (1999) evaluated 28 pediatric bipolar subjects in a retrospective chart review using risperidone. The CGI-I was the primary measure. Eighty-two percent of subjects demonstrated improvement in mania and aggression, while 69% of subjects showed an improvement in psychotic symptoms, and 8% of subjects demonstrated improved ADHD symptoms using the Clinical Global Inventory Improvement score of greater than or equal to 2.

Biederman et al. (2005) evaluated 30 patients with pediatric bipolar disorder in an 8-week open-label study using risperidone. The YMRS and the CGI-I were the primary measure. Researchers found a response

rate of 70% for manic symptoms and a response rate of 35% for ADHD symptoms. Additionally, Beiderman's research group (2005) compared olanzapine to riperidone in 31 children ages 4–6 years with bipolar I, II, and bipolar NOS. The YMRS and the Clinical Global Inventory were the primary measures. Children on risperidone had a 56% response rate compared to a 53% response rate in children on olanzapine. Frazier et al. (2001) evaluated 23 youth with bipolar disorder in an 8-week open prospective study. Olanzapine was administered at a dosage of 5 to 20 mg/day. Participants showed a 61% response rate, indicating a 30% decrease on the Young Mania Rating Score. Side effects included weight gain.

In a retrospective chart review, Marchand (2004) evaluated quetiapine as monotherapy or in combination with other agents, including lithium, oxcarbazepine, or psychostimulants, in 32 youth with bipolar types I and II, cyclothymia, and bipolar NOS. Doses for quetiapine ranged from 100 to 1,000 mg/day. Response rates scored with a greater than two point decrease on the CGI were 80% for the entire group receiving quetiapine plus a second drug and 78% for the subgroup who received quetiapine monotherapy. Patients demonstrated improvement both in manic and depressive symptoms. Patients on stimulants (62.5%) had no difficulty tolerating the addition of quetiapine. Side effects included sedation and akathisia. Patients on quetiapine gained 0.8 kg from baseline to endpoint. In addition, several small studies involving seven to eleven participants with pediatric bipolar disorder on atypical antipsychotics have demonstrated positive outcomes (Kowatch, Suppes, & Gilfillan, 1995; Masi, Mucci, & Millepiedi, 2002; Schreier, 1998; Soutullo, Sorter, Foster, McElroy, & Keck, 1999).

Clinical Implications

The nurse practitioner must monitor weight and symptoms of extrapyramidal side effects in patients on antipsychotics. Electrocardiograms should be obtained

for patients on ziprasidone. Laboratory tests should include liver enzymes, triglycerides, cholesterol level, fasting glucose levels, prolactin levels, bilirubin, serum ammonia, and complete blood count.

The nurse practitioner must monitor weight and symptoms of extrapyramidal side effects in patients on antipsychotics.

Mood Stabilizers versus Antipsychotics

DelBello et al. (2006) compared the efficacy of quetiapine to divalproex sodium in a randomized double-blind study. Fifty hospitalized adolescents with bipolar I disorder, manic, or mixed episode were randomized to quetiapine (400 to 600 mg/day) or divalproex sodium (serum levels of 80 to 120 µg/mL) for 28 days. The YMRS was the primary measure. There was no statistically significant difference between the two groups on the YMRS at 28 days; however, adolescents on quetiapine demonstrated more rapid improvement and greater remission rates as well as greater response rates on the Clinical Global Inventory–Bipolar Inventory scores compared to those adolescents on divalproex sodium. There were no significant differences between the two groups in rates of adverse effects.

Combined Medication Treatments

Findling, Calabrese, and Youngstrom (2003) evaluated 90 youth with bipolar I and II in an open-label study for 20 weeks. Remission was defined as tolerance of combined divalproex sodium and lithium therapy at prescribed levels, clinical stability, no evidence of affective cycling, and no required treatment with an

antipsychotic, antidepressant, or another mood stabilizer for four consecutive weeks. Primary measures were the YMRS, the Children's Depression Rating Scale, and the Children's Global Impressions Scale. Forty-seven percent of the subjects met criteria for remission. Seventy-five percent of subjects had a 30% reduction from baseline score on the YMRS and a CGI severity score of greater than or equal to 3, and 70% of the combined medication treatment subjects had a 50% improvement on the YMRS from baseline. Findling et al. (2006) also evaluated 38 children who relapsed after treatment with either lithium or divalproex sodium monotherapy. This prospective 8 week open-label combination trial with lithium and divalproex sodium used the Children's Depression Rating Scale Revised, the YMRS, and the Clinical Global Impressions Scale as primary outcome measures. Eighty-nine percent of the subjects responded to the treatment with the lithium and divalproex sodium combination. The four patients who did not respond to the combined lithium and divalproex sodium treatment received an adjunctive antipsychotic treatment of either risperidone or olanzapine. It is important to note that 65% of the study participants were also on a stimulant medication for comorbid ADHD.

Scheffer, Kowatch, Carmody, and Rush (2005) studied 40 youths with bipolar disorder and ADHD in an 8-week open trial of divalproex sodium followed by a 4-week randomized double-blind placebo-controlled crossover with amphetamine salts for treatment of ADHD. Patients in the crossover trial continued to receive divalproex sodium. The primary measures were the YMRS and the Clinical Global Impression-Improvement Scale. Eighty percent of patients had a reduction of greater than 50% on the YMRS in manic symptoms with the anticonvulsant. However, only 7.5% patients had a reduction in ADHD symptoms with divalproex sodium monotherapy. For the 30 subjects in the crossover trial, mixed amphetamine salts were significantly more effective than placebo for ADHD symptoms. No worsening of manic symptoms resulted from the use of amphetamine salts.

At this writing, there is only one double-blind study evaluating the combined treatment of an atypical antipsychotic and anticonvulsant. Delbello, Schwiers, Rosenberg, and Strakowski (2002) treated 30 bipolar adolescents in a 6-week randomized double-blind placebo-controlled study. All subjects received divalproex sodium and were randomized to either adjunctive quetiapine or placebo. The YMRS and the Clinical Global Inventory were the primary outcome measures. Both the medication and placebo groups experienced an initial reduction in symptoms; however, those randomized to adjunctive quetiapine had an 87% response rate at endpoint compared to those treated with divalproex sodium monotherapy, who demonstrated a 53% response rate. Whereas sedation was a side effect, reductions in depression, mania, and psychotic symptoms were found as a result of the combined treatment. Pavuluri, Henry, Devineni, et al. (2004) also evaluated the combination of the anticonvulsant, lithium, or divalproex sodium, in conjunction with risperidone in a 6-month open-label prospective study of 37 pediatric patients with bipolar disorder. The primary outcome measures were the YMRS and the Clinical Global Impression Scale for Bipolar Disorder. Results were measured by a 50% change from baseline on the YMRS. Response rates for divalproex sodium plus risperidone were 80% and 82% for lithium plus risperidone. Concomitant medications were also used, including psychostimulants for children diagnosed with ADHD, clonidine was used on a short-term basis for acute states of mania, and trazadone was used for children with persistent sleep disturbance. The use of these adjunctive medications confounds the effects of the study results. Pavuluri, Henry, Devineni, et al. (2004) evaluated 64 bipolar type I pediatric patients in a medication algorithm treatment study. In the first phase, eight patients were placed on second generation antipsychotic monotherapy, which consisted of quetiapine, ziprazidone, or olanzapine. Only 4 of the 8 subjects were able to remain on monotherapy for over 6 months. Forty subjects (36 received a mood stabilizer as first choice, and 4 failed antipsychotic

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treatment alone) received mood stabilizer monotherapy. Only 7 (17%) of 40 patients placed on a monotherapy with a mood stabilizer (lithium or divalproex sodium as first choice followed by carbamazepine) showed complete response. Then 53 subjects received combined therapy with a mood stabilizer plus another mood stabilizer, an antipsychotic, trazadone, or a psychostimulant. Thirty-three of the 53 subjects (62%) who received a combined treatment option attained complete response as measured by the Clinical Global Inventory–Bipolar Inventory. Children who were placed on a psychostimulant for their comorbid ADHD combined with a mood stabilizer and did not demonstrate any worsening of symptoms of mania. Weight gain was a major side effect with all primary medications, particularly with the antipsychotics. Side effects were usually dealt with by lowering the medication dose as the first option. The researchers concluded that monotherapy was not an effective treatment for long-term stabilization of symptoms present in pediatric bipolar disorder with or without psychiatric comorbidities.

Discussion

In evaluating the mood stabilizers, it becomes apparent that divalproex sodium and lithium are particularly useful in treatment of acute mania. Lithium may be more useful in children with classic euphoric mania without psychotic symptoms or comorbid ADHD (Kowatch & Delbello, 2005). Whereas divalproex sodium performed slightly better when compared to lithium in one study (Kowatch et al., 2000), response rates for the two medications were equal in four other studies (Calabrese et al., 2005; Davanzo et al., 2003; Findling et al., 2005; Pavuluri, Henry, Carbray, et al., 2004). Divalproex sodium has demonstrated response rates ranging from 46 to 80% when used as monotherapy for short-term stabilization of bipolar symptoms. Divalproex sodium is effective and well tolerated in combination with other drugs such as the antipsychotics, and the combination of the two usually requires a

lower dose of the antipsychotic medication (Singh, Muzina, & Calabrese, 2005). Carbamazepine has been used less due to lower efficacy when compared to lithium and divalproex sodium and side effects of aplastic anemia and Stevens-Johnson's rash. Additionally, carbamazepine is not recommended in conjunction with sodium divalproex because of the CYP450 drug interactions (Kowatch & Delbello, 2005). In studies evaluating monotherapy with lithium alone or compared to divalproex sodium at 6 weeks, 14 weeks, and 20 months, researchers concluded that these mood stabilizers could not sustain a decrease in depressed or manic symptoms over time, and in some studies a second medication was warranted to achieve symptom remission (Calabrese et al.; Findling et al., 2005; Geller, Williams, et al., 1998).

Furthermore, the evidence strongly supports the use of quetiapine, risperidone, and olanzapine as monotherapy for acute short-term management of bipolar disorder in children. Response rates have been between 53% and 82%. It is difficult to do a head-to-head comparison of studies, as some are open label or retrospective chart reviews and others are double-blind placebo-controlled studies. Nevertheless, the research data suggest that these atypical antipsychotics may be a good first-line treatment for pediatric bipolar disorder, especially in youth with psychotic symptoms. Findling and colleagues' (2003) findings demonstrated that youth with bipolar disorder and psychotic symptoms on lithium and divalproex sodium monotherapy did not achieve remission of symptoms. There is only one double-blind randomized 28 day study done with children (DelBello et al., 2006), comparing a mood stabilizer (divalproex sodium) to an antipsychotic (seroquel). Both medications were equally effective in obtaining acute and short-term stabilization of bipolar symptoms as measured by the YMRS; however, quetiapine performed better with regards to scores on the Clinical Global Inventory for Bipolar Disorder, more rapid action, and improved response and remission rates compared to divalproex sodium.

Even more compelling, the combined treatments of a mood stabilizer (lithium or divalproex sodium) and an antipsychotic (risperidone or quetiapine) or the mood stabilizers (lithium plus divalproex sodium) may hold promise for long-term remission of symptoms. Clinicians must always weigh the drug benefit with the adverse effect profile. Weight gain, metabolic problems causing diabetes, elevated lipid and cholesterol levels, and sedation must be closely monitored with the use of the antipsychotics and the mood stabilizers. These adverse effects are even more significant for children on combination therapy. Education on nutrition and exercise is essential to prevent obesity and elevated lipid and cholesterol levels. Despite these interventions, children who experience a 5% increase in body weight should be evaluated for other medication options.

Evidence strongly supports the use of quetiapine, risperidone, and olanzapine as monotherapy for acute short-term management of bipolar disorder in children.

Children with bipolar disorder and ADHD require both a mood stabilizer and a sustained-release stimulant medication for symptom control if they can be tolerated together without adverse effects. Many studies demonstrated the safe and effective use of antipsychotics or anticonvulsants combined with stimulants (Pavuluri, Henry, Devineni, et al., 2004; Pavuluri et al., 2005; Scheffer et al., 2005). All of these medication options require close monitoring for adverse side effects, which vary according to the drug. Priority is given to stabilizing mania or psychosis and then addressing any depressive symptoms. As there is very little evidence or guidance around the safety and effectiveness of the

selective serotonin reuptake inhibitors (SSRIs) for use in the depressive symptoms of pediatric bipolar disorder in the pediatric literature, their use is cautioned. Leverich et al. (2006) conducted a study with adults with bipolar illnesses placed on trials of venlafaxine, sertraline, and bupropion as adjuncts to their mood stabilizer. Rates of conversion to hypomania and mania caused by the antidepressants were 11.4 and 7.9%, respectively, in the acute trials, and 21.8 and 14.9%, respectively, in the continuation trials. Furthermore, the rate of switching in children diagnosed with unipolar depression to mania/hypomania was between 2 and 6% in a review of six studies evaluating the SSRIs in the children with major depression (Hamrin & Scahill, 2005). Therefore, clinicians should be cautious in using SSRIs for children and adolescents with bipolar disorder because they can cause activation, agitation, hypomania, or mania. Children may be more sensitive to switches than adults.

Implications for Future Research

The majority of studies in pediatric bipolar disorder are open label or retrospective chart reviews, which measure acute responses to pharmacological intervention. Whereas they yield important information, the majority of the studies were only 8 weeks in length and lack the rigor of randomized controlled trials. The majority of studies contained small sample sizes, thereby limiting the generalizability of this data to the larger population. Randomized controlled trials that compare multiple drugs, including adjunctive medication responses, are necessary to improve efficacy in the treatment of pediatric bipolar disorder. Furthermore, longer-term studies are needed to evaluate the effects on mood stabilization, remission outcomes, and ramifications of adverse effects.

Conclusions

Pediatric bipolar disorder represents the beginning of a severe and chronic mental illness which affects

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global functioning. It is highly heritable, but early detection and treatment can significantly improve functioning. Symptom presentation differs between children and adults, and further refinements of the diagnostic criteria and course of illness are underway. Monotherapy with mood stabilizers has not demonstrated effectiveness in long-term remission of pediatric bipolar symptoms.

Recent research indicates that combined treatment with two mood stabilizers or a mood stabilizer and an antipsychotic may offer the hope of long-term remission for children with pediatric bipolar disorder, youth with acute manic symptoms plus psychosis, and rapid and mixed cycling. Because relapse rates are high in this population, rigorous double-blind randomized and placebo-controlled studies are needed to evaluate long-term outcomes of medication trials.

Recent research indicates that combined treatment with two mood stabilizers or a mood stabilizer and an antipsychotic may offer the hope of long-term remission for children with pediatric bipolar disorder, youth with acute manic symptoms plus psychosis, and rapid and mixed cycling.

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