Current research in child and adolescent bipolar disorder

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Although recently more research has considered children with bipolar disorder than in the past, much controversy still surrounds the validity of the diagnosis. Furthermore, questions remain as to whether or not childhood expressions of bipolarity are continuous with adult manifestations of the illness. In order to advance current knowledge of bipolar disorders in children, researchers have begun to conduct phenomenological, longitudinal, treatment, and neuroimaging studies in youths who exhibit symptoms of bipolar illness, as well as offspring of parents with bipolar disorders. Regardless of the differences between research groups regarding how bipolar disorder in children is defined, it is agreed that pediatric bipolarity is a serious and pernicious illness. With early intervention during the period of time in which youths are exhibiting subsyndromal symptoms of pediatric bipolarity, it appears that the progression of the illness to the more malignant manifestation of the disorder may be avoided. This paper will review what is currently known and what still is left to learn about clinically salient topics that pertain to bipolar disorder in children and adolescents.

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Children and adolescents diagnosed with a bipolar (BP) disorder face substantial obstacles. Besides the human suffering associated with the mood symptomatology which they experience, greater academic problems, difficulties with peers, and high levels of family dysfunction are often found in youths with bipolar disorder.[1,2] Furthermore, children and adolescents with bipolar disorder have an increased risk of substance use, suicidal ideation, suicide attempts, and completed suicide.[3,4] In fact, Goldstein et al[5] found that approximately 32% of 405 youths under the age of 18 with a bipolar spectrum disorder reported having a previous serious suicide attempt. In the hope of reducing the substantive sequelae associated with this condition, research has begun to examine how best to recognize early-onset bipolar disorder in children and effectively treat these patients earlier in their course of illness.

Prevalence of bipolar disorder

The lifetime prevalence of a bipolar spectrum disorder in adults has been estimated to be approximately 4.5%, with subsyndromal bipolar disorders being more prevalent (2.4%) than Bipolar I Disorder (BP-I) or Bipolar II Disorder (BP-II).[6] Epidemiological studies have found bipolar spectrum disorders to be present in approximately 0.1% to 1% of children and adolescents (see ref 7 for review). Recently it has been noted that the number of office visits for youth with bipolar disorder has increased

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Selected abbreviations and acronyms

ADHD	*attention deficit–hyperactivity disorder*
BPD	*bipolar disorder*
BP-NOS	*bipolar disorder not otherwise specified*
CBT	*cognitive behavior therapy*
DVPX	*divalproex*
IPSRT	*interpersonal and social rhythm therapy*

40-fold over the past 10 years, indicating that either this syndrome was under-recognized in the past, or that children are now being diagnosed incorrectly.[8] As will be discussed later, there is substantial symptom overlap that exists between bipolar spectrum disorders and other psychiatric conditions. In fact, it is possible that it is this symptom overlap that may account for the differences between the past and present rates at which the diagnosis of bipolarity is given to children and adolescents.

Phenomenology

Phenomenology studies have begun to explore the symptom presentation of bipolar disorder throughout early childhood, adolescence, and into adulthood.[9-12] As a result of current research, there is a growing body of evidence to support the assertion that elevated mood may be a key symptom in pediatric BP spectrum disorders, which distinguishes this condition from other psychiatric illnesses.[13] For example, Axelson et al[4] found that approximately 82% of youths with bipolar disorder not otherwise specified (BP-NOS) and 92% of children and adolescents with BP-I reported elevated mood. Furthermore, Findling et al[14] found that elevated mood was the best predictor of BP-NOS or cyclothymic disorder in offspring of a parent with bipolar disorder.

Although elevated mood is a distinguishing symptom in pediatric bipolarity, youths with bipolar disorders have been shown to exhibit substantive rates of aggression and irritability.[13,15,16] For instance, Danielyan et al[9] found that 88.5% of their sample reported aggression and 84.6% reported irritability. However, it should be noted that symptoms of aggression and irritability, although prominent in pediatric bipolarity, are symptoms of many other childhood psychiatric disorders such as disruptive behavior disorders and depression. Therefore, due to their lack of diagnostic specificity, irritability and aggression may not be the best means by which to differentiate pediatric bipolar illness from other psychiatric conditions in the young.

Other common symptoms observed in children and adolescents with bipolar illness across multiple pediatric studies include other diagnostic symptom criteria for mania described in the *DSM-IV*[17]: increased energy, distractibility, pressured speech, grandiosity, and racing thoughts (see ref 13 for review).

Notably, it appears that most children and adolescents meet *DSM-IV* criteria for BP-NOS rather than the symptomatic manifestations of BP-I or BP-II.[12] Additionally, it appears that the most common reason that children and adolescents meet *DSM-IV* criteria for BP-NOS but do not meet criteria for BP-I or BP-II is not due to lack of meeting an adequate number of symptom criteria, but rather failing to meet episode duration criteria.[4] However, despite the fact that subjects do not meet full *DSM-IV* criteria for BPI or BP-II, patients with BP-NOS and cyclothymic disorder also suffer from impairing mood symptoms.[4,14] In short, although the rates at which symptoms are reported in pediatric bipolar illness appear to vary somewhat across research sites, it is clear that there is a group of children and adolescents who present with symptoms of bipolar spectrum disorders as defined by *DSM-IV* criteria.[17]

Comorbidity

In addition to mood episodes and their associated symptoms, adults and children with bipolar disorder also have been reported to experience high rates of comorbid psychiatric diagnoses. In a nationally representative sample of adults, over 90% of respondents with a bipolar spectrum disorder reported at least one comorbid diagnosis.[6] The most frequent comorbid diagnoses found in adults with bipolar disorder in this study were anxiety disorders. Similarly to adults, high rates of comorbid diagnoses have been found in children and adolescents with bipolar disorders. For example, Tillman et al[18] found that almost 98% of 91 children and adolescents with a bipolar spectrum disorder examined also suffered from a comorbid psychiatric disorder. Kowatch et al[13] reported in a meta-analysis that attention deficit-hyperactivity disorder (ADHD) was the most frequent comorbid diagnosis in children and adolescents with bipolar disorder. Other common comorbid diagnoses in youth with bipolar disorder include oppositional defiant disorder (ODD), anxiety disorders, conduct disorder (CD), and substance use disorders.[13] Rates of comorbid psychiatric diagnoses reported in youth with bipolar disorders vary from 11%

to 90% presenting with ADHD, 46% to 75% with ODD, 5% to 37% with CD, 12% to 77% with anxiety disorders, and up to 40% of adolescents with a substance use disorder.[4,10,12,19-24] One possible explanation for the varying and high rates of reported comorbid diagnoses in youths with a bipolar spectrum disorder may be the result of overlapping symptoms across diagnoses that may be attributable to other disorders. For example, inattention, distractibility, impulsivity, psychomotor agitation, and sleep disturbances can be characteristic of both children and adolescents with bipolar disorder as well as ADHD.[25] As noted above, irritability and aggression are common symptoms observed in adolescents with bipolar disorder. However, these symptoms are also characteristic of a disruptive behavior disorder (DBD).

As might be expected, children and adolescents diagnosed with a bipolar disorder and a comorbid psychiatric diagnosis have a more complicated clinical presentation, and often have confounding issues that need to be addressed in treatment. For instance, in those youths with bipolar disorder and other comorbid conditions, both the youths and parents reported more family conflict and lower family cohesion in comparison with youths with bipolar disorder only.[2] In both the pharmacological and therapeutic treatment of bipolar disorder, comorbid diagnoses further complicate the treatment plan by necessitating intervention for multiple psychiatric conditions.

Longitudinal course

Age of onset

Most patients experience their first mood episode between the ages of 17 and 42 years, with a median age of onset of 25 years.[26] However, there is evidence to suggest that children do in fact experience the onset of symptoms of bipolar disorder prior to the age of 17 years.[19,27] In addition, retrospective studies examining adults with bipolar disorder have reported childhood onset of symptoms in a substantive number of subjects. For instance, Perlis et al[28] found when patients recalled their first mood episode, approximately 65% of adults experienced onset of symptoms prior to the age of 18. Moreover, 27.7% of adults reported that they experienced their first mood episode before the age of 13 years.[28]

Age of onset appears to impact the course of illness.[29] For example, in a retrospective study of adults, patients with childhood or adolescent onset of bipolar symptoms experienced a greater number of mood episodes and were more likely to have comorbid psychiatric conditions and higher rates of rapid cycling.[30] In this same study, adults with an onset of symptoms at 12 years of age or younger had the greatest incidence of bipolar and unipolar disorders in their parents. This younger age at onset subgroup experienced a higher incidence of dysphoric mania, and a higher prevalence of a lifetime diagnosis of an anxiety disorder and drug abuse compared with adults who reported an age of onset of 13 years or greater.[30]

Additionally, the age of onset of a parent's bipolar disorder has been found to have implications in their offspring. For example, Tsuang and Faraone[31] found in adults that there was a higher risk of developing a mood disorder if a subject had relatives with an earlier age of onset of a mood disorder in comparison with subjects whose relatives had a later age of onset.

Rather than relying on retrospective studies conducted in adults, researchers have begun to examine the impact of age of onset in children and adolescents with bipolar disorder. Youths with early onset of bipolar disorder prior to the age of 12 have been found to have more first-degree relatives with a family history of ADHD, conduct disorder, anxiety disorders, substance dependence, suicidal behavior, and suicide attempt and completion in comparison with those subjects with a later onset of bipolar symptoms at 12 years or later.[32] In addition, it has been reported that children and adolescents with childhood onset of bipolar disorder were more likely to have suffered from ADHD than those with onset during adolescence.[33]

Symptom course

It appears that after illness onset, children and adolescents with bipolar disorder spend the majority of time fluctuating between syndromal and subsyndromal mood episodes, with short periods of euthymia interspersed.[19] For instance, Birmaher et al[34] found that in 263 youths with a bipolar spectrum disorder, subjects were symptomatic during approximately 60% of the 2-year follow-up period. Furthermore, DelBello et al[35] found that adolescents that had been hospitalized with a BP-I diagnosis, during the year following their index inpatient stay, spent a predominant amount of their lives symptomatic. More specifically, these adolescents spent 84% of the year experiencing at least subsyndromal symptoms following

their hospitalization. In addition, Geller et al[21] reported that in youths experiencing mania, manic episodes lasted approximately an average of 80 weeks in duration. Similarly, in a pediatric cohort with bipolar disorder followed for 2 years, only 68% of the cohort experienced minimal or no symptoms for 8 consecutive weeks after their index episode.[34] Furthermore, in those subjects that recovered from their index episode, a median of 78 weeks elapsed from the onset of the presenting mood episode until symptom remission.[34]

The polarity of mood episodes that occur during the course of bipolarity appear to change as patients with bipolar disorder age. In adults with bipolar disorder, evidence suggests that depression is the predominant mood state, with patients spending approximately three times as much time depressed as manic or hypomanic.[36] However, in children and adolescents, researchers have reported that hypomanic and manic symptoms dominate, with depressive episodes being less frequent.[19]

Moreover, the mood state of the initial mood episode has been found to influence time until symptom remission. For instance, Strober et al[37] reported that adolescent patients who presented initially in a manic or mixed episode had a shorter time until mood stabilization in comparison with patients who experienced a depressive mood episode initially. Additionally, the longitudinal outcome appears to be worse in children and adolescents who have an earlier age of onset of diagnosis, with lower social economic status, rapid mood fluctuations, psychosis, mixed episodes, more comorbid diagnoses, and family psychopathology being reported.[38]

Evolution of symptoms

There is evidence to suggest that mood and symptoms of other psychiatric diagnoses in patients may evolve over time. For instance, mood symptomatology in adults appears to become more severe with increased number of mood episodes. In addition, adults appear to experience fewer periods of euthymia throughout their lifetime.[39] Moreover, with time, mood episodes that occurred as a result of a psychological stressor may begin to occur spontaneously without a precipitant.[39]

There is also some evidence to suggest that an evolution of mood symptoms may occur across the diagnostic categories of the bipolar spectrum disorders over time. For instance, it appears that patients may experience symptoms that meet diagnostic symptom criteria for BP-NOS and cyclothymia prior to meeting diagnostic symptom criteria for more syndromal diagnoses of BP-I and BP-II.[3,40] Birmaher et al[34] found that approximately 20% of patients initially diagnosed with BP-II converted to BP-I, and 25% of patients initially diagnosed with BP-NOS converted to BP-I or BP-II over a mean of 2 years of follow-up monitoring.

ADHD and anxiety symptoms have also been observed to precede mood symptoms in patients later diagnosed with bipolar disorder.[24,40,41] It has been suggested that the high rates of DBDs and ADHD in children of parents with bipolar disorder may be indicative that DBD and ADHD symptoms may be prodromal manifestations of bipolar disorder.[42] By examining children and adolescents at high risk of developing a bipolar disorder prospectively, this endeavor offers an opportunity to better investigate early symptoms and biological markers of bipolar disorders.

High risk studies

It has been suggested that if children are treated soon after the initial onset of mood symptoms, the developmental impact of the psychiatric illness may be minimized.[39] Furthermore, it appears that bipolar disorders are highly heritable conditions.[43-45] High rates of affective disorders in first-degree relatives have been reported in children with bipolar disorder. For instance, Faedda et al[20] found that 90% of patients with bipolar disorder had a family history of bipolar disorder. Additionally, it has been well documented that children and adolescents with parents diagnosed with a bipolar disorder are at high risk of developing bipolar disorder themselves.[14,46,47] Therefore, in an attempt to better study the course of bipolar disorder and treat patients as soon as possible after symptom onset, patients who are at risk for developing pediatric bipolarity are now being examined.

Children of parents with a mood disorder (depression and/or bipolar disorders) not only have an increased risk for developing bipolar disorder, but also other psychiatric disorders. For instance, offspring of parents with a mood disorder were found to be at risk for depression, anxiety, ADHD, DBD diagnoses, and more impaired psychosocial functioning.[14,42,47-49] Furthermore, independent of diagnosis, children and adolescents of parents with bipolar disorder have been shown to exhibit higher rates of hostility and irritability in comparison with offspring of parents without a psychiatric disorder.[50]

Moreover, having only one parent versus both parents being afflicted with bipolar disorder appears to have additional implications for the youth's course of illness. For instance, offspring of two parents with bipolar disorder have been found to experience more severe depression and irritability, lack of mood reactivity, and rejection sensitivity in comparison with children with only one parent with bipolar disorder.[47] Therefore, a patient's family history may offer insight into the probability of a child presenting with or eventually developing bipolar disorder.

Biological underpinnings

Genetic predispositions

Due to the observed high heritability of bipolar disorders, several genetic etiologies of bipolar spectrum disorders have been explored. Multiple genomic regions have been associated with bipolar disorder and the age of onset of mood symptoms.[51-54] For instance, regions on chromosomes 2, 4, 6, 8, 11, 12, 13, 16, 18, 21, 22, and X have been found to be possibly linked to bipolar disorder (see ref 55 for review).[43,55-57] Furthermore, several functional candidate genes have been identified to be possibly linked to bipolar disorder including catechol-O-methyl transferase (COMT), brain-derived neurotropic factor, tyrosine hydroxylase, D-amino acid oxidase activator, and neuregulin (see ref 57 for review).[52,57] In addition, earlier age of onset and increased severity of illness in subsequent generations of family members have led to genetic anticipation being hypothesized in bipolar disorder (see ref 58 for review). More specifically, it has been suggested that trinucleotide repeats may be involved in the genetic predisposition to eventual development of a bipolar disorder.[58]

Structural brain differences

With advances in imaging techniques, researchers have begun to investigate whether or not structural differences in individuals afflicted with bipolar disorder exist when compared with individuals without a psychiatric illness. Examinations of neuroanatomical structure differences of children with bipolar disorder compared with children without psychiatric disorders have reported conflicting results. However, it has been found that youths with bipolar disorder may have structural brain differences when compared with children and adolescents with other psychiatric conditions and youths without psychiatric diagnoses. These differences include smaller hippocampal volumes, smaller cerebral volumes (bilateral parietal and left temporal lobes), and smaller cingulate volumes.[59-62] Recently, in one of the largest samples of youths with bipolar disorder who underwent a magnetic resonance imaging (MRI) study, larger right nucleus accumbens of the basal ganglia were found in this patient population in comparison with children and adolescents with no psychiatric diagnoses.[63] Additionally, a significant inverse relationship was found between the right nucleus accumbens volume and the number of medications the youth was currently receiving.[63]

Due to the involvement of the amgydalae in emotion processing, this area of the brain has also been examined. For instance, Chang et al[64] found that youths with at least one parent with bipolar disorder and a bipolar disorder I diagnosis had significantly smaller left and right amgydalar volumes in comparison with healthy offspring of parents with no psychiatric disorders. In addition, Blumberg et al[65] found adults and adolescents with bipolar disorder have decreased volumes of the medial temporal lobe structures, especially in the amygdala in comparison with subjects without a psychiatric diagnosis. Moreover, abnormalities in the amygdala-striatal-ventral prefrontal cortex circuit, which is involved with mood regulation, have been found in pediatric bipolar disorder (review in ref 66).

In a review of adult and youth research, subjects with a recent onset of bipolar disorder were found to have ventricular, white matter, caudate, putamen, amygdala, hippocampus, and subgenual prefrontal cortex volume differences (see ref 67 for a review). Furthermore, relatives of individuals with bipolar disorder showed a reduction of the subgenual prefrontal cortex in several studies, suggesting a possible neuroanatomical marker for youth at risk for developing bipolar disorder.[67]

There has been some evidence to suggest a possible change of brain structures over time in adults with bipolar disorder. For instance, over a 4-year period, adults with bipolar disorder showed a greater decline in hippocampal, fusiform, and cerebellar gray matter density than adults without a psychiatric disorder.[68] Moreover, in one longitudinal examination of children prior to and after the development of bipolar disorder, an increase in left temporal cortex gray matter volume and decreased bilateral anterior cingulate cortex gray matter volume

was found in comparison with children without a psychiatric diagnosis or other psychotic disorder over the course of 4 to 8 years.[69]

Functional neuroimaging

Differences in areas of brain activation during neurocognitive tasks in patients with bipolar disorder have also been examined in an attempt to provide insights into the pathophysiology of this condition. For instance, during mood episodes, adults with bipolar disorder have been found to exhibit attentional, memory, and executive functioning impairments during mood episodes, which are sustained to a lesser degree during euthymic periods.[70] It has been suggested that these continued cognitive impairments during euthymic periods may be a result of underlying dysfunctional neurophysiology.[71] More specifically, using functional MRI (fMRI), euthymic adults with bipolar disorder were found to perform similarly in completion of an attentional task to healthy controls. However, the euthymic bipolar group showed greater activation in the anterior limbic region in compared with healthy controls.[72] Furthermore, Strakowski et al[71] found that in adults with bipolar disorder who were euthymic, the same pattern of activation in an fMRI during the Stroop interference condition was not found in the healthy controls, suggesting possible deficits in impulse control in the patient group. In comparison with children without a psychiatric disorder or a first-degree relative with a psychiatric disorder, youths with bipolar disorder showed deficits in engaging striatal structures and the right ventral prefrontal cortex using fMRI during unsuccessful motor inhibition.[73] Additionally, Chang et al[74] found that children and adolescents with bipolar disorder who also had at least one parent with a bipolar disorder showed increased activation in the prefrontal areas including the bilateral anterior cingulate cortex, bilateral caudate, putamen, thalamus, dorsolateral prefrontal cortex, and inferior frontal gyrus while performing cognitive and affective tasks in comparison with normal controls. This increased cerebral activation may suggest that children with bipolar disorder may require increased activation of prefrontal areas of the brain during periods of euthymia in order to counteract a hyperactive limbic system.[74] By researchers examining and characterizing putative biological markers of early onset bipolar disorder, neuroimaging may eventually be able to provide clinically salient information early in the course of illness.

Neuropsychological and social-cognitive factors

Emotional and cognitive processing has been examined in youth with bipolar disorder. Evidence suggests that children and adolescents may misperceive emotions during social interactions with others. McClure et al[75] found that sad, happy, and fearful peer facial expressions were misinterpreted more often by children with bipolar disorder in comparison with children with anxiety disorders or subjects with no psychiatric diagnosis. In addition, when viewing neutral faces, youth with bipolar disorder perceived more hostility and experienced more anxiety in comparison with youth without a psychiatric disorder.[76] In another study, children and adolescents with bipolar disorder were more likely to mistakenly characterize facial emotions than youths without a psychiatric disorder.[77] Moreover, the pediatric patients with bipolar disorder were less likely to choose appropriate responses when presented with interpersonal situation vignettes when compared with a healthy control group.[77] These emotional and social interpretation deficits may be due to neural circuitry differences. For example, Rich et al[78] found that youths with bipolar disorder have less functional connectivity in areas that may be involved in processing facial expressions and emotional stimuli. These areas include the neural circuitry between the left amygdala and areas bordering the right posterior cingulate/precuneus and the right fusiform gyrus/parahippocampal gyrus.

Other studies have found that youths with bipolar disorder exhibit less cognitive flexibility in adapting to changing contingencies in cognitive testing.[77,79] Pavuluri et al[80] found evidence to suggest that activation patterns in brain regions are different in pediatric bipolar patients in comparison with healthy controls when subjects observed angry and happy faces. These activation differences implicate a disturbance in affect neurocircuitry which may contribute to emotional dysregulation and social cognitive deficits in youths with bipolar disorder.[80] An understanding of these emotional and cognitive processing findings may have clinical relevance, as they might allow clinicians to direct a portion of their psychotherapy to address interpersonal skills and allow educators to modify lesson plans in order to accommodate the possible cognitive deficits.

Neurochemical differences

Similarly to serotonergic dysfunction observed in depressive conditions, using positron emission tomography

(PET), a lower serotonin transporter binding potential (proportional to serotonin transporter number) was found in adults with bipolar disorder in comparison with adults with no psychiatric conditions.[81] In addition, using magnetic resonance spectroscopy (MRS), elevated gray matter lactate and γ-aminobutyric acid levels have been found in adults with bipolar disorder in comparison with adults without a psychiatric diagnosis.[82] Furthermore, unmedicated youth with bipolar disorder were found to have significantly lower glutamine levels in the anterior cingulate cortex compared with subjects with a bipolar disorder who were currently receiving medications and subjects without a psychiatric diagnosis, using MRS.[83] By determining neurochemical differences in youth with bipolar disorder in comparison with normal controls, pharmacotherapies could eventually be developed that could target the neurochemical underpinnings of pediatric bipolarity.

Advances in the treatment of bipolarity in children

Psychopharmacology

Unfortunately, historically there have been limited studies of methodological rigor in children and adolescents with bipolar disorder. Current recommended treatments in pediatric bipolar disorder include mood stabilizers and antipsychotic medications that may be coprescribed with adjunctive treatments administered for the treatment of comorbid psychiatric conditions.[84]

Acute treatments

There have been a limited number of placebo-controlled trials that have been performed to investigate efficacy in the acute treatment of pediatric bipolar illness. Psychotropics that have been found to be superior to placebo in the acute treatment of children and adolescents with bipolar disorder presenting with manic or mixed episodes include olanzapine,[85] risperidone,[86] quetiapine,[87] and aripiprazole.[88]

Several studies have examined the efficacy of treatment with divalproex (DVPX) in children with BP-I presenting in a mixed or manic episode. Using DVPX extended-release in a double-blind trial, there was not a significant improvement of manic symptoms after 4 weeks compared with placebo.[89] However, DVPX was found to be efficacious in a double-blind study that compared 8 weeks of treatment with DVPX, lithium, and placebo.[90] Furthermore, although the decrease in manic symptoms in the lithium group did not reach statistical significance in comparison with the placebo group, there was a decrease of greater magnitude in manic symptoms in the lithium group when compared with the placebo.[90] Notably, this trend for lithium to be efficacious may become more definitively substantiated in subsequent studies in which higher lithium doses or a larger sample size is employed.

Failed placebo-controlled trials in the acute treatment of pediatric bipolar disorder include topiramate[91] and oxcarbazepine.[92] It should be noted that the trial examining the efficacy of topiramate was underpowered due to cessation of the study after results of the compound in adults failed to show efficacy. However, when comparing the mean decrease in total Young Mania Rating Scale (YMRS) scores over time, statistical significance was almost reached, with the topiramate group showing a greater change from baseline scores. Therefore, due to sample size considerations, whether or not topiramate truly does or does not have efficacy in this patient population remains to be seen.[91]

Open-label trials examining the effectiveness and safety of additional agents and medications mentioned above when administered to younger cohorts have also shown positive preliminary results. For example, in youths with bipolar disorder presenting currently with manic or mixed states, ziprasidone[93-95] and lithium[96,97] may be effective in reducing manic symptoms. Moreover, in studies of patients too young to be included in the aforestated placebo-controlled trials, olanzapine and risperidone were found to be effective in children as young as 4 years of age.[98,99] Open-label treatment with carbamazepine has also been reported to provide amelioration of manic symptoms in youths with bipolar disorder.[100]

When examining the treatment of youths with bipolar disorder presenting with depression, open-label trials have noted that lithium monotherapy,[101] lamotrigine monotherapy, and lamotrigine adjunctive treatment[102] may be effective in alleviating mood symptoms. Finally, treatment with open-label clozapine has described as being effective in youths who were treatment-resistant.[103,104] Although ziprasidone, carbamazepine, lithium, lamotrigine, and clozapine have shown positive effects in open-label trials, randomized placebo-controlled trials are needed to produce more definitive conclusions.

While some salutary effects have been found in drug monotherapy studies, it appears that most children and adolescents do not experience complete symptom remission with thymoleptic monotherapy. Therefore, in an attempt to more completely address mood symptoms, combination pharmacotherapy has been examined in several clinical trials. In fact, in open-label studies, combination psychotropic treatments appear to be more successful than monotherapy treatments in pediatric bipolar disorder. For example, after 6 weeks of treatment with lithium, DVPX sodium, or carbamazepine, only 38% to 53% of subjects experienced symptom recovery, with those patients in the carbamazepine group experiencing the least symptom recovery.[100] However, a proportion of subjects who did not originally respond to lithium, DVPX sodium, or carbamazepine monotherapy responded to combination treatment with two of the abovementioned mood stabilizers and adjunctive stimulants, antipsychotic agents, or an antidepressant medication.[105]

In addition, DelBello et al[106] found in a double-blind study that treatment with quetiapine plus valproate was more effective than treatment with quetiapine monotherapy in youths with bipolar disorder. Furthermore, combination treatment with both risperidone and lithium or risperidone and DVPX was found to be effective and safe in the treatment of children and adolescents with bipolar I disorder over a 6-month period.[107] Combination treatment with lithium and DVPX has been found to ameliorate mood symptoms in several studies.[105,108,109] Finally, positive results were found with combination treatment with lithium plus either risperidone or a neuroleptic.[97,107]

Recently, other treatment options have been explored in pediatric bipolarity. For instance, Wozniak et al[110] found open-label treatment with omega-3 fatty acids to improve manic symptoms in youth with bipolar disorder. Although the results of the abovementioned open-label trials are promising, randomized, placebo-controlled trials in children and adolescents are needed to provide more definitive results. *Table I* includes the dosing and most frequently reported adverse events in the abovementioned studies.

Maintenance treatments

While bipolar disorder is a chronic condition, little attention has focused on long-term maintenance treatments in youth. In one of the few maintenance trials, Kafantaris et al[111] randomized adolescents who had been stabilized on lithium monotherapy for a minimum of 4 weeks to either lithium or placebo for 2 subsequent weeks of treatment. Results showed that there was not a significant difference between treatment groups in rates of symptom exacerbation. Although this study provides preliminary insights regarding the continued use of lithium in adolescents with mania, definitive conclusions about lithium as a maintenance treatment cannot be determined from these data. Although this was an important trial, methodological limitations included a small sample size, the study's brevity, and the fact that there was a relatively abrupt discontinuation of lithium over 3 days in those subjects randomized to receive placebo in the discontinuation phase. In another maintenance double-blind trial, the efficacy of lithium or DVPX monotherapy for up to 76 weeks in youths who had been stabilized on combination lithium and DVPX treatment was examined.[112] In this study, no difference in length of study enrollment was found between the lithium and DVPX sodium treatment groups, with both groups ending the study after a mean of approximately 20 weeks.[112] These results appear to indicate that once a patient responds to a combination treatment, discontinuation of one of the agents used in combination therapy may lead to symptom relapse.

Psychosocial treatments

Favorable results in the treatment of bipolar disorder are not limited to medication trials. Several psychosocial treatments have shown positive results in the treatment of youth with bipolar disorder. For example, dialectal behavior therapy has been reported to significantly improve suicidality, self-injurious behavior, emotional dysregulation, and depressive symptoms after 1 year of sessions in adolescents diagnosed with a bipolar spectrum disorder currently receiving psychotropic medications.[113] In addition, a 21-session adjunctive family-focused treatment (FFT) that included psychoeducation, communication enhancement training, and problem-solving skills training was found to decrease depressive symptoms, maniac symptoms, and behavior problems in adolescents with bipolar disorder.[114] Moreover, individual family treatment (IFP) and multifamily psychoeducation groups (MFPG) were developed to provide support, psychoeducation, and increase problem-solving and communication skills in families with a child with a mood disorder.[115] Both IFP and MFPG have been shown to

increase the understanding of mood disorders, ameliorate mood symptoms, improve the family environment, and increase mental health service utilization.[115]

Additionally, cognitive behavior therapy (CBT) was found to reduce manic and depressive symptoms in youth diagnosed with a bipolar disorder spectrum disor-

	Sample size	Design	Subject ages (y)	Dose	Most frequently reported adverse events
Olanzapine[85]	161	Placebo-controlled	13-17	2.5-20 mg/day; Mean 8.9 mg/day	Appetite increase, weight increase, somnolence,and sedation
Risperidone[86]	169	Placebo-controlled	10-17	0.5-2.5 mg/day 3-6 mg/day	Somnolence, headache, fatigue
Quetiapine[87]	277	400 mg vs 600 mg vs placebo	10-17	400 mg/day or 600 mg/day	Somnolence, sedation, dizziness, headache
Aripiprazole[88]	296	10 mg vs 30 mg vs placebo	10-17	10 mg or 3 0 mg	Somnolence, extrapyramidal symptoms, fatigue
DVPX extended release[89]	150	Placebo-controlled	10-17	Starting dose 15 mg/kg/day; titration to clinical response and/or serum level of 80-125 µg/mL	Headache and vomiting
DVPX or lithium[90]	153	DVPX, lithium, and placebo	7-17	target DVPX serum level 85-110 µg/mL; lithium serum 0.8-1.2 mEq/L	Not described
Topiramate[91]	56	Placebo-controlled	6-17	target dose 400 mg/day	Decreased appetite, nausea, diarrhea, paresthesia, and somnolence in topiramate group
Oxcarbazepine[92]	116	Placebo-controlled	7-18	Mean dose 1515 mg/day (maximum dose 900–2400 mg/day)	Dizziness, nausea, somnolence, diplopia, fatigue, and rash
Ziprasidone[95]	21	Open-label	6-17	Mean dose: 56.2 (34.4) mg/day	Sedation, headache, and gastrointestinal problems
Lithium[97]	100	Open-label	12-18	Lithium titrated to serum levels ranging from 0.6 to 1.2 mEq/L	Weight gain, polydipsia, polyuria, headache, and tremor. Note: some subjects were receiving adjunctive antipsychotic medication in this trial
Carbamazepine[100]	13 (this was part of a study where subjects received lithium or DVPX as well)	Open-label	8-18	Dosages were titrated until serum levels were reached: lithium, 0.8 to 1.2 mEq/L; carbamazepine, 7 to 10 mug/L; divalproex sodium, 85 to 110 ìg/L.	Nausea, sedation, rash, and dizziness
Lamotrigine monotherapy or as an adjunctive treatment[102]	20	Open-label	12-17	Target dose: 100 mg/day subjects currently taking DVPX; 100- 200 mg/day all other subjects; mean final dose 131.6 mg/day	Headache, fatigue, nausea, and sweating
Clozapine[104]	10	Open-label	12-17	142.5 +/- 73.6 mg/day (range 75-300 mg/day)	Increased appetite, sedation, enuresis, sialorrhea
Omega-3 fatty acids[110]	20	Open-label	6-17	omega-3 fatty acids 1290 mg-4300 mg combined EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)	Gastrointestinal problems (constipation, diarrhea, and upset stomachs), colds, and headache

Table I. Selected acute trials in the treatment of pediatric bipolar disorder. DVPX, divalproex

der after 12 sessions.[116] CBT supplemented with family-focused therapy has also shown to ameliorate bipolar symptoms and increase global functioning scores in patients with bipolar disorder.[117] Furthermore, the child- and family-focused CBT program was effective in maintaining long-term management of mood symptoms over 3 years in youths with bipolar disorder.[118]

Interpersonal and social rhythm therapy (IPSRT) is another treatment that uses some of CBT's behavioral interventions to address mood symptoms. However, IPSRT also focuses both on the youth's expectations in their own interpersonal life, and attempts to help the patient maintain stable social and sleep routines.[119] In adults, IPSRT has been found to be effective in prolonging the time until patients experience a new mood episode.[120] Based on these adult data, IPSRT may be an effective treatment for adolescents with bipolar disorder.[119] However, due to difficulties in extrapolating adult based behavioral interventions in preadolescents, IPSRT has not been studied in younger children. In short, multiple psychosocial treatments have been reported to be effective and are becoming more refined to address issues specific to youth with bipolar disorder. These treatments may prove to be useful in increasing medication treatment adherence and providing the additional assistance needed where medication is not able to fully treat all aspects of pediatric bipolarity.

Future areas of research

Although recent research has broadened the knowledge about bipolar disorder in youth, there are many unanswered questions that remain. More phenomenology studies may provide insights into whether or not the comorbid symptoms of additional psychiatric disorders that are seen in this population are distinct, separate entities, or simply part of this mood disorder when it presents during childhood. Furthermore, as children appear to experience more elevated mood and irritability in comparison with adults who report more depressive symptoms, future longitudinal examinations may provide answers to the question of whether or not symptoms of childhood bipolarity evolve into more adult-like presentations over time.

Examining youths who are at high risk for developing bipolar disorder, such as offspring of parents with mood disorders, provides a unique opportunity in carefully characterizing the evolution of mood symptomatology. By exploring high-risk cohorts and identifying prodromal symptoms, effective treatments can be used earlier in the course of pediatric bipolarity.[121] Furthermore, treating children and adolescents with subsyndromal expressions of bipolar disorders soon after the onset of symptoms may prevent illness progression to the more severe and prototypic presentations of the disorder.

Although technological advances have begun to allow investigators to examine the biological underpinnings of pediatric bipolarity, larger sample sizes and replication studies are needed in order to confirm or refute whether or not the genetic, anatomical, and neurochemical differences reported thus far are not chance findings. Ideally, genetic and neuroimaging methodologies could eventually be used as a diagnostic tools that could facilitate the psychiatric assessment and treatment processes. Although there is a growing body of evidence that pertains to the acute monotherapy pharmacological treatment of pediatric bipolar illness, future studies are also needed to investigate various combination psychotropic treatments and adjunctive psychosocial therapies. In addition, longer term safety and maintenance efficacy studies with medications are still few in number and are clearly needed.

In conclusion, with earlier, accurate identification and diagnosis of bipolar disorders, psychotropic and psychosocial treatment can be initiated earlier in the course of the illness. It is hoped that with the development of safe and effective interventions, the probability that the child suffering from bipolar illness will develop into a well-adjusted adult with high academic, family, and social functioning will be better than it is at present. ❑

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Investigación actual en el trastorno bipolar en niños y adolescentes

Aunque en la actualidad hay más investigación que ha incluido niños con trastorno bipolar que en el pasado, todavía existe mucha controversia alrededor de la validez del diagnóstico. Además persisten preguntas si acaso las expresiones de bipolaridad en la niñez constituyen un continuo con las manifestaciones de la enfermedad en el adulto. Para avanzar en el conocimiento actual de los trastornos bipolares en los niños los investigadores han comenzado a realizar estudios fenomenológicos, longitudinales, terapéuticos y de neuroimágenes en jóvenes que presentan síntomas de enfermedad bipolar, como también en hijos de padres con trastornos bipolares. A pesar de las diferencias entre grupos de investigación respecto a cómo está definido el trastorno bipolar en niños, hay acuerdo en que la bipolaridad pediátrica es una enfermedad seria y dañina. Con una intervención precoz durante el período de tiempo en el cual los jóvenes presentan síntomas subsindromáticos de bipolaridad pediátrica, parece que la progresión de la enfermedad hacia la manifestación más maligna del trastorno se puede evitar. Este artículo revisará el conocimiento actual y lo que todavía falta por aprender acerca de tópicos clínicamente destacados que pertenecen al trastorno bipolar en niños y adolescentes.

Travaux actuels sur les troubles bipolaires de l'enfant et de l'adolescent

La valeur du diagnostic des troubles bipolaires reste encore très controversée chez les enfants, bien que des travaux récents s'y intéressent plus que par le passé. Un certain nombre de questions demeurent, comme celle de savoir si la bipolarité dans l'enfance est en continuité avec les manifestations pathologiques de l'âge adulte. Les chercheurs ont entrepris des études longitudinales phénoménologiques et thérapeutiques ainsi que des études de neuro-imagerie chez les jeunes qui présentent des symptômes de troubles bipolaires, mais également chez les descendants de parents bipolaires, afin de faire avancer l'état actuel des connaissances sur les troubles bipolaires de l'enfant. La bipolarité pédiatrique est reconnue pour être une pathologie sérieuse et pernicieuse, quelles que soient les différences de définition entre les équipes de recherche. Si les jeunes sont traités précocement, dès l'apparition des symptômes subsyndromaux de la maladie bipolaire pédiatrique, la progression vers les formes les plus sévères pourrait être évitée. Cet article passe en revue les connaissances actuelles et ce qu'il reste à apprendre à propos de sujets cliniquement pertinents liés aux troubles bipolaires chez l'enfant et l'adolescent.

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