

## Challenges in the diagnosis and treatment of pediatric bipolar depression

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*There has been great public and academic interest in the diagnosis and treatment of bipolar disorders (BD) in children and adolescents over the past decade, originally in the US, but now extending internationally. Much of the interest in pediatric BD has focused on the unique manifestation of mania in younger populations. Depression is often overlooked, both as a topic, and as a clinical reality, in these children. While it is becoming clear that adults with BD spend the majority of their symptomatic time in depressive rather than manic episodes, less is known about the pediatric experience of bipolar depression. However, children and adolescents with BD clearly do experience significant depressive symptoms as well as depressive episodes, and therefore early recognition and treatment is necessary. This review addresses what is known about the prevalence, presentation, and treatment of depressive symptoms and episodes in youth with BD, and includes a discussion about the recognition and treatment of bipolar depressive episodes that occur before the first manic episode.*

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**T**here has been great public and academic interest in the diagnosis and treatment of bipolar disorders (BD) in children and adolescents over the past decade, originally in the US but now extending internationally. Thus, in the US in the past decade, diagnoses of BD in children under 18 years old have risen 4000% in the community.<sup>1</sup> Whether this increase is due to increased recognition, increased incidence, or overdiagnosis is not clear. However, it is becoming clear that BD begins in childhood 50% to 66% of the time.<sup>2,3</sup> Therefore, if the incidence of BD (I or II) in adults is 4%,<sup>4</sup> then there are at least 1 to 2 million children in the US alone with BD or the beginning manifestations of the disorder. A recent study comparing age at onset of BD in a US population found that 30% of adults with BD in the Netherlands and Germany had childhood/adolescent onset.<sup>5</sup> Thus, while possibly fewer than in the US, there are also likely great numbers of youth in Europe with BD.

Much of the interest in pediatric BD has focused on the unique manifestation of mania in younger populations. Academic controversy has centered around the role of extreme irritability in pediatric mania: whether it can be a proxy for euphoria<sup>6</sup>; whether *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria can be used in children under 12; and whether children with BD eventually become adults with DSM-IV-defined BD.<sup>7</sup> Depression is often overlooked, both as a topic and as a clinical reality, in these children. If BD is indeed so prevalent in children in the US and internationally, then

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# Clinical research

## Selected abbreviations and acronyms

<b>BD</b>	<i>bipolar disorder</i>
<b>CDRS-R</b>	<i>Children's Depression Rating Scale-Revised Version</i>
<b>MDD</b>	<i>major depressive disorder</i>
<b>SSRI</b>	<i>selective serotonin reuptake inhibitor</i>

depressive symptoms and episodes in pediatric BD deserve much greater study. This review will address what is known about the prevalence, presentation, and treatment of depressive symptoms and episodes in youth with BD and include a discussion about the recognition and treatment of bipolar depressive episodes before the first manic episode.

## Bipolar depression episodes in children and adolescents

Adults with BD spend approximately 9% of their time in manic or hypomanic episodes, whereas they spend 32% of the time in depressive episodes.<sup>8</sup> Children and adolescents with BD clearly experience significant depressive symptoms as well as depressive episodes.<sup>9</sup> However, the phenomenon of depression is less studied in pediatric BD. In a phenomenological study of 438 children and adolescents with bipolar spectrum disorders, 53% had a history of a major depressive episode.<sup>10</sup> Suicidal thoughts and behaviors were common as well, with 76% having past suicidal ideation, and 31% having made a prior suicide attempt. Thus, depressive symptoms are common in youth with BD. It is not clear if children with BD are commonly misdiagnosed with unipolar depression, but this phenomenon is common in adults.<sup>11</sup> It should also be noted that irritability is commonly a presenting symptom of *depression*, rather than only mania, in children. Thus, the DSM-IV allows for the predominant mood to be irritability or dysphoria for children to meet criteria for a depressive episode. Irritability is a common symptom in children with BD, even outside a clearly established manic episode.<sup>12,13</sup> Therefore, it is possible that a certain portion of irritability in children with BD stems from a more depressive etiology. This is important to remember, in that, much as adults with BD are often misdiagnosed with unipolar depression,<sup>11</sup> children with BD should not have their symptoms of irritability misdiagnosed as mania if they are truly stemming from depression.

Finally, mixed episodes occur frequently in pediatric BD.<sup>14</sup> In adults, these episodes have been thought to be more dif-

ficult to treat than “pure” mood episodes, and also carry the highest risk of suicide attempts.<sup>15,16</sup> Similarly, in a pediatric BD cohort, mixed episodes were one predictor of suicide attempt.<sup>17</sup> Thus, depressive symptoms may also occur within the context of mania symptoms in children, and therefore such children should also be carefully assessed for potential mixed episodes.

There are several reasons why such depressive episodes and symptoms in children with BD may be missed by clinicians. Foremost, manic symptoms usually are what bring the child into the office, including symptoms of high energy, impulsivity, recklessness, sleeplessness, hypersexuality, and irritability and anger. Children presenting with more subtle symptoms of anhedonia and fatigue are not always as obvious in presentation to parents or teachers as those presenting with such manic symptoms. Irritability, as mentioned above, is also often mistaken as mania and not recognized as a symptom of depression. Finally, in younger children such depressive episodes are not as common as for adolescents with BD, but depressive symptoms may often intermingle with manic symptoms, and thus be underidentified. Clinicians may benefit from carefully eliciting depressive symptomatology in any child with BD, and recognizing any type of suicidal ideation, even passive, as a red flag for a serious depressive episode.

Nonetheless, due to the morbidity and mortality of depression in youth with BD, it is necessary to treat these children. One may look to the treatment of bipolar depression in adults for some guideposts, as this topic has been more studied in adults. There exist many treatment options for patients with bipolar depression. While antidepressants have historically been the first line of treatment for bipolar depression, concern over the propensity for antidepressants to cause manic switching or cycle acceleration has led to questioning of this approach.<sup>18</sup> It is becoming clear that overall, the addition of antidepressants to mood stabilizers for adult bipolar depression offers no greater benefit than placebo,<sup>19</sup> and up to 44% of adults with BD have experienced a switch into mania or a mixed episode with an antidepressant trial.<sup>20</sup> Thus, several expert consensuses have recommended nonantidepressant medications as first-line treatment for adults with bipolar depression, including lithium, lamotrigine, olanzapine-fluoxetine combination,<sup>21</sup> and quetiapine.<sup>22</sup> Other options showing some efficacy in controlled trials include divalproex, olanzapine, and pramipexole.<sup>23</sup>

Despite these adult data, it is still important to remember that children are distinct neurodevelopmentally, and

so may not respond as adults do to psychotropic medications, both in positive and negative ways. Indeed, it appears that youth, particularly peripubertal children, may be more susceptible to deleterious effects of selective serotonin reuptake inhibitors (SSRIs) than adults. In an analysis of an HMO database of 87 920 patients aged 5 to 29 years old, children 10 to 14 years old were at the highest risk of switching from a diagnosis of MDD to BD after being prescribed an SSRI.<sup>24</sup> However, despite case reports of SSRI-induced mania in depressed children,<sup>25,26</sup> one study found no evidence retrospectively that antidepressant exposure in depressed children led to higher rates of mania than children without such exposure.<sup>27</sup> It is possible that bipolar youth are more susceptible to AIM. In a retrospective chart review, 42 children with BD who were prescribed SSRIs were seven times more likely to improve in depressive symptoms than children with BD who were not prescribed any other medication,<sup>28</sup> but three times more likely to experience a subsequent manic episode. Furthermore, in a retrospective study of 54 children with BD, 50% had a manic episode within 1 month of starting an SSRI, and 25% had new-onset suicidal ideation.<sup>29</sup> Thus, it is possible that bipolar youth may account for some of the concerns regarding SSRIs and suicidality that eventually led to the black-box warning on all antidepressants mandated by the US FDA.<sup>30</sup>

Thus, alternative treatments need to be considered in children and adolescents with BD, perhaps even more so than for adults. While no placebo-controlled studies have yet been reported in pediatric bipolar depression, two prospective treatment studies in adolescents with bipolar depression have been reported. Chang and colleagues studied the effectiveness and tolerability of lamotrigine as mono- or adjunctive therapy in an 8-week open-label study of 20 adolescents with BD experiencing a depressive episode.<sup>31</sup> The authors reported statistically significant improvement in depressive symptoms, as measured by the Children's Depression Rating Scale-Revised Version (CDRS-R).<sup>32</sup> Sixty-three percent of subjects were classified as responders, with at least a 50% decrease in CDRS-R score between baseline and end point, and 47% were considered remitters by virtue of a score of 24 or less on the CDRS-R and a Clinician Global Impression-Severity rating of "not ill" or "mildly ill." Additionally, 84% of subjects showed "much" or "very much" improvement by the end of the study by the Clinical Global Impression-Improvement scale. Despite

the historical risk of serious rash with lamotrigine, particularly in children, no serious rashes occurred in this study. Furthermore, there was no significant weight gain. Patel and colleagues<sup>33</sup> conducted a 6-week open-label study of lithium monotherapy in 27 depressed adolescents with bipolar I disorder. Forty-eight percent of subjects were considered responders by a 50% reduction in CDRS-R score from baseline to end point. Commonly reported side effects were headaches (74%) and nausea/vomiting (67%). Thus, while promising, these studies point to the need for larger, placebo-controlled studies of these and other agents (eg, quetiapine, bupropion) in youth with bipolar depression. Another agent that might be studied in this regard is omega-3 fatty acid supplements, given some mild efficacy in preventing adult bipolar depression, and in treating adult bipolar depression.<sup>34</sup>

### Depressive symptoms

Even when youth with BD are not in full depressive episodes, it is becoming clear that they often experience subsyndromal depressive symptoms as well as mixed states. Birmaher and colleagues studied 263 children and adolescents with BD I, II, and not otherwise specified (NOS) over 2 to 3 years.<sup>35,36</sup> Subjects were symptomatic 60% of the time, but only in full syndromal depressed or manic episodes 22% of the time. Furthermore, fluctuations in mood were very common. Children with BD changed between mania and depression an average of 16 times per year, with 34.1% shifting polarity more than 20 times per year.

Because manic symptoms are often the first targeted symptoms in youth with BD, these patients often experience residual or emergent depressive symptoms, even with treatment. An older report found 3 out of 6 (50%) of manic children placed on lithium to have a significant worsening of depressive symptoms.<sup>37</sup> In a more recent study of 100 manic adolescents treated prospectively with lithium, mean HAM-D scores decreased overall from 12.63 to 6.74 over 4 weeks.<sup>38</sup> It is not reported how many subjects had significant residual depressive symptoms at the end of the study. However, having depressive symptoms at the start of the study did not predict whether or not the subject responded to lithium by mania criteria. In another open study, Kowatch and colleagues reported on the naturalistic prospective treatment of 35 manic children and adolescents who had previously been treated with 6 weeks of monotherapy with either lithium, val-

# Clinical research

proate, or carbamazepine.<sup>39</sup> Two subjects (5.7%) had a depressive episode despite treatment with two concurrent mood stabilizers (lithium, divalproex, or carbamazepine). Antidepressants were subsequently added to the medication regimens with reported good response. Of 90 children and adolescents with BD treated openly with divalproex and lithium combination therapy, none continued to have significant depressive symptoms requiring discontinuation from the study.<sup>40</sup>

More recent large placebo-controlled studies offer some insight into the natural course and treatment of depressive symptoms in youth with BD. For example, olanzapine was compared with placebo in a 3-week study of 158 youth with acute manic or mixed episodes.<sup>41</sup> Eight percent of subjects on olanzapine and 14% of subjects on placebo switched to a full depressive episode by the end of the study. This was not a significant difference between groups, and the change in depressive symptomatology, while not reported, was also not different between groups. Thus, it would appear that at least for the acute treatment of depressive symptoms in the context of pediatric manic or mixed episodes, olanzapine is not effective.

Similarly, in a study of divalproex versus placebo in 150 youth (10 to 17 years old) with manic or mixed episodes, there was no difference in the amount of change in CDRS-R scores between groups.<sup>42</sup> In a study of 116 similarly diagnosed youth, oxcarbazepine resulted in a 7.9-point decrease in CDRS-R score, versus 6.4 for placebo, a nonsignificant decrease.<sup>43</sup> Thus, as yet it does not appear that these commonly used treatments for children with BD result in effective changes in depressive symptoms. Due to the predominance of subsyndromal depressive symptoms in bipolar youth, it would be important to conduct studies specifically examining treatment of these symptoms versus placebo.

## First-episode bipolar depression

In a questionnaire of adults with BD, depressed mood was the most common presenting symptom before the onset of a full mood episode.<sup>44</sup> The initial episode is commonly (>50%) depressive.<sup>3</sup> Furthermore, 50% to 66% of adults report onset of symptoms before the age of 18 years, with 28% occurring before 13 years.<sup>2,3</sup> Therefore, children with depression may be experiencing a first-episode bipolar depression. Geller et al report 20% to 49% of children with MDD experience a full manic

episode by adulthood.<sup>45</sup> A positive family history of BD would seem to further elevate the risk of future mania in a depressed child; however, the exact risk in these children is not known. Given that many if not most of these children will *not* ever experience mania, careful diagnosis and biological markers for predication would be essential. Unfortunately, at this time there are no clear biological markers that do predict such likelihood, despite recent advances in neuroimaging and genetics research. In the future, markers such as decreased amygdalar volume, increased limbic activity, and the short allele of the serotonin transporter gene, may all be combined to calculate relative risk of BD development.<sup>46</sup> Until then we are left to rely on careful clinical assessment and family history.

Proposed clinical clues of first episode bipolar depression include an acute onset, psychosis, prominent irritability and labile mood, and poor or brief hypomanic reactions to antidepressants.<sup>47</sup> Furthermore, features of atypical depression, including hypersomnia, hyperphagia, and other neurovegetative symptoms, may indicate risk for future manic episodes.<sup>48</sup>

Despite the uncertainty of actual BD risk, early interventions in youth with depression and family histories of BD are beginning to be studied. Geller and colleagues performed the first such study<sup>49</sup> in 30 prepubertal children, all with MDD and family histories of mood disorder. Forty percent had a parent with BD, 40% had a more distant relative with BD, and 20% had a family history of unipolar depression only. Subjects were randomized to lithium or placebo, and after 6 weeks no differences were found between the two groups in improvement in depressive symptoms. The final Clinical Global Assessment of Severity scores in both groups did improve from baseline, but remained below 60, indicating continuing clinical problems. As there was a significant distribution of subjects who responded well and subjects who responded poorly, some subjects may have had unique factors associated with response, but whether family history was a factor is unknown. Nonetheless, lithium may have limited efficacy in youth with depression at high risk for BD.

In another early intervention study, Chang and colleagues investigated the effectiveness of open divalproex in 24 bipolar offspring with mood and/or disruptive behavioral disorders.<sup>50</sup> None of the subjects, aged 7 to 17, had bipolar I or II disorder, but all had at least some mild affective symptoms as manifested by a minimum score of 12 on the

Young Mania Rating Scale (YMRS) or Hamilton Rating Scale for Depression (HAM-D). Of these subjects, 21% (5) were diagnosed with MDD, and 8% (2) with dysthymia. Subjects were tapered off of any current medications, and then begun on divalproex monotherapy, eventually reaching a mean final dose of 821 mg/day (serum level = 79.0+/-26.8 ug/mL). After 12 weeks, 78% of subjects were considered responders, having general improvement in mood and functioning, with the majority showing improvement by week 3. Both YMRS and HAM-D scores decreased significantly compared with baseline. Depressive symptoms appeared to resolve especially rapidly, with mean HAM-D scores achieving the end point mean by week 1. This rate of response may have been due to placebo response, receiving support from an academic institution, being in a study, and having regular visits to a physician. However, this placebo response would have been carried throughout the 12 weeks of the study. Of note, 6 out of 7 (86%) of subjects with MDD or dysthymia were considered responders. Again, caution should be applied to these results given the small sample size and lack of a control arm.

Despite these promising findings regarding divalproex, Findling and colleagues found divalproex to be no more effective than placebo in preventing worsening of mood symptoms in youth with cyclothymia or bipolar disorder not otherwise specified who were bipolar offspring.<sup>51</sup> In this study, 56 subjects 5 to 17 years old were randomized to divalproex or placebo and assessed over an acute 8-week period, and then followed monthly for up to 5 years, until clinical intervention was needed for mood symptoms. There was no difference between the treatment arms in time to discontinuation from the study. However, both groups did show significant improvement in depressive and manic symptoms over time. Notably, divalproex was superior to placebo in time to discontinuation in a subset of patients who had three or more first- or second-degree relatives with an emotional and/or behavioral problem.<sup>52,53</sup> It should also be noted that subjects in this study differed from those in the study by Chang and colleagues in that they had not had a past full depressive episode, and they were required to have a past significant 4-hour period of elation, indicating that they may have had less symptoms of depression. Nonetheless, there was no difference between divalproex and placebo for efficacy regarding depressive symptoms.

Quetiapine would seem a good candidate for use in first-episode bipolar depression, given its efficacy in adult

bipolar depression.<sup>54</sup> DelBello and colleagues<sup>55</sup> conducted a 12-week study of open quetiapine for bipolar offspring with mood disorders (mean age =14.7 years), that were considered subsyndromal to full BD (no subjects had a history of mania). 11 (55%) had BD-NOS, 3 had bipolar II disorder, 3 (11%) had dysthymia, 2 cyclothymia, and 1 MDD. Thus, almost all subjects had a bipolar spectrum disorder, and as such these subjects were farther along the progression line for BD than the previously discussed studies involving valproate. Quetiapine was begun at 100 mg/day, then increased every day up to 400 mg/day, with flexible dosing thereafter to achieve 300-600 mg/day based on clinical need. 15 subjects completed the study, and final mean dose was 460 mg/day. Response was considered a "1" or a "2" on the CGI-BP (Much or moderate improvement in bipolar symptoms). After 1 week there were 4 responders (25%), which grew to 81% by week 12. Of note, the one subject with MDD was a non-responder, but all three subjects with dysthymia were responders. YMRS score decreased from 18.1 to 8.7, and mean CDRS-R score decreased from 38.2 to 27.7. Therefore, quetiapine may have clinical utility in this population, but larger controlled studies are needed to clarify its role in first episode bipolar depression in youth. It should be remembered that these studies did not address prevention of mania, as longer longitudinal studies are needed to address that issue. Agents such as lithium, divalproex, and quetiapine may be efficacious in decreasing depressive symptoms in these children at risk for BD, but is unclear if they are more effective than placebo or actually prevent or delay mania. In none of these studies, however, did these agents precipitate mania, so in this sense they may prove to be safer than antidepressants in this population. As for other bipolar depressed states, these and other agents deserve further study in this population.

### Psychotherapeutic/psychosocial interventions

Psychotherapy may prove to be an effective adjunctive or alternate treatment in depressed youth with or at risk for BD, as it may be more targeted than medications, without the potential for physical or behavioral adverse effects. Various psychotherapeutic approaches, including cognitive-behavioral therapy (CBT), dialectical-behavioral therapy (DBT) and family therapy, are beginning to demonstrate efficacy in pediatric BD. In an open study of DBT

# Clinical research

in 10 adolescents with BD, depressive symptoms and suicidal ideations and behaviors decreased significantly over 1 year.<sup>56</sup> In a small controlled study of CBT for adolescents with BD, significant decreases in parent and child reported depressive symptoms were reported in the CBT condition. However, compared with control BD youth who did not receive CBT, there were no differences in post-treatment depression scores by clinician assessment.<sup>57</sup> These individual therapy approaches show promise and should be studied in larger, controlled studies.

A recent study of family-focused therapy (FFT) in 58 adolescents with BD found that FFT was more effective than “enhanced care (EC),” a series of psychoeducational sessions.<sup>58</sup> Subjects receiving FFT recovered faster from their baseline depressive symptoms than did subjects receiving EC. While FFT did not more effectively prevent relapse of depressive episodes, subjects receiving FFT spent fewer weeks in depression than subjects in EC. These novel approaches to prevention of depression could be similarly applied to bipolar offspring. A modification of FFT is now being studied for bipolar offspring with MDD or BD-NOS.<sup>59</sup>

Therefore, depression in the context of BD in youth may be particularly responsive to psychotherapeutic interventions, potentially more so than mania. Common themes of these interventions are psychoeducation, behavioral and cognitive interventions, including reducing stress and

improving coping strategies, and mood regulation techniques. Future studies incorporating larger samples, with youth with bipolar depression, depressive symptoms, or unipolar depression at risk for BD would be highly illuminating to the field.

## Conclusions

As the existence of BD in youth is becoming less controversial, clinicians and researchers are now able to concentrate on understanding the full spectrum of symptoms experienced by these patients, and researchers are able to concentrate on all aspects of the illness, including depressive symptomatology. It is clear that while mania is impairing in this condition, depressive symptoms may ultimately be just as if not more damaging, particularly leading to suicidal thoughts and behaviors. Recognition of depressive episodes in bipolar youth and in youth at high risk for BD is essential for the purposes of early intervention and prevention of progression of the disorder. Meanwhile, it is becoming clear that SSRIs have dangerous potential in this population, while certain mood stabilizers, antipsychotics, and psychotherapies may be better alternatives. Treatment options are slowly growing and future research will allow clinicians to more confidently identify and treat depression in the context of pediatric BD. □

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### Desafíos en el diagnóstico y tratamiento de la depresión bipolar pediátrica

En la última década ha existido un gran interés público y académico acerca del diagnóstico y tratamiento de los trastornos bipolares (TB) en niños y adolescentes; esto ocurrió originalmente en los EE. UU. y luego se extendió internacionalmente.

Gran parte del interés en el TB pediátrico se ha concentrado exclusivamente en la manifestación maníaca de los grupos de menor edad. La depresión en estos niños a menudo es pasada por alto, ya sea como tópico o como una realidad clínica. Aunque se está aclarando que los adultos con TB pasan la mayor parte del tiempo sintomático con episodios depresivos más que maníacos, poco se sabe acerca de cómo experimentan los niños la depresión bipolar. Sin embargo, los niños y adolescentes con TB claramente sufren síntomas depresivos como también episodios depresivos significativos; por lo que es necesario que el reconocimiento y tratamiento sean precoces. Esta revisión se orienta hacia el conocimiento sobre la prevalencia, la presentación y el tratamiento de los síntomas y episodios depresivos en los jóvenes con TB, e incluye una discusión sobre el reconocimiento y tratamiento de los episodios depresivos que ocurren antes del primer episodio maníaco.

### Remise en cause du diagnostic et du traitement de la dépression bipolaire chez l'enfant

Ces 10 dernières années ont été le théâtre d'un intérêt collectif et spéculatif croissant pour le diagnostic et le traitement des troubles bipolaires (TB) des enfants et des adolescents, à l'origine aux USA puis dans le monde entier. Seules les manifestations maniaques ont été jugées dignes d'intérêt dans les TB des plus jeunes, chez qui la dépression est souvent négligée, à la fois comme sujet et comme réalité clinique. Alors qu'il est clairement reconnu que les adultes ayant des TB passent plus de temps en période dépressive qu'en période maniaque, l'expérience pédiatrique en la matière est moins bien connue. Les enfants et les adolescents présentant des TB font cependant l'expérience de symptômes dépressifs significatifs comme d'épisodes dépressifs caractérisés, c'est pourquoi un diagnostic et un traitement précoces sont nécessaires. Cet article propose une revue des données de prévalence, des manifestations et du traitement des symptômes et épisodes dépressifs chez les jeunes ayant des TB ainsi qu'une discussion sur l'identification et le traitement des épisodes dépressifs bipolaires intervenant avant le premier épisode maniaque.

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