

# Bipolar disorder in childhood and adolescence

## Transtorno afetivo bipolar na infância e na adolescência

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### Abstract

Many advances in the knowledge of childhood- and adolescent-onset bipolar disorder have been seen over the last 15 years. Current efforts focus on investigating clinical features, developing more instruments for early diagnosis and improving treatment research. The present study aims to present the main clinical characteristic of the disorder in children and adolescents, as well as the nomenclature, description of clinical phenotypes and the most common cycling pattern in youths. A discussion of comorbidity, differential diagnosis and advances in psychopharmacological treatment will also be presented.

**Keywords:** Bipolar disorder/diagnosis; Bipolar disorder/therapy; Child; Adolescent

### Resumo

Os conhecimentos sobre transtorno afetivo bipolar com início na infância e na adolescência têm avançado muito nos últimos 15 anos. Atualmente, os esforços estão dirigidos para investigar o quadro clínico, para o desenvolvimento de instrumentos que auxiliam diagnóstico precoce e investigações de melhores formas de tratamentos de crianças e adolescentes portadores do transtorno. O presente texto tem objetivo de apresentar as principais características clínicas do transtorno em crianças e adolescentes, assim como as denominações, as descrições de tipos clínicos e do padrão de ciclagem mais comum da doença em jovens. Discussões sobre comorbidades, diagnóstico diferencial e avanço em tratamento farmacológico também serão apresentados.

**Descritores:** Transtorno bipolar/diagnóstico; Transtorno bipolar/terapia; Criança; Adolescente

### Introduction

Until 15 years ago, there was some dispute regarding whether bipolar disorder (BD) occurs in children. Currently, such occurrence has been confirmed, and the focus has shifted to investigating the clinical presentations of childhood- and adolescent-onset BD (CABD), developing instruments that aid in early diagnosis, as well as investigating improved forms of treatment.<sup>1-5</sup>

It is usually difficult to recognize symptoms of depression or (hypo)mania in children, especially since children may have difficulties in recognizing and naming their own feelings. The low prevalence reported may also be due to the fact that characteristics considered atypical in adults seem to be the rule and not the exception in children. Therefore, few professionals include BD as a possible diagnosis when assessing a child.<sup>1,3,5-12</sup>

It is known that epidemiological data vary according to age, course of the illness and the presence or absence of comorbidities.<sup>13-14</sup> Although epidemiological studies have shown that BD affects adult men and women equally, it seems to be more common in boys than in girls. Faedda et al demonstrated that, during prepuberty, boys have an approximately four times greater chance of being diagnosed with BD than do girls.<sup>1</sup> In addition, Findling et al. reported an incidence ratio of two boys for every one girl in the study sample.<sup>7</sup>

Both DSM-IV<sup>13</sup> and ICD-10<sup>14</sup> cite the fact that clinical profiles may differ according to age range and suggest equivalent or substitute symptoms for children and adolescents, although these arrangements seem to be inadequate for the diagnosis of CABD.<sup>15</sup> In a debate promoted by the National Institute of Mental Health, it was determined that, in clinical practice, there are two types of children in which a diagnosis of BD might be suspected. The first type would present all symptoms and characteristics required by the DSM-IV<sup>13</sup> for a diagnosis of type I or type II BD,<sup>12</sup> and the second would present some (albeit not the main) symptoms of

BD and would suffer from chronic mood instability with severely affected global functioning. The second type normally receives a diagnosis of unspecified BD (UBD) since only some of the characteristics of BD are presented.<sup>12</sup> A diagnosis of UBD has been employed as a useful working diagnostic for cases that were considered hard to define by most researchers.<sup>12</sup>

In order to define a diagnosis, it is essential to describe the clinical profiles of children in detail, making a careful and systematized assessment of all symptoms and noting the frequency and severity of each symptom. The following instruments are currently recommended to strengthen the case for a diagnosis of CABD:<sup>12</sup> Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS – version PL),<sup>16</sup> K-SADS with a session for affective disorders and rapid cycling of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS)<sup>17</sup> and the WASH-U-KSADS itself.<sup>17</sup> Note that the Brazilian version of K-SADS-PL has already been validated and is available in our milieu.<sup>18</sup> Another instrument that creates a semi-structured environment for exploring symptoms and independent signals for diagnosis is the Child Behavior Checklist (CBCL).<sup>19</sup> This instrument has been employed in recent research and is also currently available for use in clinical practice in Brazil.<sup>21</sup>

### Clinical aspect

Children with BD may be perceived as irritable, even in euthymic states, and most of these children should be diagnosed with oppositional defiant disorder even during euthymia.<sup>7</sup> Some researchers have also interpreted anxiety symptoms of children in euthymic states as a sign of an abnormally and persistently altered mood state associated with CABD.<sup>7</sup> The initial manifestation of early-onset BD is typically a depressive episode. Studies such as those conducted by Akiskal<sup>2</sup> and Findling et al<sup>7</sup>

showed that, over the course of a four-year follow-up period, approximately half of the children with BD presented depressive profiles prior to the first (hypo)mania episode.<sup>22</sup>

The characteristics of the depressive episode in children with CABD are very early onset (before the age of 13), psychomotor retardation alternating with agitation, psychotic symptoms, (hypo)mania reactions after the use of antidepressants, hypersomnia and hyperphagia.<sup>1-2,23</sup> In depressed children, these characteristics are also considered predictive of a higher risk for later appearance of a (hypo)mania episode.<sup>1-2</sup> Therefore, in CABD patients (as in the adult population) suicide attempts are more frequent.<sup>3,15,23</sup>

Children in (hypo)mania crisis may present increased irritability and mood instability, alone or together with elevated mood and euphoria. These children may exhibit self-destructive behavior, as well as aggressive towards others,<sup>8,23</sup> and there are multiple reports of model children who suddenly became "as wild as animals".<sup>9,24</sup> Such children become hyperactive, talking much more, and much more rapidly, than usual and are more easily distracted. They are constantly restless and excited, along with a loss of judgment. These children complain of racing thoughts and present reduced objectivity or flight of ideas. In addition, such children may fantasize and have delusions of grandeur, imagining that they possess magical powers, understand the "language of the angels", or will become very wealthy. Strange and extravagant behavior, such as hypersexuality, is much more evident in adolescence.<sup>7-11,23</sup> Carlson points out that irritability and emotional lability occur more frequently in children younger than 9 years, whereas euphoria, excitement, paranoia and delusions of grandeur are more frequently reported in older children.<sup>24</sup> Although still regarded as significant, the decreased need for sleep is, by some researchers, no longer considered essential for the diagnosis of (hypo)mania in children.<sup>25</sup>

Children and adolescents alike may have psychotic symptoms during (hypo)mania crises. The most commonly reported psychotic symptoms in children are visual hallucinations (e.g. seeing heads floating in the air), auditory hallucinations (e.g. "the devil and an angel are talking to me") and persecutory delusions (e.g. "other boys are after me because they are jealous"). Delusions of grandeur (e.g. having the power to control the future) have also been reported.<sup>1,5,26</sup> Geller and colleagues found that 23% of (hypo)manic children and adolescents suffered from hallucinations (principally of a commanding, imperative or religious nature) and 34.6% suffered from delusions (mostly grandiose, persecutory, referential or self-blaming in nature).<sup>8</sup> In such cases, the hallucinations are more varied and are not restricted to auditory hallucinations (e.g. the patient hearing someone calling his or her name), as in cases of depression. The presence of psychotic symptoms in an adult with BD indicates worse prognosis and greater difficulties for treatment. However, it has not been determined whether this is also true for children and adolescents.<sup>7-8</sup>

Another characteristic of BD is a mixed affective state. Children and adolescents with BD commonly present behavioral changes, become more extravagant, exhibit psychomotor and mental hyperactivity, and become more socially outgoing. Nevertheless, such children relate having uncomfortable feelings and losing hope that anything will ever make them happy again.<sup>27</sup> Since the mixed affective state is not common in adults, this tends to be a characteristic of children and adolescents with CABD.<sup>27</sup>

Another characteristic is that children and adolescents often present more rapid mood swings than adults do and may even alternate between depressive and (hypo)manic states several times over the course of a single day.<sup>28</sup> Findling et al. noted that most children and adolescents with BD (50%) present ultra-rapid cycling or continuous course, with no periods of euthymia

between episodes.<sup>7</sup> Geller et al. point out that, in addition to the requisite elated, euphoric or grandiose behavior typically seen in CABD hypo(mania) crises, the duration of the crisis may vary. These authors also call attention to ultra-rapid or continuous cycling in children, symptoms which had previously been little recognized.<sup>8-9,11</sup> One of the children with type-II BD diagnosis studied by Geller et al. presented 104 episodes on 104 different days, each lasting  $\pm 4$  hours.<sup>28</sup>

The distinction between a mixed affective state and ultra-rapid or continuous cycling in early-onset BD is not always an easy one to make. Leibenluft et al proposed that (hypo)mania crises lasting 4 hours or more should be investigated further. This should be done so that swings within the same mood state (e.g. depression or euthymia) are not considered a change in phase and so that the mixed state (the simultaneous presentation of euphoric and depressive symptoms) is not confused with a continuous cycling pattern.<sup>25</sup>

In 2003, Leibenluft et al<sup>25</sup> suggested the designation of three clinical CABD phenotypes. The first well-defined ("narrow") phenotype consists of cases that meet all of the DSM-IV criteria for BD diagnosis, with the requisite elated, euphoric or grandiose behavior. The duration of the episodes should be as stated in the DSM-IV guidelines, and the beginning and end of each phase should be well defined. Preexisting patterns of behavior should not be confused with BD symptoms. This clinical profile corresponds to DSM-IV type-I or type-II BD.<sup>13,25</sup>

The second is the intermediate phenotype and consists of two subphenotypes, the first of which describes patients presenting symptoms of euphoria, elation or grandiosity, as well as other (hypo)manic symptoms, although the duration of the episodes is generally less than that established by the DSM-IV to define a (hypo)mania crisis. The other intermediate phenotype describes patients presenting no euphoric or grandiose behavior, although such patients present increased irritability and other long-lasting (hypo)manic symptoms.<sup>25</sup> Patients in these intermediate phenotypes are often diagnosed with unspecified (hypo)mania (UBD).

The third is the ill-defined ("broad") phenotype, which includes children who are constantly in a bad mood (upset or sad), presenting explosions of hyperactivity in response to negative emotional stimuli. These children display motor hyperactivity, distraction, insomnia, racing thoughts and pressure to speak, as well as three or more uncontrollable rage crises per week within the last four weeks. In addition, these children have chronic relationship problems with parents, colleagues or siblings, a situation that significantly hinders global functioning.<sup>25</sup>

Most children have chronic stress factors in their family and social environments.<sup>7</sup> The most recent study by Craney & Geller calls attention to the finding that the level of maternal care is a predictive factor for relapse after remission. This finding is compatible with those of studies involving expressed emotions, which are predictive of relapse in schizophrenic and BD patients.<sup>9,11</sup> Additional psychosocial and psychodynamic factors of CABD are best left for future texts.

### Comorbidities and differential diagnosis

High rates of comorbidity have been reported between CABD and attention deficit-hyperactivity disorder (ADHD),<sup>29-30</sup> conduct disorder (CD),<sup>31-32</sup> anxiety disorders, panic disorders, social phobia, agoraphobia,<sup>33</sup> and psychoactive substance dependence or abuse.<sup>32</sup> In addition to high comorbidity rates, CABD is also the differential diagnosis for ADHD, CD and early-onset schizophrenia.<sup>1,34</sup>

The difficulties in differentiating early-onset clinical (hypo)mania presentations from ADHD and CD are well known. Children with CABD are typically misdiagnosed with ADHD or CD, and those

with severe forms of ADHD or CD are misdiagnosed as having CABD.<sup>1,23,29,31</sup> Symptoms present in behavioral disorders including social dysfunction such as hyperactivity, aggressiveness and flouting social rules may also be present in children and adolescents with CABD.<sup>8-9,11,28</sup>

Faraone et al<sup>35</sup> suggested that BD-ADHD comorbidity may be characteristic of CABD. Biederman et al concluded that CABD and ADHD are two distinct pathologies, although they pointed out that ADHD cases that later presented CABD were those that presented, from the outset, high comorbidity rates, the lowest scores in diagnostic interviews (CBCL) and a family history of affective disorders.<sup>29</sup> Therefore, these were severe ADHD cases. Kim and Miklowitz affirmed that the same distinction could be made between BD and CD and emphasized the possibility that (hypo)manic symptoms are an indicator of the severity of psychopathology in childhood and not necessarily in BD.<sup>31</sup>

To date, what remains unclear is whether the comorbidities are actual comorbidities or prodromal BD symptoms. Wozniak et al. proposed that there is a BD subtype that is always associated with ADHD symptoms and suggested that this subtype might even constitute a distinct nosographic entity in which BD and ADHD symptoms occur simultaneously in children.<sup>36</sup> The same may apply to cases involving the simultaneous occurrence of BD and CD.<sup>36</sup> Studies involving children considered to be at high risk for developing BD, ADHD or CD (such as the offspring of adults with BD, ADHD or CD) may represent a means of clarifying this question.<sup>29-30,37-38</sup>

In order to avoid mistakes and difficulty in differentiating CABD from ADHD, Geller et al considered only the principal (hypo)manic symptoms, such as euphoria, mood elevation or delusions of grandeur, in the CABD diagnosis. Other symptoms, such as irritability and hyperactivity were classified as very unspecific for differentiating between the two diagnoses.<sup>8-11</sup> Children with CABD exhibit greater mood involvement, and their activities tend to be more focused than are those of children with ADHD alone. Psychotic symptoms present in some (hypo)manic patients and absent in ADHD cases also facilitates making the distinction.<sup>15</sup> Researchers also call attention to the distinction between the real decreased need for sleep or antidepressant-induced insomnia seen in BD cases and the initial insomnia or chronic decrease in need for sleep seen in ADHD cases.<sup>25</sup>

Mood-incongruent hallucinations, paranoia and disorganized thoughts are symptoms that commonly lead to diagnostic confusion between BD and schizophrenia.<sup>23,26,34,39</sup> In comparing patients with adult-onset BD to CABD patients, McGlashan found that, among early-onset cases, 83% met the criteria for schizoaffective disorder at the onset of the illness.<sup>39</sup>

### Treatment

The treatment of children and adolescents with BD has traditionally been based on what was previously indicated for adults. The scientific community has shown its concern and promoted debates in order to evaluate which kind of treatment should be prioritized. What should the treatment duration be? What impact would early treatment have on the course of the illness? No answers to these questions have yet been found.<sup>12</sup> The current consensus is that, once the diagnosis has been determined, the established treatment for BD should be immediately prescribed. This includes the administration of a mood stabilizer and the use of antidepressants or antipsychotics (as needed in depressive and (hypo)manic phases, respectively), psychotherapy, family counseling, psychopedagogical management and, if necessary, neuropsychological rehabilitation.

Prior to initiating psychopharmacological treatment in children and adolescents, clinical and laboratory evaluations are compulsory. The aim of such evaluations is to rule out physical

conditions (e.g. hormonal dysfunction) and to trace a basal profile for future periodic control exams. Electrocardiograms, as well as evaluations of hematology, hepatic function, thyroid function, renal function and metabolic aspects, are recommended.

For the treatment of bipolar depression in children and adolescents, the rules previously established for adults are applied. Although the same drugs prescribed for adults are used, we must bear in mind that controlled studies involving children and adolescents have not been conducted for most of these drugs lack and that, currently, some are even contraindicated. It is also important to remember that the isolated use of an antidepressant is inadvisable in children with a family history of affective disorder. In the presence of any previously cited risk factor, it is recommended that the antidepressant be prescribed in combination with a mood stabilizer.

Controlled drug trials involving children and adolescents with BD are still rare. In the case of monotherapy with a mood stabilizer, there has been only one controlled study (conducted by Geller et al) using lithium in adolescents with BD and concomitant substance abuse. The lithium treatment proved efficient in the improvement of both conditions.<sup>40</sup> In open clinical trials, lithium, divalproex sodium and carbamazepine, each used in isolation, have proven efficient in managing CABD.<sup>26,38,41</sup> A number of clinical trials involving monotherapy with olanzapine<sup>42</sup> and risperidone<sup>43</sup> have been published and have shown these drugs to be efficient in controlling the acute (hypo)manic phase and in the maintenance treatment of CABD.

The efficacy of new anticonvulsants, such as gabapentin, topiramate and lamotrigine in the acute (hypo)manic phase and in BD maintenance treatment have not yet been determined in cases of CABD. The prescription of these drugs in CABD cases is based on adult cases and is recommended after inefficient therapeutic attempts with, or intolerance to, lithium, divalproex sodium or carbamazepine.<sup>38,44-45</sup> Recent studies have shown the possibility of, and the need for, using a combination of two stabilizers for control and maintenance treatment of CABD.<sup>38,42-43</sup> All research to date has shown that the type of treatment given does not seem to be predictive of the evolution of the disease.<sup>11</sup>

In the case of polytherapy, double-blind controlled studies have come into popular use. Such studies involve the use of a fixed, specific drug (generally a mood stabilizer or anticonvulsant) in combination with another drug, usually an atypical antipsychotic or placebo. The combinations of divalproex sodium with risperidone, divalproex with quetiapine, lithium with atypical antipsychotics and lithium with anticonvulsants were all considered efficient in controlling CABD crises.<sup>38,42-43</sup>

A recent study conducted in the United States determined that children and adolescents diagnosed with BD are usually treated with sodium valproate (79%), lithium (51%) or gabapentin (29%). Other drugs used are carbamazepine (21%), topiramate (14%), oxycarbamazepine (6%) and lamotrigine (4%). These patients usually receive from three to five types of medication simultaneously and typically had other previous attempts with another six to ten drug types.<sup>43</sup> No similar studies have been conducted in our milieu.

There are also increasing numbers of reports involving monotherapy with atypical antipsychotics, such as olanzapine and risperidone, for controlling the acute phase of CABD, as well as for maintenance treatment.<sup>38</sup> Most children in the study conducted by Bhangoo et al (77%) had previously been treated (unsuccessfully) with antipsychotics. However, the authors do not know if this is due to the presence of psychotic symptoms during crises or to the influence of recent studies suggesting the effects of mood stabilizers.<sup>42-43</sup>

Bhangoo et al. were concerned about the amount of drugs prescribed by community physicians, apparently with no

systematization or orientation. In 15% of the cases, these physicians had never prescribed lithium, but had prescribed new anticonvulsants such as gabapentin, topiramate and lamotrigine.<sup>43</sup> Geller<sup>7</sup> and Findling et al<sup>10</sup> also called attention to the failings in CABD diagnosis and treatment conducted by community physicians in the United States. Lacking specific training in recognizing (hypo)manic symptoms in children and adolescents, these physicians tend to underdiagnose or overdiagnose, putting patients at risk for prolonged suffering and inefficient treatment. This may, in fact, be the current state of affairs in Brazil.

Other etiologic aspects, neuropsychological findings and neuroimaging findings will be presented in future texts.

### Conclusions

Many questions concerning CABD remain unanswered, and some seem more discomfiting than others. We must ask ourselves: "How early can a diagnosis of CABD be made?"; "What is the predictive value of early CABD presentation in children and adolescents?"; and (in cases presenting "prodromal and predictive signs") "What are the risks and benefits of treating children and adolescents with prodromal symptoms?". The answers remain indefinite.<sup>12</sup>

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