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UPDATE ARTICLE

Mood disorders in childhood and adolescence

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The identification and treatment of mood disorders in children and adolescents has grown over the last decades. Major depression is one of the most common and debilitating disorders worldwide, imposing a massive burden to the youth population. Bipolar disorder is being increasingly recognized as having its roots early in life, and its presentation during childhood and adolescence has been submitted to extensive research. This review aims to highlight clinical aspects of the current knowledge on mood disorders in the pediatric population, presenting updated information on epidemiology, diagnostic procedures, and management strategies. Limitations of available evidence and future directions of research in the field are also discussed.

Keywords: Child; adolescent; bipolar; depression; mood

Introduction

Children and adolescents are frequently referred to psychiatric consultation due to mood complaints. Over the last decades, there has been an increase in the recognition of mood disorders among young individuals, a reflection of the adoption of a developmental perspective to psychopathology. Longitudinal studies clearly indicate mood disorders begin early in life, with the majority of first episodes occurring before adulthood.[1] Diagnostic criteria originally created for the adult population are also progressively being adapted to capture the specificities of depressive and maniac episodes in childhood and adolescence.

This review will focus on the clinical aspects of the two major diagnostic categories of mood disorders: unipolar depression and bipolar disorder (BD). Together, they represent a large burden to young people worldwide, accounting for more than one-tenth of the global burden of disease among 10 to 24 year-olds.[2] Unipolar depression is the single most important source of disability (among all causes) for this age group, corresponding to 8.2% of the disability-adjusted life-years (DALYs); and BD is ranked fourth, with 3.8% of the DALYs. The impact of mood disorders on mortality is also marked. Suicide, one of the leading causes of death among young people, is associated with depression in at least half of the cases in adolescence.[3] This effect is even more common in the pediatric bipolar population, with twice the number of suicide attempts in comparison with individuals with unipolar depression.[4]

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Depression

Epidemiology

Data on the prevalence of depression in the first years of life are limited due to the scarcity of appropriate diagnostic criteria from a developmental point of view. Studies to date suggest a relatively low occurrence of depressive episodes in preschool children, affecting approximately 1 to 2.5% of this population, with no significant gender differences. Conversely, the estimates of unipolar depression prevalence up to the end of adolescence resemble those found in the adult population, with 4 to 9% of subjects presenting with a depressive episode in a 12-month period.[5,6]

During adolescence, the cumulative risk for the occurrence of a depressive episode rises from 5 to 20%.[3,7] Many factors may explain this increase in the incidence of depression after puberty. Adolescence is a crucial developmental period, with the confluence of biological, psychological, and social changes that can predispose to the occurrence of mental disorders.[8] With the onset of puberty, there is a rapid physical maturation process and cognitive growth (with increased capacity for abstract thinking and generalizations) as well as social and interpersonal transitions, with changes in the relationship with school, family, and peers.[9]

One of the most consistent findings in the literature is the increase in the female/male ratio of individuals presenting with depression symptoms after puberty. This discrepancy has been shown not only in referred samples, but also in population-based studies, and thus is not likely to occur due to referral bias. Although the reasons for such difference are not completely understood, it is suggested that hormonal changes have a role in this phenomenon, acting more in order to increase the sensitivity to environmental stressors than actually causing depression *per se*.

A major risk factor for the development of depressive disorders is the high familial loading of depression.[10] Different types of investigation, such as adoption, twins or high-risk studies, corroborate the pivotal role of the familial component in the etiology of major depression, probably through gene-environment interactions.[11] As for the adult population, it is believed that the incidence and recurrence of depressive episodes can be mediated or moderated by stress factors such as losses, neglect or abuse, conflicts, and frustrations. However, the effects of such stressors seem to be mainly conditioned by the way the child interprets and deals with such adversities.

The median duration of a major depressive episode in children and adolescents referred to treatment is approximately 8 months. Although the majority of patients recover from a first episode, data from clinical and community studies suggest probabilities of recurrence from 20 to 60% in the first 2 years after remission, reaching 70% after 5 years.[12]

Diagnosis

Even though depressive symptoms can be understood as a continuum, a diagnostic decision is usually necessary to define the need for treatment. The American Association of Child and Adolescent Psychiatry recommends key screening questions for depression (sad or irritable mood and anhedonia) in every psychiatric evaluation.[13]

As with any assessment of children and adolescents, it is essential to establish a connection and a confidential relationship with the child or young person, and information gathering from the largest number of informants (child/adolescent, parents, school) is the best strategy to capture the underlying psychopathology. When there is need to prioritize one source of information, the literature seems to suggest that internalizing symptoms in general - and depressive symptoms particularly - tend to be more frequently reported by patients in comparison with caregivers or teachers.

Several lines of evidence point to the importance of including the family in the understanding, prevention, and treatment of depressive disorders. Unfortunately, the currently available diagnostic criteria neglect the importance of this issue.[5] It is recommended that family assessment takes into account various sociocultural factors that may influence the presentation, description, and interpretation of symptoms, focusing not only on problems, but also including positive aspects, which could be essential in planning therapeutic approaches.[13]

Despite the advances achieved with the adoption of operational classification systems (DSM and ICD), the difficulties in diagnosing depression in children and adolescents are higher than those found in older individuals. This is because the current diagnostic criteria were developed for the adult population, neglecting many of the developmental differences between children/adolescents and adults.

With regard to age differences, the only adaptations of the DSM-IV-TR for the diagnosis of a major depressive episode in children are inclusions of irritable mood as one possible cardinal symptom and of failure to make expected weight gain as a marker of appetite or weight change. Furthermore, the DSM-IV-TR also reduces from 2 to 1 year the minimum duration of symptoms required for characterizing a dysthymic disorder. ICD-10 has no adjustments related to developmental aspects. Figure 1 shows a suggestion of diagnostic algorithm for depressive episodes.

Even though the current criteria are reasonably applicable to older adolescents, symptoms such as excessive guilt, indecisiveness or suicidal ideation have little applicability among young children. Moreover, even in adolescents, depression is often less recognized than in adults, possibly due to factors such as fluctuation of symptoms, mood reactivity, and strong irritability.[3]

The presentation of depressive symptoms may vary according to age groups. Regarding mood changes, younger children show more temporal variability, making harder to characterize a mood episode. Adolescents often conceal their mood changes, frequently presenting as social isolation. Anhedonia may be manifested as difficulty in having fun in younger children, but in adolescents it may be manifested as boredom. The melancholic aspects of depression (reduction of energy, sleep changes, and appetite/weight disturbances) are more often seen in adolescents than in younger individuals. Conversely, somatic complaints are more common in children, but can also be found in adolescents.[5]

Children may have difficulty verbalizing their feelings or may even deny that they are depressed. Thus, special attention should be given to observable manifestations such as changes in sleep patterns, irritability, poor academic performance, and social withdrawal.[13] For the longitudinal assessment of mood symptoms, it may be useful to adopt a mood diary or timelines, and use special dates like birthdays, holidays or school holidays as anchors. Mood is recorded ranging from very happy to very sad/angry; in addition, stressful events and possible treatments should also be registered. The use of timelines can be extremely valuable in identifying triggers, in assessing treatment response, and in the identification of possible manic or hypomanic episodes (especially in the differentiation of these in relation to return to euthymia).[13]

The diagnostic assessment of depressive disorders can make use of formal procedures such as structured/semi-structured interviews or rating scales. In addition to general interviews to assess mental disorders in childhood and adolescence (e.g., the Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS] and the Development and Well-Being Assessment [DAWBA]), specific instruments have been developed for the assessment of depressive symptoms in children and adolescents. Among the specific scales more frequently used worldwide and available in Brazilian versions are the Children's Depression Rating Scale (CDRS), the Children's Depression Inventory (CDI), and the Kutcher Adolescent Depression Scale (KADS).

Several other problems in childhood and adolescence may present as depressive symptoms and should always be considered in the differential diagnosis: bereavement

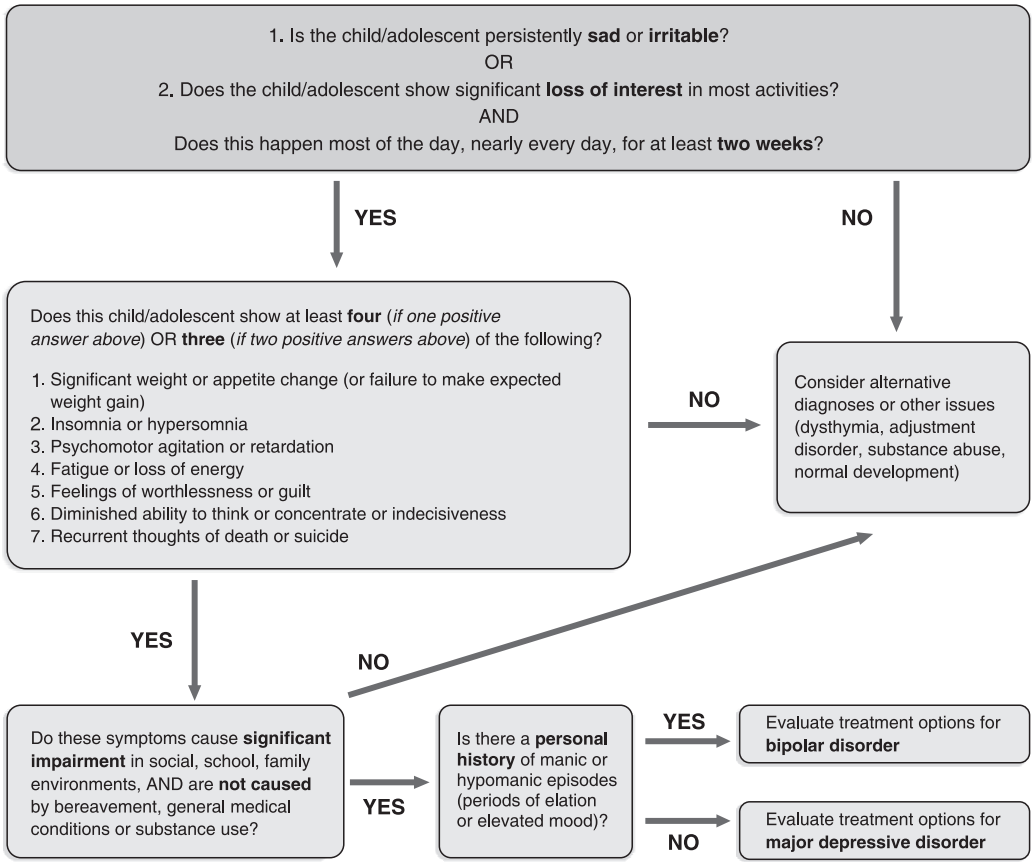

Figure 1 Diagnostic algorithm for depressive episodes in children and adolescents

or adjustment disorders, oppositional defiant disorder, substance use disorders, hypothyroidism, anemia, infections, cancer, and autoimmune diseases. Conversely, one should remember that depression may end up not being diagnosed in cases where the chief complaint or reason for the consultation is physical symptoms, anxiety, school refusal, decline in academic performance, substance use or externalizing problems.[3]

Depending on the clinical context, 40 to 90% of children and adolescents with depressive disorders have at least one psychiatric comorbidity, and 50% of young people have two or more concurrent diagnoses. Among the most prevalent comorbid diagnoses are anxiety disorders, followed by disruptive disorders, attention deficit disorder/hyperactivity (ADHD), and in adolescents, substance use disorders.[13]

One of the areas of greatest uncertainty in the evaluation of a first depressive episode in a child or adolescent is whether the episode is part of a unipolar or a BD. Some risk factors for BD may be useful in the diagnostic decision, although none of them has sufficient predictive power to differentiate both disorders: among them are a strong family history of BD or psychosis and a history of pharmacologically induced mania or hypomania.[13] Schizophrenia is another rare diagnosis in adolescence, but also a differential diagnosis to be considered, given that depressive symptoms may precede or accompany psychotic features.[3] Another problematic area is the assessment of depressive symptoms in patients with intellectual disabilities or mental retardation. Because these individuals often present with symptoms on multiple domains, greater efforts are needed for the identification of mood symptoms in this high-risk population.[14]

Similarly to what happens to adults, risk assessment is essential in children and adolescents with depression. Among young individuals, it is also important to differentiate suicidal from other self-injury behavior, in which the goal is to alleviate negative feelings. This type of behavior usually involves repetitive cuts, seeking more relief from anger, sadness or loneliness than the end of life.

Regarding suicide assessment, recent findings show that a 4-question screening instrument, the Ask Suicide-Screening Questions (ASQ), can identify the risk for suicide in patients presenting to pediatric emergency departments, with high sensitivity and negative predictive value. This new screening tool comprises questions assessing current thoughts of being better off dead, current wish to die, current suicidal ideation, and past suicide attempt, with a sensitivity of 96.9% (95% confidence interval [95%CI] 91.3-99.4) and a specificity of 87.6% (95%CI 84.0-90.5).[15]

Treatment

Every treatment plan for depression in children and adolescents should take into consideration developmental

aspects, including psychoeducation, family support, assessment of comorbid conditions, and risk behaviors. Moreover, given the nature of chronic and recurrent depressive disorders, clear objectives should be established together with patients and their families not only for the acute treatment of the current episode, but also for phases of consolidation and maintenance, monitoring and preventing new episodes.

Similarly to the management of depression in adults, mild episodes can be addressed satisfactorily with psychoeducation and support measures targeting environmental stressors. A recent meta-analysis suggests the benefit of physical activity on depressive symptomatology among children and adolescents, with a small but significant effect size for the intervention.[16] However, for cases in which the symptoms are more intense, more specific strategies are often necessary.

In the pediatric population, evidence suggests the efficacy of pharmacological agents, cognitive behavioral therapy (CBT) or interpersonal therapy (IPT) - all these interventions, however, present only intermediate effect sizes in randomized controlled trials. Given that studies with children and adolescents usually focus on the treatment of depressive episodes, the management of dysthymic or unspecified depressive disorders is frequently extrapolated from the available literature on major depression.[17]

The psychotherapeutic techniques with the largest evidence base in terms of efficacy for the treatment of depressive episodes in children and adolescents are CBT and IPT. Psychodynamic approaches have also been widely employed, despite the absence of clinical trials evaluating this type of intervention.

Meta-analyses that investigated the efficacy of psychotherapy in the pediatric population (including 35 trials with children and adolescents[18] and 11 trials only with adolescents[19]) suggested the efficacy of CBT, but with effect sizes around 0.3. The largest clinical trial for adolescents with depression performed to date (Treatment of Adolescent Depression Study, TADS) randomized 439 individuals to one of four options: CBT, fluoxetine, CBT + fluoxetine combination, or placebo.[20] In this study, however, no significant differences in the response between CBT and placebo were detected (43 and 35%, respectively). Another large clinical trial (Treatment of Resistant Depression in Adolescents, TORDIA, n=334) evaluated strategies for resistant depression and suggested that adding CBT to antidepressants may be beneficial.[21] A role played by CBT may be preventing new episodes, as demonstrated in a clinical trial that suggested an eight times reduction in the risk of relapse in the first 6 months.[22]

A smaller body of evidence also points to the efficacy of IPT in the treatment of depressive episodes in adolescents. Clinical trials to date have compared IPT to conventional treatment, with no high quality controlled studies assessing IPT vs. antidepressants or placebo.[17] There is a general idea that IPT is especially beneficial for adolescents with high levels of interpersonal conflict with parents, high levels of depressive symptoms, and comorbid anxiety.[23] Family-focused interventions also have the advantage of approaching critical issues of the child's context, emerging as a promising strategy in recent years, especially in young children.[5,24]

On the path to define the best treatment option for depression, the Improving the Mood with Psychoanalytic and Cognitive Therapies (IMPACT) trial is an ongoing study that is planned to recruit 540 individuals to compare effectiveness and define superiority in reducing relapse among three approaches, combined with the use of fluoxetine as needed: CBT, short term psychoanalytic therapy, and specialist clinical care.[25]

Children and adolescents appear to show a response pattern different from that observed in adults with respect to antidepressants - both in terms of efficacy and adverse effects (Table 1). Nonetheless, except for the use of lower initial doses to avoid side effects, the use of antidepressants in children and adolescents generally follows the same doses used in adults.

A meta-analysis that evaluated the use of various selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, and nefazodone in 13 randomized trials including 2,910 participants showed that antidepressants were effective in treating major depression among children and adolescents. There was a significant response of 61% in patients treated with active drug compared with 50%

Table 1 Most used antidepressants to treat unipolar depression in children and adolescents

Medication	Dose	Side effects
Fluoxetine*	20 to 60 mg/day	Fluctuations in appetite, weight changes, nausea, diarrhea, constipation, dry mouth, insomnia, but also sedation, agitation, tremors, headache, dizziness, sweating, sexual side effects, vivid dreams, akathisia, disinhibition, bruising and rare bleeding, rare hyponatremia, rare hypotension.
Escitalopram*	10 to 30 mg/day	
Citalopram	20 to 60 mg/day	
Fluvoxamine	50 to 300 mg/day	
Sertraline	50 to 200 mg/day	
Venlafaxine	37.5 to 225 mg/day	Headache, nervousness, insomnia, sedation, nausea, diarrhea, decreased appetite, asthenia, sweating, SIADH, hyponatremia, dose-dependent increase in blood pressure.
Duloxetine	20 to 40 mg/day	Nausea, diarrhea, decreased appetite, dry mouth, constipation, insomnia, sedation, dizziness, sweating, increase in blood pressure (up to 2 mmHg), urinary retention.
Bupropion	3 to 6 mg/kg/day	Dry mouth, constipation, nausea, weight loss, anorexia, myalgia, insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus, sweating, rash, hypertension, rare seizures.

SIADH = syndrome of inappropriate antidiuretic hormone.
* FDA-approved for depression treatment in children and adolescents.

among those who received placebo (number needed to treat [NNT] = 10). Specific data for fluoxetine suggest a NNT = 5, which is possibly associated with a greater half-life of the drug (smaller effect in cases of poor adherence) and a better design of the studies evaluating this drug.[23] An analysis of the 10 studies cited in the meta-analysis for which results grouped according to age were available found that the response to antidepressant treatment was significant for adolescents (62 vs. 49%), but did not reach statistical significance among children (65 vs. 58%) - possibly due to the high placebo response in this age group. In this meta-analysis, the only antidepressant that demonstrated efficacy in both children and adolescents was fluoxetine.[26]

Currently, the only drugs approved by the FDA for the treatment of depression in youth are fluoxetine (from age 8) and escitalopram (after 12 years). Other SSRIs used in clinical practice are sertraline and fluvoxamine, especially in cases of comorbidity with anxiety disorders, for which they are approved by the FDA. Paroxetine has limited use in the younger population, as it demonstrated little evidence of superiority compared to placebo.[17]

Other antidepressants studied in the pediatric population include venlafaxine, duloxetine, and bupropion - and the efficacy of the latter two was only suggested in open studies. In the TORDIA study, venlafaxine showed to be as effective as other SSRIs in the treatment of refractory depression, although resulting in more adverse effects, including suicidality among those with high levels of suicidal ideation at baseline. Tricyclic antidepressants have no evidence of effectiveness in treating depression in children and adolescents, as they were not more effective than placebo in meta-analyses (Box 1).

Despite the limited number of clinical trials assessing the efficacy of combined strategies, the use of more than one treatment intervention is also an option, especially in cases of moderate to severe depression. The two major clinical trials in the United States suggest that this strategy may actually be beneficial. In the TADS, a combination of CBT + fluoxetine showed a better response in comparison with other interventions, especially in terms of reducing suicidal ideation, functional recovery, and proportion of remissions at week 12. Similarly, in the TORDIA study, the addition of CBT to the new medication was associated with a better clinical response. In the British study Antidepressant and Psychotherapy Treatment (ADAPT),[28] the combination of CBT + pharmacotherapy was not superior to SSRI monotherapy at week 28, but the inclusion of patients with greater severity may have influenced the results (a more severe subgroup analysis of the TADS also showed the same result). In the long term, the follow-up of individuals randomized for monotherapy or combination therapy suggests that they converge both in the TADS (36 weeks) and in the TORDIA study (72 weeks). Factors such as uncontrolled naturalistic follow-up and spontaneous remission over time, however, make these results difficult to interpret.

Giving the variability and uncertainty about the best treatment available for depressive disorders, the Cochrane Collaboration has recently released three meta-analyses investigating the effectiveness and safety of different depression treatment alternatives. Regarding the effectiveness of pharmacological, psychological, and combined treatment, there was limited evidence to conclude about the superiority of any treatment over another.[29] In respect to the effectiveness and safety of pharmacological treatment options for child and adolescent depression, the systematic review of the literature highlighted the high heterogeneity among available studies, but suggested that fluoxetine should be the treatment of choice if pharmacological treatment is considered.[30]

The same authors also reviewed the available evidence on interventions for preventing relapse and recurrence of depression in children and adolescents,

Box 1 Use of antidepressants and suicidality in young individuals

In 2004, the FDA made the decision to include a black box warning about the risk of suicidality associated with antidepressant use among individuals under 25 years of age. This initiative was taken after a meta-analysis involving more than 4,400 children and adolescents suggest an increased risk of adverse events of suicidal ideation or behavior during the first few months of treatment with antidepressants. The risk of these events was 4% with SSRIs compared with 2% in the placebo group. More recently, another meta-analysis including seven studies not evaluated in the initial review found an increased risk of suicidal behavior/thoughts with antidepressants (2.5% in contrast with 1.7% with placebo).[26]

Based on the fact that for the treatment of depressive disorders the number needed to treat (NNT) in this age group is at least 10 and the number needed to harm (number needed to harm, NNH) is 112, it was concluded that the benefits associated with the use of antidepressants outweigh the potential risks. Moreover, the year after the inclusion of the warning from the FDA, the number of prescriptions of SSRIs in the United States fell and suicide rates increased for the first time after 10 years of decline or stability.[27]

In summary, the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents should be cautious, observing the emergence of suicidal thoughts or behavior, and unexpected changes in behavior, such as insomnia, agitation, and social withdrawal. Knowledge about the characteristics of such events and an active attitude seeking to mitigate predisposing factors should be part of any therapeutic strategy. Suicide-related events usually happen more early in treatment (3-5 weeks) and among those who do not respond to drugs, having as high predictors suicidal ideation at baseline, greater severity of symptoms, family conflict, and alcohol and/or drugs use.

concluding that there is little evidence to establish which type of treatment approach is most effective, suggesting that psychological therapies showed encouraging results, but need replication in larger studies. The pharmacologic intervention studies showed considerable diversity, but some studies showed benefit.[31]

Adopting a developmental perspective for understanding the origins and persistence of mental disorders has led to the search for preventive strategies to avoid the incidence of depressive episodes. Studies suggest that the treatment of mothers with depression is associated with a lower incidence of psychiatric diagnoses and better responses to treatment with CBT in children,[32] which reinforces the need for a comprehensive family assessment and interventions directed at caregivers when needed.

Meta-analyses of preventive strategies suggest that programs focusing on at-risk individuals (based on factors such as family history or presence of subsyndromal symptoms) are more effective than universal strategies.[3] Such interventions, generally employing psychoeducational and cognitive-behavioral techniques, have yet to be rigorously tested in future studies, which should also include cost-effectiveness analysis. A recent classroom-based CBT approach to prevent depressive symptoms in high-risk adolescents, however, failed to show benefit with the intervention.[33]

Bipolar disorder

Epidemiology

The first clues to the investigation of BD in children and adolescents derived from studies of adults with BD. Around 0.3 to 0.5% of the adults recall their disorder onset in childhood (before age 10), and over 60% before age 18.[34,35] An epidemiological study in prepubertal children conducted in the United States found a prevalence estimate of 0.1% of hypomania (BD type II), and no cases of mania (BD type I) in children aged 9 to 13 years.[36] A community-based investigation of mental disorders in Brazil assessed 1,251 subjects from 7 to 14 years in Taubaté and did not detect any cases of BD using the DAWBA.[37]

A different situation is observed among adolescents. In a recent large community research, 10,123 adolescents were evaluated using a modified version of the Composite International Diagnostic Interview (CIDI). The authors found that 2.5% of youth met criteria for lifetime BD type I or II and 1.7%, for mania only.[38] No large epidemiological study assessed adolescents in Brazil to date. Clinical samples have revealed prevalence estimates ranging from 1.7 to 4.2%.[39] In Brazil, a study found 36 subjects with pediatric BD (PBD; $<$ 15 years old) in a sample of 500 patients from a child and adolescent psychopharmacology outpatient program.[40] These data combined suggest the prevalence of BD type I and II in children and adolescents to be between 0.1 to 2.5%.[34,38,41]

Hereditary factors play an important role in BD etiology, and BD heritability has been suggested to be 0.56. The risk of BD in offspring of parents with BD is highly variable across studies, ranging from 2.8% (Netherlands) to 14-50% (United States). When family members of children and adolescents with BD are evaluated, the risk in first-degree relatives varies between 12 and 35%. In adults, the rates are around 5 to 10%, suggesting a larger genetic component in the early-onset form of BD.[42-44]

In naturalistic studies of BD among children and adolescents, the recovery rates are high (70 to 100%), but the recurrence rate in 2 to 5 years is up to 80%.[45-47] Moreover, most of the time these patients experienced subsyndromal and syndromal mood symptomatology and frequent mood fluctuations, as reported in the Course and Outcome of Bipolar Youth (COBY, n=263) 2-year follow-up study.[48] This may explain the fact that 80% of children and adolescents suffering from BD do not reach functional remission.[49]

The functional impairment of patients with PBD is remarkable. The disorder interferes with emotional, cognitive, and social development across the lifecycle. Indeed, these patients have a high risk for substance abuse, legal problems and suicide attempts.[50-53]

The main factors associated with poor BD prognosis are the following: earlier age of onset, duration of symptoms, rapid cycling, mixed episodes, psychotic symptoms, comorbidities such as ADHD and anxiety disorders, low socioeconomic status, negative life events, presence of psychiatric disorders in the family, absence of psychotherapy, low adherence to pharmacological treatment, use of antidepressants and alcohol.[45-48,54-56]

Diagnosis

It is important to mention that there are no tests to diagnose BD. Currently, no neuroimaging technique or neuropsychological test is specific to BD, and they have only been used for research purposes. The diagnosis is based on a careful symptom review, and sometimes only longitudinal follow-up may reveal the symptoms. As with other diagnoses in child and adolescent psychiatry, several sources of information are preferred.

BD is present when significant, persistent, and impairing changes in mood are observed (mania or hypomania, and depression).[57] Different research groups have been trying to establish what symptoms are important and their duration, in an attempt to correctly classify mood changes in children and adolescents. Youth with BD present more instability than adults with BD, more mixed and psychotic symptoms, and worse outcomes. Major focuses of controversies in PBD are irritability, which may be present in other psychopathologic entities, and the duration of symptoms.[58] Table 2 presents the criteria proposed by different research groups. From a clinical perspective, nonetheless, it is recommended that DSM-IV-TR and ICD-10 operational criteria remain the gold standard until new data becomes available.

Diagnostic challenges are amplified by the high proportion of comorbidity with disruptive disorders, especially ADHD. The presence of comorbidities may confer worse functional outcome and response to treatment.[60]

Table 2 Criteria adopted to diagnose BD in children and adolescents by main research groups

Research center	Criteria adopted
Washington University School of Medicine[59]	- DSM-IV-TR + requirement of at least one cardinal manic symptom (elation and/or grandiosity); irritability is not considered alone due to its low specificity. - Episode: whole duration of illness; cycles: mood changes lasting a minimum of 4 hours.
Massachusetts General Hospital, Harvard Medical School[49]	- DSM-IV-TR. - When severe irritability is present, there is no need for change in the usual mood pattern.
University of Pittsburgh Medical Center[46]	- BD-NOS definition: DSM-IV-TR modified in relation to the number of symptoms; if elation is present it is required more two symptoms of the DSM-IV-TR item B; and if irritability is present, three symptoms. - Duration of symptoms: at least 4 hours/day for 4 days (not necessarily consecutive days).
National Institute of Mental Health (NIMH)[58]	- Four different groups to cover the different presentations: - restricted phenotype (DSM-IV-TR), including cardinal symptoms and duration; - two intermediate phenotypes: one with hypomania or mania but without fulfilling the duration criteria (1 to 3 days), and the other without hypomania or mania, but irritability instead; - broad phenotype named severe mood dysregulation, chronic irritability, marked reactivity to negative stimuli; and hyperarousal, at least three times a week, for more than 1 year.

BD-NOS = bipolar disorder not otherwise specified.

Semi-structured interviews, checklists, and symptom scales may help in the differential diagnosis. The most commonly used instruments are the K-SADS,[61] the Child Behavior Checklist (CBCL),[62] and the Young Mania Rating Scale (YMRS).[63] All of them have been validated in Brazil, and, as mentioned before, do not provide a definitive diagnosis, but may suggest comorbidities, and allow symptom follow-up.[64-66]

Treatment

Pharmacological treatment in children and adolescents with BD is mandatory not only in the acute phase that may involve crisis stabilization for psychosis, suicidal behavior or agitation, but also to prevent relapses and recurrences. The mainstay for the management of BD is the use of medication along with enhancement of social skills and family support. The major goal is to achieve mood stabilization so that the patients can achieve their optimal emotional, cognitive, and social development.[67] For a review, see Peruzzolo et al.[68]

Even though short-term clinical trials have been increasing in number, current algorithms lack evidence-based data for many facets of PBD, such as bipolar depression, or absence of response to other agents. Moreover, the full impact of long-term use of the medications used to treat these children and adolescents has not been determined. Table 3 displays the most used mood stabilizers and atypical antipsychotics to treat BD in children and adolescents in clinical practice and their most common side effects.

One of the most important clinical trials in PBD is the Treatment of Early Age Mania (TEAM) study that evaluated 279 children and adolescents with DSM-IV BD type I. Patients were randomly assigned to receive lithium, divalproex sodium or risperidone for 8 weeks. Risperidone presented higher response rates in comparison with lithium (68.5 vs. 35.6%) and divalproex sodium

Table 3 Most used mood stabilizers and atypical antipsychotics to treat BD in children and adolescents

Medication	Dose	Side effects
Mood stabilizers		
Lithium	10 to 30 mg/kg/day	Polyuria, polydipsia, diarrhea, nausea, weight gain, acne, hair loss, tremor, ataxia, thyroid and renal abnormalities (diabetes insipidus), cognitive deficits.
Divalproex sodium	15 to 60 mg/kg/day	Sedation, nausea, vomiting, weight gain, tremor, hair loss, thrombocytopenia, liver toxicity, pancreatitis, polycystic ovary syndrome, increase testosterone.
Carbamazepine	10 to 20 mg/kg/day	Sedation, nausea, vomiting, ataxia, dizziness, liver toxicity, Stevens-Johnson syndrome, spinal cord suppression, hyponatremia.
Oxcarbazepine	8 to 10 mg/kg/day	Drowsiness, nausea, vomiting, headache, dizziness, sedation, bone marrow suppression.
Lamotrigine	25 to 300 mg/day	Dizziness, tremor, drowsiness, nausea, headache, skin rash, Stevens-Johnson syndrome.
Topiramate	25 to 300 mg/day	Dizziness, sedation, psychomotor retardation, cognitive change.
Atypical antipsychotics		
Risperidone	0.5 to 6 mg/day	Weight gain, sedation, increased salivation, gynecomastia, abdominal pain, nausea, hyperprolactinemia, dyslipidemia and diabetes mellitus.
Olanzapine	5 to 20 mg/day	Weight gain, dizziness, sedation, constipation, dry mouth, tachycardia, dyslipidemia and diabetes mellitus.
Quetiapine	25 to 600 mg/day	Drowsiness, sedation, dizziness, weight gain, dry mouth, constipation, tachycardia, dyslipidemia and diabetes mellitus.
Aripiprazole	2.5 to 45 mg/day	Drowsiness, nausea, vomiting, constipation, headache, dizziness.
Ziprasidone	40 to 160 mg/day	Activation symptoms, dizziness, sedation, nausea, dry mouth.

(68.5 vs. 24.0%), but had potentially serious metabolic effects (increased weight gain, body mass index, and prolactin level). There were no significant differences between lithium and divalproex sodium.[69]

In 2011, a systematic review of randomized controlled trials published from 1989 to 2010 on the pharmacotherapy of pediatric mania was published.[70] The authors found 29 open-label and 17 randomized clinical trials of antimanic agents conducted with 2,666 children and adolescents with BD. The main conclusions were that the best results were found in the double-blind studies of aripiprazole, olanzapine, quetiapine, and risperidone. Other mood stabilizers (lithium carbonate, divalproex sodium, and carbamazepine) had modest effects when used as monotherapy in the treatment of PBD. Negative findings were reported in controlled clinical trials of topiramate and oxcarbazepine. In an open-label study, adjunctive lamotrigine had antidepressant and antimanic effects in PBD. Additional clinical trials are required to assess the treatment efficacy for depressive episodes and for the comorbidity with ADHD, as well as to evaluate the safety and efficacy of psychotropic drugs in children younger than 10 years.

Currently, the only drugs approved by the FDA to treat BD in childhood and adolescence for manic episodes are risperidone and aripiprazole for children aged 10 years or older, and lithium for children over 12 years. For acute mania in BD type I, quetiapine for children older than 10 years and olanzapine for adolescents from 13 years have been also approved. No medication has been approved to treat all phases of PBD.[71]

The medication should be chosen according to scientific evidence, mood state, presence of psychotic or suicidal symptoms, aggressiveness, potential side effects, previous history of patient or parent drug response and the patients and their families' preference.[67] For instance, in a depressive episode, lithium could be chosen based on studies in adults, and lamotrigine as an alternative. The adjunctive treatment with SSRIs or bupropion may be required, but should be indicated with caution due to the risk of inducing manic switch. Maintenance time recommended for antidepressants is 8 weeks after depressive symptoms remission.[72] Although evidence-based data on the maintenance treatment for PBD is scarce, it has been recommended to maintain medication for 12 to 24 consecutive months after remission. The medication should be discontinued slowly, at a time of stability in the patient's life and carefully monitor for possible signs of instability or relapse.[72]

The main objectives of psychotherapy in the treatment of children and adolescents with BD are understanding the disease; increasing family engagement; teaching strategies for solving problems and dealing with symptoms; reducing prejudice led by the disease; and preventing further recurrences.[73]

The psychosocial interventions that have evidence-based efficacy are psychoeducation for parents and children,[74] family-focused therapy,[75,76] and CBT.[77] Psychoeducation aims to teach patients and families about the disorder and its treatment, especially the recognition of early signs of relapse. All the other modalities have a psychoeducational component. Family-focused therapy has the goals of improving family coping strategies, problem-solving skills and communication among family members. CBT focuses on problem-solving and teaching strategies to deal with harmful or negative thought patterns and behaviors. Recently, a brief motivational intervention for preventing weight gain among youth with BD initiating mood-stabilizing pharmacological treatment has been proposed.[78]

Final considerations

Despite the high burden and global impact of mood disorders, until recently those conditions were neither identified nor treated in child and adolescent population. In the last two decades, an impressive growth in research on the field has been accomplished. The early accurate identification and treatment of mood disorders can have direct and indirect impact on subsequent ages, reducing disability, costs and even mortality across the lifecycle. Preventive strategies for high-risk individuals, as well as cost-effectiveness analyses for better definition of public policies should be considered priorities in future research.

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