

## Mood disorders in children and adolescents: update for pediatricians

Antonio Carlos de Farias,<sup>1</sup> Mara Lucia Cordeiro<sup>2</sup>

### Abstract

**Objectives:** To review epidemiological and etiologic aspects of diagnosis and treatment of mood disorders (MDs) in children and adolescents, with a focus on essential information for pediatricians.

**Sources:** A literature search on MEDLINE, a review of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (text revision) (DSM-IV-TR), and a critical analysis of current diagnostic criteria and scientific evidence regarding the etiology of mood disorders were performed.

**Summary of the findings:** We identified diverging opinions for and against the proposition of using the same criteria used for adults, as listed in the DSM-IV-TR, for diagnosing mood disorders in children and adolescents. Although there has been much debate in the literature on this topic in the last decade, there remains a concern that there may be a significant under-diagnosis of cases due to differing methods. Several epidemiological studies conducted in pediatric populations using different criteria and methods make it difficult to interpret the data currently published. Although the field of neurosciences has achieved major advances in understanding these pathologies, additional investigations are needed to gain a clearer picture of how genetic and environmental factors interact and influence the origin and severity of the disease and the patient's response to treatment.

**Conclusions:** MDs have a high prevalence in childhood and adolescence and have major long-term impacts on sufferer's lives. There is a need to improve diagnostic criteria, adapting them for the pediatric population, with the objective of making it simpler for clinicians, particularly pediatricians, to make diagnoses and initiate early intervention. Advances in the area of epigenetics may aid in the development of new preventative, diagnostic, and therapeutic approaches.

*J Pediatr (Rio J). 2011;87(5):373-81.* Mental health, child behavior, mood disorders, depressive disorder, bipolar disorder, differential diagnosis, comorbidity, epigenetics.

### Introduction

Diagnosis of mood disorders (MDs) in children and adolescents has long been a much-debated topic, with some scientists arguing that diagnostic criteria specifically for this age group are needed,<sup>1,2</sup> while others consider that the criteria in the current American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (text revision) (DSM-IV-TR)<sup>1</sup> are adequate.<sup>3</sup> Clinical practice has shown that the way in which symptoms present varies as a function of age or, more specifically, as a

function of brain development stage and of the ramifications of this development on a child's cognitive and emotional capacity to perceive and express their feelings.<sup>4</sup> There is some consensus that the pathologies that make up the MD spectrum have been underdiagnosed,<sup>5,6</sup> which could indicate a need to make small adjustments to the criteria in the next (fifth edition) version of the DSM (DSM-V) in order to take into account the ways in which different symptoms present during the successive phases of child development.

1. MD. Mestre. Doutorando, Biotecnologia Aplicada à Saúde da Criança e do Adolescente, Faculdades Pequeno Príncipe, Curitiba, PR, Brazil. Pesquisador, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, PR, Brazil.

2. PhD. Pós-doutora, Neurobiologia, Brain Research Institute, University of California (UCLA), Los Angeles, CA, USA. Doutora, Medicina Molecular e Farmacologia, UCLA, Los Angeles, CA, USA. Neurocientista, UCLA, Los Angeles, CA, USA. Professora titular, Programa de Pós-Graduação em Biotecnologia na Aplicada à Saúde da Criança, Faculdades Pequeno Príncipe, Curitiba, PR, Brazil. Coordenadora, Pesquisas em Neuropsicofarmacologia, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, PR, Brazil. Professora adjunta, Departamento de Psiquiatria e Ciências Biocomportamentais, Escola de Medicina, UCLA, Los Angeles, CA, USA. Pesquisadora, Instituto Semel de Neurociência e Comportamento Humano, UCLA, Los Angeles, CA, USA.

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There is also a consensus on retaining certain criteria that are considered essential. For example, the criteria that symptoms are not secondary to other conditions (e.g. chronic use of prescription or illicit substances) or chronic systemic diseases (thyroid dysfunction, neoplasms, etc.), which are frequently associated with MD-like symptoms, but require a different treatment approach.

The main objective of this article is to review the treatment, clinical, epidemiological, and etiologic features of MDs that are most common in childhood and adolescence, particularly with respect to depressive disorders (DD) and bipolar disorders (BD), in order to provide pediatricians with a basis for early diagnosis and intervention.

## Diagnosis

The current model for classification and diagnosis of mental disorders is complex and open to criticism. Some authors consider the normative criteria to be inadequate and limited, both those listed in the International Classification of Diseases (ICD-10) and those listed in the DSM-IV-TR.<sup>7</sup> Psychiatric disorders are the result of interactions between many different factors and have multiple symptoms, which demands a classification format that is multiaxial.<sup>8</sup> Adherence to criteria based on the presence of a fixed number of specific symptoms may lead professionals who are unfamiliar with this diagnostic format to give undue weight to specific criteria, overvaluing them with respect to the true impact they have on the life of the person being assessed. Sometimes, a single symptom can have a greater impact on a person's functioning than the entire remaining constellation of symptoms listed for a given disease. Extending this format to the pediatric population, in which symptoms vary over development, introduces another complicating factor and raises the question of how should fixed criteria, based on fixed symptoms, be used in a population that is in constant transformation. Although they have their limitations, it is important to emphasize the importance of using the ICD-10 and the DSM-IV-TR<sup>1</sup> as normative parameters that can be constantly improved and are essential to scientific progress. Everything that has been discussed so far must be taken into account when assessing children suspected of having MDs.

Mood abnormalities are characterized by oscillations between states of depression and/or euphoria. The DSM-IV-TR<sup>1</sup> uses parameters to classify symptoms by type characteristics, intensity, duration and quantity. They can be classified as episodic (single occurrences) or may be included as part of a disorder if they are recurrent or chronic. Episodic forms of MDs are classified into the following groups: 1) major depressive episodes; 2) manic episodes; 3) mixed affective episodes; or 4) hypomanic episodes. Meanwhile, chronic or recurrent forms are classified into one of the following five groups: 1) DD (including major DD [MDD];

dysthymic disorder [DTD], and DD not otherwise specified [NOS]); 2) BD (including BD I, BD II, cyclothymic BD, and BD-NOS); 3) MDs due to a general medical condition; 4) substance-induced AD; and 5) MD-NOS.

The essential prerequisite for an accurate diagnosis is taking a detailed clinical history, including information related to development, the patient's own and familial disease history, family and interpersonal relationships, and lifestyle habits. It is also of fundamental importance to determine whether mood symptoms are having an impact on social and/or academic performance. During initial screening, behavioral inventories such as the Child Depression Inventory (CDI) and the Young Mania Rating Scale (YMSR) can be useful, as can structured and semi-structured psychiatric interviews such as the Diagnostic Interview Schedule for Children (DISC) and the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS), which are based on the criteria defined in the DSM-IV.<sup>1</sup> Clinical assessment should cover possible organic causes, such as, for example, endocrine dysfunctions, chronic systemic diseases, chronic infections, and other neuropsychiatric diseases. Furthermore, cultural, academic and social factors that will only emerge during the course of the interview also need to be taken into account. It is also very important to investigate possible comorbidities, since MDs are often combined with other neuropsychiatric disorders.<sup>9</sup>

## Forms of clinical presentation

MDD is characterized by recurrent depressive episodes that are not induced by chemical substances and are unrelated to any general medical condition. It is also important to rule out previous episodes of mania or hypomania, which are a defining characteristic of BD,<sup>1</sup> and enable differential diagnosis between DD and BD.<sup>1</sup> According to the DSM-IV-TR,<sup>1</sup> symptoms must occur over a minimum of 2 consecutive months, with a negative impact on several features of the sufferer's life. MDD is characterized by depressive moods that cause a loss of interest in play as well as social and academic activities. In preschool children the most common symptoms are as follows: somatic complaints such as headaches and abdominal pains, facial hypomimia, hair-trigger crying, irritability, aggression outbreaks, reduced or increased motor activity, and inappropriate behavior intended to attract the attention of parents or teachers. In elementary school-aged children, the most common symptoms are inattention or lack of concentration, lack of interest in activities previously considered enjoyable, spontaneous manifestations of worry or despair about life, worsening academic performance and provocative or challenging behavior including auto- or hetero-aggression. In adolescents, the symptoms just described can be accompanied by apathy, withdrawal, anger, despair, lack of interest, anxiety, low self-esteem, fear of the future and, in the most severe cases, suicidal behavior.<sup>10</sup> In some situations, adolescents will start to abuse medications,

alcohol or illicit drugs, mistakenly perceiving that this practice can relieve their depressive symptoms. Hence, it is very important that clinicians always investigate the possibility of MDD in adolescents that abuse alcohol or drugs.

A less severe form of depression than MDD, DTD is a chronic and frequent form of depression that is primarily observed in adolescents. It can occur in isolation or in combination with other behavioral disorders, of which attention-deficit hyperactivity disorder (ADHD) is one of the most common. According to the DSM-IV-TR,<sup>1</sup> DTD is diagnosed on the basis of one or more depressive episodes on the majority of days, affecting the greater part of the day and recurring for at least 2 years in adults, or at least 1 year in children.<sup>1</sup> It is characterized by irritability, bad moods, negativity and melancholic personality traits. Sufferers may also exhibit other symptoms related to appetite, drowsiness and lack of energy and concentration, but DTD is differentiated from BD by the absence of any prior history of hypomanic or manic episodes.

Diagnosis of BD in children is complicated by the fact that, rather than cycling between episodes of mania and depression over well-defined periods of time, as is observed in adults, childhood BD progresses with rapid and drastic mood swings, generally more than once a day, which makes it more difficult to identify the two-phase cycle. Manic symptoms observed in children include irritability, aggression, fits of rage, psychomotor agitation, grandiosity, reduced need for sleep, reduced appetite and hypersexuality.<sup>11</sup> In small children, hypersexuality may be absent and a premature and romanticized desire for the opposite sex may be observed instead. Despite these differences in forms of presentation and progression, the consensus is that the criteria listed in the current DSM-IV-TR for adults can be used for children and adolescents with minor changes,<sup>3</sup> although this presumption is debatable.

Some children present a clinical phenotype that is a little different from the classic descriptions of BD in childhood. Such cases may be chronic and non-episodic and involve heightened irritability, aggression and explosions of rage (temper tantrums). The current DSM-IV-TR classification does not provide guidance for diagnosing such children, but these children are likely to receive a BD diagnosis. Therefore, one of the proposals for the DSM-V is to add a new diagnosis that could include such children in a diagnosis termed temper dysregulation disorder with dysphoria (TDD).<sup>12</sup> The main reason for the addition of this disorder is that there are differences from BD in terms of presentation, sex distribution and prognosis of affected individuals.<sup>12</sup> This new classification will certainly generate heated debate and will merit its own literature review, as more scientific evidence emerges.

Adolescents and young adults have high suicide rates. The World Health Organization (WHO) has calculated that suicide is one of the top five causes of death among 15-

to-19-year-olds.<sup>13</sup> The prevalence of mental disorders in people who commit suicide has been calculated at 80 to 100%.<sup>11</sup> It is therefore essential that the initial consultation include a detailed suicide risk assessment covering: sex (boys are more likely to commit suicide than girls); family history (people with a family history of suicide are two to four times more likely to do the same); and comorbidities (suicide is more likely if BD is combined with personality disorders, substance-related disorders, ADHD or disruptive behavior disorders).<sup>11</sup> One characteristic that is observed in some children and adolescents and which should lead a physician to suspect suicide risk is intentional self-harming behavior. In stressful situations, these patients may cut themselves, burn themselves or pull out their own hair, eyelashes, nails, cuticles, etc. This type of behavior is different from attempting suicide because the person who does it knows that it will not result in death.<sup>14</sup> There is a proposal to include a designation for children exhibiting such behavior in the next DSM (DSM-V) in the category of "Disorders usually first diagnosed in infancy, childhood, or adolescence"; possibly under the name of "Non-suicidal self-injury disorder" (NSSI). The estimated prevalence of NSSI is 4% and its significant effects are not restricted to those related to negative feelings of guilt, but also include medical complications, such as, for example, infections.<sup>14</sup>

### **Differential diagnosis**

When dealing with children with suspected of having MD, it is important not to overvalue an isolated or episodic occurrence of a symptom or to consider such instances to be pathognomonic of a given disease. For example, psychomotor agitation, impulsivity, irritability, aggression, lack of motivation and emotional reactivity can all occur in MD, but can also be observed in individuals with other mental disorders, including ADHD, schizophrenia, disruptive disorders (conduct disorder, oppositional defiant disorder), substance abuse disorders, pervasive developmental disorders and personality disorders and can even be the result of systemic diseases.<sup>11</sup> Specifically with respect to BD and ADHD, symptoms of irritability, hyperactivity, sleep problems, distraction and impulsivity can be observed in both pathologies, whereas grandiosity, exalted mood and hypersexuality only occur in BD. Recent studies actually do suggest that symptoms of grandiosity, hypersexuality, accelerated thinking, increased energy and a reduced need for sleep are all associated with BD but not with ADHD.<sup>15,16</sup> Investigating these symptoms can therefore aid clinicians in differentiating between the two pathologies and, as a result, place them in a position to correctly direct the initial stages of treatment.

The presence of comorbid mental disorder should also be considered given that a large proportion of both MDD and BD cases can be combined with other psychiatric disorders,<sup>17</sup> particularly anxiety disorders, ADHD and disruptive behavior

disorders (oppositional defiant disorder, conduct disorder). It is also important to differentiate MDs from schizophrenia, since affective symptoms in childhood and adolescence can be prodromal of this pathology, and a manic state can be associated with acute psychosis.<sup>11</sup>

### **Epidemiology**

An analysis of the epidemiological features of mental disorders also touches on elements that are currently being debated. The difficulties involved with using full and detailed clinical assessments in epidemiological studies, which is an essential prerequisite for adequate diagnosis, mean that the majority have relied on simplified questionnaires or inventories based on the ICD or DSM criteria. Restricting diagnosis to these criteria allows for a real possibility that comorbidities will be overlooked, despite being a factor that has a major impact on prognosis and treatment.<sup>18</sup> The use of differing diagnostic methodologies has led to different prevalence rates and, as a result, variations in estimates of MD rates. While limited, such studies are and continue to be necessary, because they provide insights into distribution, possible factors of risk and protection and causes of mental diseases. Notwithstanding, epidemiological estimates vary depending on the method used for diagnosis and whether or not the method investigates the potential presence of comorbidities. Studies have indicated MDD prevalence rates to be in the range of 0.5 to 2.5%, with boys and girls being equally affected.<sup>19</sup> In adolescence, the rates vary between 2 and 8%, with twice as many girls being affected as boys.<sup>11</sup> A study conducted in the United States using the DSM-IV criteria, reported DTD prevalence rates of 0.9% in preschool children, 1.9% in schoolchildren and 4.7% in adolescents.<sup>20</sup> The authors of another review reported prevalence rates of 2% prevalence in children and of 4 to 8% in adolescents, with both sexes being affected equally in children, but twice as many girls being affected as boys among adolescents.<sup>21,22</sup> An epidemiological study of MDD in Brazil found prevalence rates of 0.4 to 3% in children and 3.3 to 12.4% in adolescents.<sup>23</sup> A study of a group of 100 adolescents found that 18% of those who had gotten into trouble with the legal system had a diagnosis of MDD, whereas in adolescents who had not been in trouble with the law the estimated rate of MDD was just 4%.<sup>24-26</sup> It has been shown that MDD prevalence can change depending upon regional, economic and personal factors such as the life stage of patients or even as a result of the methodology used to investigate it.

The prevalence rate of BD in childhood is difficult to measure and generally underestimated. The concept that this pathology can have onset at such an early age is relatively recent due to the debate on diagnosis discussed above. Diagnosis has increased recently,<sup>27-29</sup> but is still made on the basis of the same criteria listed in the DSM-III-R and

DSM-IV-TR for adults. A study of a sample of schoolchildren, aged 14 to 18 years, found a prevalence of types I and II BD of around 1%.<sup>27</sup> Another study investigated a sample of patients referred to a mental diseases clinic (a clinical sample) and reported a prevalence rate of 7.2% among patients less than 15 years old.<sup>30</sup> Prevalence also varies as a function of patient age and sex, the clinical course of the disease and the presence or absence of comorbidities.<sup>9</sup> In adolescence, BD affects more boys than girls, but in adulthood the incidence is equal for both sexes.<sup>31</sup> When BD has onset in childhood, it is associated with a worse prognosis,<sup>32</sup> in terms of academic and social problems, suicide risk and behavioral problems.<sup>33,34</sup>

### **Etiology**

MDs have multifactorial etiologies. There is complex interaction between genetic and environmental factors. The genetic contribution involves effects on the processes of anatomofunctional brain formation and development and on innate characteristics of the temperament. Environmental factors such as stress, significant losses, moving or changing schools, problems at school, interpersonal conflicts, drug or alcohol use, teenage pregnancy and sexual abuse generally have a triggering or prolonging effect on this condition.<sup>35</sup>

### **Genetic factors**

Some studies have shown that a family history of any type of AD confers an increased risk that a child will develop MDD.<sup>36</sup> Twin studies have further demonstrated an influence of genetic factors. Concurrence for MDD was observed in 64% of monozygotic and 24% of dizygotic twins examined. The rates for BD were 79 and 19%, respectively.<sup>37</sup> Wender et al.<sup>38</sup> investigated a sample of 71 adopted children with MDD and found that their biological parents had a prevalence of MDD that was eight times greater and a suicide rate that was 15 times greater than that of the adoptive parents.

Studies of genetic links have not yet identified the specific gene or genes that cause AD to occur. Among the genes that have been most intensively investigated, certain variations in a single gene or different genes (polymorphisms) have been detected, and those with the greatest association were related to serotonergic and dopaminergic neurotransmitter proteins.<sup>39-41</sup>

### **Neurobiology**

Studies examining the neurobiology of MDs have historically focused on dopaminergic, adrenergic and serotonergic neuronal circuits. The hypotheses relating MD with the availability of these neurotransmitters were highly simplified and were not based on structure and physiology, but rather on pharmacological observations. The initial observation that a medication used to reduce pressure (called

reserpine) exhibited adverse effects that included symptoms of depression led scientists to propose the "monoamine hypothesis." This model emphasized the view that depression may be the result of a deficiency in brain monoamine levels (dopamine and serotonin), while mania may be attributed to excessive activity of these neurotransmitters.<sup>42</sup> Basically, all antidepressants that act directly (e.g., tricyclics) or indirectly (e.g., monoamine oxidase inhibitors) increase the availability of these neurotransmitters in the synaptic cleft. More recent research has also demonstrated the efficacy of selective serotonin reuptake inhibitors (SSRIs), which could provide additional support for the monoamine hypothesis.<sup>43,44</sup> Clinical observations, however, continue to challenge the monoamine hypothesis. For example, when an antidepressant is administered, neurotransmitter levels have been observed to increase within a maximum of 3 hours, although the corresponding clinical improvement does not occur until 2 to 3 weeks later. Another issue is that, to date, no consistent and reproducible demonstration has been made of deficiencies in noradrenaline, serotonin and/or their metabolites in depressed patients, whether from urine, blood or cerebrospinal fluid.<sup>45</sup> Furthermore, evidence has shown that antidepressants are generally effective at improving affective symptoms in just 50% of patients.<sup>46</sup> As a result of the aforementioned inconsistencies, newer hypotheses have been postulated. Among them, one that has attracted much attention is the receptor desensitization hypothesis, which relates the delayed effect of antidepressants to changes in the number and sensitivity of monoaminergic receptors. Since the effect manifests later rather than earlier, researchers have speculated that depression could be explained by increased beta-adrenergic receptor sensitivity.<sup>47</sup> However, it is also possible that these changes may indicate a chronic adaptation of monoaminergic neurons, rather than a therapeutic mechanism,<sup>48</sup> and so this possibility is unlikely to be the only mechanism involved. Another possibility is that, since neuroreceptors are proteins, they can only increase or reduce in quantity via synthesis and breakdown, which are processes that require time, which could explain the delayed anti-depressive effect. Other *in vivo* and *in vitro* studies<sup>49-51</sup> have shown that mood stabilizers such as lithium and valproic acid can alter the expression of genes that are essential for catecholaminergic neurotransmission. When a neurotransmitter or a drug binds to the post-synaptic receptor, a cascade of intracellular events takes place that culminates in an alteration of the expression of nuclear genome genes.<sup>52</sup> With respect to mood stabilizers, some authors have proposed the hypothesis that the consequence of these events is an alteration in the synthesis of the molecular components essential for neurotransmission, which may in turn influence normal functioning of those areas of the brain that modulate mood.<sup>49,53</sup> This entire process, from drug-receptor binding to second-messenger cascade, altering gene expression, and synthesis of neurotransmitter-regulating proteins, takes time. Furthermore, proteins that

act in the nerve terminal must travel via axonal transport to neuronal terminals. Thus, this entire process could explain the delayed therapeutic effect of mood stabilizers. This cascade of molecular events may be the essence of the therapeutic effect of mood stabilizers.<sup>49,50</sup> Consistent with this hypothesis is the observation that several proteins that are essential for neurotransmission are synthesized in the neuronal cell body and transported to the terminal by "slow axonal transport" at a velocity of 0.2 to 2.5 mm/day.<sup>54,55</sup> All of these neurochemical and neurobiological phenomena suggest there is a more complex relationship between monoamines and MDs.

One study demonstrated that children with MDD exhibit increased growth hormone (GH) secretion during sleep.<sup>56,57</sup> Many different mechanisms have been linked to this observation, but two are of particular interest. The first is that nocturnal GH secretion causes a functional serotonin deficit due to the relationship between this system and the hypothalamic axis; and the second is that increased cholinergic activity can cause nocturnal GH secretion.<sup>58</sup>

Other mechanisms have also been suggested. For example, studies have linked MDD with stress and increased glucocorticoid activity<sup>59</sup> and there have been reports of morphologically abnormal hippocampi in MDD patients.<sup>60</sup> It is not surprising that there are several different theories and proposals regarding the neurobiological and neurochemical mechanisms involved in MDs given that the diseases in this spectrum exhibit a constellation of disruptive symptoms, ranging from cognitive/emotional problems and somatic problems, to dysregulation of the circadian rhythms of sleep and appetite.

### **Epigenetics**

Although little research has been conducted to date with the objective of evaluating epigenetic contributions to the origin of mental disorders, this new area of investigation could help explain several clinical features of mental disorders. For example, such studies could examine the following questions: Why is there disagreement for certain disorders between monozygotic twins? Why do some people respond differently to treatment? Why are MDD more prevalent among adult females than males? Answering these questions will likely involve more technologically sophisticated biotechnological to acquire knowledge regarding gene transmission, the effects of environmental variables on the origin, course of the disease, patients' response to treatment, and prognosis. Epigenetics deals with the reversible regulation of several genetic functions that do not necessarily alter the sequence of the DNA<sup>61</sup> and can take place through methylation of the DNA, modification of the proteins that package DNA with histone or through interference from RNA.<sup>62</sup> Depending on whether the cells affected are somatic or reproductive, the information may or may not be transmitted to succeeding generations.<sup>63</sup>

For example, DNA methylation takes place when a methyl group (-CH<sub>3</sub>) is added to a specific region of the DNA, the fifth carbon atom position of a residue of cytosine phosphate guanine (CpG), within CpG-enriched areas of the genome. These methylated residues interfere with the genomic transcription and translation machinery and often silence gene expression.<sup>64</sup> Indeed, it has been suggested that the majority of patients with fragile X syndrome have a cytosine guanine guanine (CGG) replication in the 5' untranslated region of the FMR1 gene of the X chromosome with more than 200 repetitions of the CGG. This abnormality causes hypermethylation and silences the gene as a result.<sup>65</sup> Perhaps, a similar mechanism could explain the way that some mental diseases are transmitted? There is no doubt that further research in this innovative area will be needed to decipher the etiological mysteries of MDS.

Our understanding of the molecular, chemical and genetic mechanisms of interactions between environmental and genetic factors is still incipient, especially in relation to MDs. Research into these aspects is very promising because it should contribute to more effective diagnosis and treatment and to the development of preventative measures that can readily be put into practice.

### **Psychosocial factors**

Evidence from epidemiological studies indicates that environmental factors such as exposure to stressful situations can trigger presentation of mental disorders, particularly MDD. Epigenetics may be able to explain the molecular mechanisms involved in this kind of emergence. For example, hormones fulfill a fundamental function in gene expression; an aberration (caused by stress, for example) can change hormonal homeostasis. In the specific case of stress, it has been shown that the hypothalamic-pituitary-adrenal (HPA) axis responds to critical situations, producing increased quantities of hormones such as cortisol, which can alter gene expression.<sup>66</sup> In a recent study<sup>67</sup> the impact of stress on the HPA axis was assessed in an experiment in which newborn rats were separated from their mothers for 3-hour periods from 2 to 14 days old. The results showed that this separation induced differences in both behavior and hormonal homeostasis and that these changes correlated with methylation at the promoter region of the glucocorticoid gene in the hippocampus. This study exemplifies how the environment, in the form of stressful factors, can have consequences for gene expression, a defining feature of epigenetics.

### **Treatment**

Treatment for MDs should be instituted as early as possible in order to prevent more complex situations, such as social isolation, school absenteeism and threats of suicide. According to the American Academy of Child

and Adolescent Psychiatry,<sup>68</sup> the ideal treatment is multidisciplinary, combining medication with psychotherapy and concentrating equally on dysfunctional symptoms and the psychosocial factors involved in the progression and exacerbation of the disease.

Psychological treatment with cognitive-behavioral techniques involving both the child and his or her family and focusing on behaviors that initiate and perpetuate depressive symptoms is essential.

Psychopharmacological treatments for MDD<sup>69</sup> and BD are similar to those for adults, but there are still uncertainties related to the appropriate treatment duration and which medications have the greatest efficacy with the lowest incidence of adverse secondary effects. One study showed that tricyclic antidepressants (e.g., imipramine, clomipramine) were no more effective than placebo.<sup>70</sup> Two SSRIs have been approved by the Food and Drug Administration (FDA) for pediatric use: sertraline and fluoxetine.<sup>71</sup> However, the FDA has recommended that care be taken with these medications since it was found that there was an increased incidence of suicide among adolescents who took them.<sup>72</sup> It is very important that pediatricians be aware that SSRIs should be preferred for MDD cases only after exhaustive work-ups have conducted to rule out BD, since these medications can induce manic states, which are a precipitating factor for attempted and actual suicide.

Lithium carbonate, carbamazepine, oxcarbazepine, valproic acid, disodium valproate, lamotrigine and topiramate have all been used to stabilize mood and improve irritability in cases of childhood BD.<sup>73</sup> However, the major problem with these drugs is the heterogeneous manner in which patients respond and the high incidence of side effects, particularly with lithium carbonate, which has a narrow therapeutic/toxic ratio, meaning that it must be monitored periodically in the bloodstream.<sup>74</sup> The FDA recommends that lithium be restricted to children over 12 years old.<sup>75</sup> Risperidone is an atypical antipsychotic that has also been approved by the FDA for treatment of acute phase mania in mixed state children and adolescents aged 10 to 17 or for irritability when there is comorbidity between BD and an autism spectrum disorder in children and adolescents aged 5 to 16.<sup>76</sup>

There is scientific evidence showing that electric shock treatment can be effective for some adult patients with DD that is refractory to currently available medications. However, this treatment modality has not been validated in children and adolescents.<sup>77</sup> Experiments with animal models have shown that the hippocampi of rats subjected to electric shock treatment exhibited a region of increased acetylation of the H3 histone protein in promoter-gene 3 and brain derived nerve growth factor (BDNF). These changes correlated with an increase in expression of the BDNF gene.<sup>78</sup> Though additional experiments are still needed, some authors have

reported that chronic treatment with antidepressants also increases BDNF expression.<sup>79-81</sup>

Neurostimulation techniques have also been investigated for treatment of depression in adults whose depression is refractory to pharmacological treatment.<sup>82</sup> Stimulation procedures may include noninvasive techniques such as transcranial stimulation (magnetic, electrical) or invasive techniques in which neurosurgery procedures are employed to implant electrodes into brain areas such as the cingulate gyrus and the anterior and subcallosal capsule and thereby conduct deep brain stimulation. The guiding hypothesis for such intervention is that the electrical impulses emitted can affect neuronal excitability, thereby reestablishing electrochemical equilibrium in critical areas detected by functional neuroimaging. Although these procedures are promising on the basis of the clinical improvements observed in patients in some longitudinal studies,<sup>82</sup> there is still a need to reproduce the results in randomized studies with control groups and also to validate them in pediatric populations.

## Conclusions

The most recent research with adults shows that the MD symptoms emerge at much earlier ages than was previously thought. It is necessary that pediatricians be capacitated and sensitized to recognize the symptoms of MD, since they are the professionals most often called on by children's families for guidance. The diagnostic criteria in the DSM-IV-TR for MD in children and adolescents need revision that takes into account evidence in the fields of normal and pathological neurodevelopment. The ideal format would be to list them separately for each specific age group, making it easier for pediatricians to arrive at an early diagnosis and make the necessary referrals for appropriate intervention.

We conclude that current scientific knowledge on the contribution of genetic, environmental and epigenetic factors in the etiology of MD has begun to reveal the complexity of these pathologies, which in turn illustrates the need for research that compiles detailed information on many different clinical, environmental, ethnic and molecular variables from large samples with and without these pathologies.

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Correspondence:  
Mara Lucia Cordeiro  
Instituto de Pesquisa Pelé Pequeno Príncipe  
Av. Silva Jardim, 1632  
CEP 80250-120 - Curitiba, PR - Brazil  
Tel: +55 (41) 3310.1036  
Fax: +55 (41) 3322.1446  
E-mail: mcordeiro@pelepequenoprincipe.org.br