Impact of bipolar disorder on selected areas of pediatric development: a research update

Manpreet K Singh, MD & Kiki D Chang, MD †

†Author for correspondence Stanford University School of Medicine, Division of Child and Adolescent Psychiatry, 401 Quarry Road, Stanford, CA 94305-5540, USA Tel.: +1 650 725 0956; Fax: +1 650 723 5531; E-mail: kchang88@stanford.edu

Pediatric bipolar disorder (BD) is a serious psychiatric disorder that has a significant impact on pediatric development. In this review, we examine peer-reviewed publications pertaining to childhood BD to determine the impact of BD on pediatric emotional, cognitive, and psychosocial development. Phenomenological, genetic, family, neuroimaging, and treatment studies revealed that BD may have long-term effects on emotional, cognitive, and psychosocial domains of pediatric development. The long-term developmental impact of BD may be profound and multidimensional. Additional longitudinal and biological studies are warranted to clarify the relationships among various predictors of poor outcome since they may have important diagnostic and treatment implications.

Keywords: development, emotion dysregulation, mania, neurocognitive, pediatric bipolar disorder, psychosocial

future medicine part of fsg

Bipolar disorder (BD) is a serious and common psychiatric disorder, affecting individuals across their lifespan. BD manifests with abnormalities in emotion regulation, cognition, and neurovegetative behaviors. The US population prevalence of BD in youth is estimated to be as high as 1% in children under 13 years, up to 2–3% in children under 19 years, and up to 5% in adolescents and young adults 12–29 years of age, based on epidemiological surveys conducted in adolescents and adults regarding age of bipolar symptom onset [1,2]. Therefore, 420,000–2,072,000 US children could suffer from bipolar I or II disorder [1]. Recent national trends suggest a 40-fold increase in the diagnosis of BD in youth in office-based settings over the last 10 years [3], and a fourfold increase in BD-related inpatient hospitalizations among adolescents [4]. This suggests a rapid increase in the clinical identification of this disorder in pediatric populations. Alternatively, these trends may also be due to overdiagnosis, high variability in how BD is diagnosed in clinical settings, or may reflect biases associated with increased academic and media interest for BD in the last decade. In addition, this recent increase in the diagnosis of BD in the US has not necessarily been observed internationally. This is possibly owing to researcher bias for or against the existence of BD in children, differing interviews used, or lack of trained child psychiatrists internationally [5].

While previously thought to begin primarily in late adolescence or early adulthood, recent data suggest that the onset of the illness begins before the age of 18 years in 50–67% of patients with BD [6,7]. The presentation and developmental course of pediatric BD vary with age and pubertal status [8–10]. However, regardless of developmental stage, increased risks for suicide attempts and self-injurious behaviors [11], recurrent syndromal or subsyndromal mood symptoms, co-occurring psychiatric disorders [12], family dysfunction [13], academic problems [14], and substance use [15] commonly occur in pediatric BD. Owing to these complexities, children and adolescents with BD require individualized and developmentally sensitive treatment approaches. Early identification and evidence-based treatment of pediatric BD are essential to prevent the chronicity of symptoms and associated complications.

Through an examination of the most recent literature, this review will provide a summary of certain factors in pediatric development that may impact and be influenced by BD, including emotional, cognitive, and psychosocial development. Specifically, we will examine whether there is evidence to support that:

1. BD symptom expression leads to emotion dysregulation, which impacts healthy brain development;
2. BD disrupts cognitive development and interferes with academic progress;
3. BD causes impairments in psychosocial development.

In this article, we will explore these hypotheses using data from clinical, epidemiological, family, neurobiological, and genetic investigations. We will also make suggestions for prevention, early intervention, and treatment of this

10.2217/17455111.1.2.199 © 2007 Future Medicine Ltd ISSN 1745-5111

disorder in pediatric populations, and will conclude with strategies for future directions for research in this field.

Methods

A literature search using NIH PubMed was conducted to identify peer-reviewed studies of children and adolescents with BD for the period of 1966 to October, 2007. The following terms were included in the search: 'bipolar disorder', 'mania', and 'development' with 'adolescents', 'children', 'youth', 'juvenile', or 'pediatric', followed by 'psychosocial', 'family', 'genetic', or 'neuroimaging'. References from identified articles were also reviewed to ensure that all relevant papers were included.

Results

We reviewed data from studies published from 1966–2007 that reported on the impact of BD on pediatric development. Most of these reports found variable developmental insults in children with BD. We examined specific data that support each of three hypothesized developmental domains affected by manifestations of BD. Selected studies to support these hypotheses are summarized in **Table 1**.

Hypothesis 1: BD symptom expression leads to emotion dysregulation, which impacts healthy brain development

Several lines of evidence have demonstrated that BD is a complex brain-based disorder that both impacts and is impacted by neuronal development. If BD is affected by certain processes in development, then it would follow that age and BD symptom expression are related. In addition, if BD impacts brain development, then there should be neurobiological evidence to support that there are brain structural or functional changes that occur in the presence of BD symptoms that otherwise do not occur in the absence of such symptoms.

BD is principally characterized by core disturbances in the regulation of emotion and attention. Symptoms produced by these disturbances manifest in variable ways in children, adolescents, and adults [16,17], which has resulted in significant debate regarding the validity of the diagnosis of BD in pediatric populations. As with other psychiatric disorders, BD is still diagnosed by the presence of a constellation of symptoms, qualifying it as a syndrome rather than a disease. Thus, as for adults, in the US children and adolescents are diagnosed using the Diagnostic and Statistical Manual Edition IV (DSM-IV) criteria for BD. Historically, symptom criteria for adult mood disturbances were applied to children, until it was recognized that children may manifest mood symptoms differently than adults. Developmentally relevant symptom presentations were considered in the update from DSM-IIIR to DSM-IV, when children were allowed to have irritability as a manifestation of depressed mood. Similar considerations for pediatric BD may be made in the forthcoming DSM-V, which will help make diagnoses easier and more relevant across all ages.

Children and adolescents with BD may present with symptoms of mania typical of adults, such as euphoria and grandiosity [18,19], hypersexuality [9], irritability [19,20], decreased need for sleep [21], and racing thoughts [22,23]. Many of these symptoms have been described in children with mania as young as 3 years of age [24,25]. The onset of puberty has been associated with increased hypersexuality in some studies [9], and in others a predominance of depressive symptomatology [26]. However, compared with adults, youths with BD often have a more chronic, relapsing course [6] and episodes lasting hours rather than days [27].

This apparent paradox of both chronicity and short episodes is a hallmark of pediatric BD, and has been described in several different studies examining the course of pediatric BD [27–30]. Developmental age-specific manifestations of mania become crucial when the boundaries between healthy emotional development and pathological and impairing mood states are less clear, as may be the case in preschool-aged children or adolescents undergoing puberty.

The chronicity of BD may blur clear distinctions between childhood and adult manifestations of this disorder, but this characteristic still supports the hypothesis that BD can impact development. One recent review synthesized retrospective evidence to support the notion that childhood BD is continuous with adult forms of BD [31], and that this chronic form of BD significantly impacts the long-term prognosis of those affected. In a recent report on 480 adults with BD, 14% experienced bipolar illness onset in childhood (≤12 years of age) and 36% in adolescence (13–18 years of age) [7]. Retrospective assessment in this study revealed that childhood or adolescent-onset BD was associated with delays to first treatment averaging more than 16 years, and was characterized by more episodes, comorbidities, and rapid cycling

Table 1. Evidence for impact of bipolar disorder on pediatric development.

Hypothesis	Evidence to support hypothesis	Selected studies to support hypothesis	Ref.
BD symptom expression leads to emotion dysregulation, which impacts healthy brain development	BD is principally characterized by core disturbances in emotion regulation and attention, which manifests differently across the lifespan	Strober *et al*. (1995)	[30]
		Perlis *et al*. (2004)	[6]
		Geller *et al*. (2004)	[28]
		Biederman *et al*. (2005)	[29]
		Birmaher *et al*. (2006)	[27]
		Geller *et al*. (2006)	[17]
		Masi *et al*. (2006)	[16]
		DelBello *et al*. (2007)	[32]
	Structural, functional and genetic data suggest that emotion dysregulation associated with BD interferes with healthy brain development	**Structural**	
		Blumberg *et al*. (2003)	[51]
		DelBello *et al*. (2004)	[37]
		Chang *et al*. (2005)	[50]
		Mills *et al*. (2005)	[49]
		Adler *et al*. (2007)	[38]
		Chemical/Functional	
		Blumberg *et al*. (2003)	[60]
		Cecil *et al*. (2003)	[48]
		Chang *et al*. (2003)	[54]
		Davanzo *et al*. (2003)	[56]
		Chang *et al*. (2004)	[46]
		Blumberg *et al*. (2005)	[59]
		Moore *et al*. (2007)	[57]
		Olvera *et al*. (2007)	[55]
		Genetic	
		Geller *et al*. (2004)	[68]
		Faraone *et al*. (2004)	[80]
		Etain *et al*. (2006)	[65]
		Geller *et al*. (2006)	[17]
BD disrupts cognitive development and interferes with academic progress	Cognitive deficits in BD occur regardless of illness state, medication exposure or ADHD and include deficits in working and verbal memory functions, attention and executive functioning	Dickstein *et al*. (2004)	[95]
		Doyle *et al*. (2005)	[101]
		Pavuluri *et al*. (2006)	[99]
		Rucklidge *et al*. (2006)	[102]
		Altshuler *et al*. (2007)	[96]
		Leibenluft *et al*. (2007)	[103]
	BD related cognitive impairment interferes with normal academic functioning and requires school intervention	Quackenbush *et al*. (1996)	[90]
		Lagace *et al*. (2003)	[91]
		Pavuluri *et al*. (2006)	[14]
BD causes impairments in psychosocial development	BD is associated with high rates of recurrent symptoms, hospitalizations, psychosis, poor medication adherence, increases in risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, which all interfere with psychosocial development	Wilens *et al*. (1999)	[15]
		Geller *et al*. (2000)	[108]
		Biederman *et al*. (2005)	[29]
		Birmaher *et al*. (2006)	[27]
		DelBello *et al*. (2007)	[32]
	Children and adolescents with BD have impairments in social cognition	McClure *et al*. (2005)	[111]
		Rich *et al*. (2006)	[112]

ADHD: Attention-deficit hyperactivity disorder; BD: Bipolar disorder.

than adult-onset BD [7]. Undetected symptoms of mania resulted in a poor long-term prognosis, where the illness was particularly refractory to treatment. The persistence of manic symptoms and their progressive resistance to treatment indirectly suggests either a continuing impact of illness on brain development or an intrinsically progressive brain disorder.

Longitudinal prospective studies examining the course of BD are useful to further examine the impact of BD on development. As also illustrated by retrospective studies of adults with BD, prospective studies of children with BD suggest that emotion dysregulation is a chronic and unremitting phenomenon that may impact aspects of healthy emotional development, including stability of mood states and symptoms [28–30] up to 7 years after onset of illness. A recent longitudinal study showed that 12 months after being hospitalized for a manic or mixed (manic and depressive) episode, only 39% of adolescents with BD had symptomatic and functional recovery [32]. In addition, only 35% of subjects reported full medication adherence in this study, and individual predictors of poor syndromic recovery included co-occurring attention-deficit hyperactivity disorder (ADHD), anxiety disorders, and disruptive behavioral disorders, along with nonadherence to psychotropic medications and lower socioeconomic levels [32]. There is as yet no published prospective study that has followed a pediatric sample with BD into adulthood to determine if pediatric BD is continuous with adult forms of BD. Nevertheless, other prospective studies in pediatric populations do demonstrate that factors influencing bipolar illness course may also impact emotional development. Predictors of symptomatic and functional outcomes may also be important targets for treatment.

The duration of continuous manic symptoms tends to be shorter in children and adolescents compared with adults, lasting hours rather than days [27]. Several researchers have described the phenomenon of ultradian cycling or switching between mania and depression multiple times a day in pediatric samples [27–29]. Owing to the transient nature of this phenomenon and the variability of definitions of episodes and rapid-cycling across ages [33], cross-sectional assessment may pose a challenge for clinicians, resulting in possible under- or misdiagnosis [34]. For this reason, researchers have tried to understand the neurobiological underpinnings of BD, as a means to clarify the often confusing phenomenology of BD and to overcome the subjectivity associated with parent and child reports [35]. The clearest evidence that symptoms of BD may impact development through disruptions in brain circuitry may be found in the neuroimaging literature. Research to date has implicated the anterior limbic network (ALN) [36–38], a network of interconnected brain regions including portions of the prefrontal cortex, as well as subcortical (striatum, thalamus, amygdala, and hippocampus), and cerebellar structures, in the neuropathophysiology of BD. Disruptions in the ALN appear to occur in cross-sectional assessments of adults and adolescents with BD, but there are limited longitudinal data to inform us of the impact of these disruptions on emotion regulation over time.

In healthy brain development, areas of the brain that perform more basic functions mature early, and areas for higher-order functions mature later. Specifically, by puberty, subcortical structures including the amygdala, basal ganglia, and thalamus have achieved structural and functional maturity [39,40], whereas the prefrontal cortex, which handles reasoning and other executive functions, is among the last brain structures to mature. A sequence of a preadolescent increase followed by a postadolescent decrease in cortical gray matter is also seen, as illustrated by structural [41] and functional MRI studies [42,43] in healthy humans. These studies demonstrate a shifting dependence from subcortical structures to prefrontal structures for the purpose of accomplishing goal-dependent behavior [44] and executive regulation of emotion. In addition, as both genetic and environmental factors contribute to brain development, recent structural neuroimaging studies in healthy twins suggest that development of late-maturing areas is less influenced by heredity than areas that mature earlier [45]. The developmental sequence described might explain why certain symptoms of BD may not be clinically evident prior to full expression and maturation of involved brain structures, and suggests vulnerabilities to abnormal development and additional targets for treatment.

Brain imaging studies in BD research have focused on structures presumed to be involved in emotion regulation, including the prefrontal cortex and limbic and paralimbic structures as represented in part in the ALN. There are two related pathways connecting these structures: the ventral-limbic pathway, which includes ventromedial prefrontal and orbital cortices and amygdala, thought to regulate emotion directly, and the dorsal subcortical pathway, which includes dorsolateral prefrontal cortex, thalamus and basal ganglia, which are thought to modulate emotion through cognitive processes. Dysfunction within the two pathways, interconnected by the anterior cingulate, has been hypothesized to underlie the neuropathophysiology of BD [46,47]. The cerebellar

vermis, amongst the latest of brain structures to reach peak volume and therefore particularly susceptible to environmental insults, has also been implicated in the pathophysiology of BD in structural and neurochemical studies [48,49].

Among the most consistent findings in pediatric BD and in contrast to adults with BD, is reduced amygdalar volume [37,50,51]. Reductions in this subcortical structure may be affected by such variables as medication exposure [50], number and severity of mood episodes, and substance use. Such factors may explain the variable volumetric outcomes in adults with BD. Reduced amygdalar volumes may lead to compensatory limbic hyperactivity manifesting as symptoms of BD, which with repeated mood episodes may lead to less emotion control, and possibly rapid cycling and treatment-resistant states, consistent with the natural progression of BD. The cerebellar vermis has also shown volume decreases in individuals with BD who have experienced multiple mood episodes [49]. Thus, brain structural changes can lead to BD symptom expression, which in turn has been proposed through a kindling mechanism to have neurodegenerative effects on the developing brain [52,53].

Data demonstrating macroscopic structural changes in select brain regions in BD imply underlying cellular and molecular dysfunction in BD that may also impact healthy brain development. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive *in vivo* neuroimaging method that yields biochemical data to quantitatively examine neuronal function in individuals with or at risk for BD. Children and adolescents with or at high risk for BD exhibit decreases in the healthy nerve cell marker N-acetyl aspartate [48,54,55], increases in myoinositol, a neuronal marker for cellular metabolism-related second messenger signaling pathways [48,56], and decreases in the excitatory neurotransmitter glutamate [57] in the dorsolateral prefrontal cortex, anterior cingulate cortex, and cerebellar vermis, relative to healthy controls. These neurochemical alterations raise the possibility that bipolar illness may be impacting brain development at a cellular level. However, it remains unclear whether any of these neurochemical changes occur prior to the onset of mania or depression, or if they are due to the differential neurochemical effects of prolonged affective symptoms or specific medications. Future longitudinal studies clarifying the neurochemical impact on the pathophysiology of BD are warranted.

As emotion regulation is a result of psychological processes that are mediated by integrated neuronal networks, functional MRI (fMRI) studies permit *in vivo* examination of various circuits involved in the regulation of emotion. Three recent studies have used fMRI to test hypotheses related to differential emotion regulation due to BD [46,58–60]. Dickstein and colleagues have shown that children with episodic BD illness have impaired attentional resource allocation with induced frustration and children who are severely mood dysregulated with a chronic nonepisodic course of illness have consistently impaired measures of early attention regardless of the emotional content of the task with which they are presented [58]. Another fMRI study by Chang and colleagues utilizing both a visuospatial working memory and an affective task involving viewing negative pictures showed increased activation of dorsolateral prefrontal cortex in pediatric subjects with BD [46]. Similar findings were reported by Blumberg and colleagues, who found significantly increased activation of the left putamen and thalamus in pediatric BD while subjects performed the color-naming Stroop task [60]. This study also showed a positive correlation between depressive symptoms and activation in the ventral striatum. In summary, these fMRI findings support the hypothesis that emotion regulation is abnormal in pediatric BD at the level of discrete prefrontal-limbic brain areas.

It should be noted that despite the recent growth in brain imaging studies in children with BD, it is likely that MRI will remain strictly a research tool in BD for perhaps the next decade. Existing MRI bipolar research has included subject samples that vary widely in age, gender, type of BD, comorbidity, and medication exposure, making it difficult to generalize results to all patients with BD. Moreover, variations in scanners and scanning protocols also make it challenging to combine the results of studies across sites, further limiting the generalizability of findings. There have also been no definitive findings specific to BD – such as a single gene or a signature functional activation pattern for pediatric BD. As such, neuroimaging in itself cannot currently be used to diagnose BD, and should rather be among a combination of biological investigations and clinical assessments used to determine the underlying pathophysiology of BD [35].

As alluded to earlier, regulation of emotion may have some inborn or genetic predeterminants. Twin and family studies have suggested high heritability of BD, approaching 78% concordance in

monozygotic twins [61], which is similar to schizophrenia and ADHD [62,63]. However, no single causative gene has emerged, suggesting that BD results from the effects of multiple genes, probably greater than 20 in many cases [64]. Efforts to isolate candidate genes have been complicated by the need for large sample sizes to detect small effects of individual genes. The European Collaborative Study of Early Onset Bipolar Affective Disorder performed a genome-wide search with 384 microsatellite markers in 87 sibling pairs ascertained through an early-onset BD type I proband (age of onset <21 years) and found the region 3p14 on chromosome 3 to have the most significant linkage using a nonparametric linkage analysis [65]. Other chromosomal locations currently being investigated include 17q24 and 18q12 [66].

Two promising candidate genes related to emotion and brain function include polymorphisms in genes that code for the serotonin transporter (5-HTT) and for brain-derived neurotrophic growth factor (BDNF). Although these polymorphisms have been associated with both depression and BD [67–69], allelic specificity has been found with certain bipolar phenotypes in children. For example, the presence of the s-allele on the 5-HTT gene may increase the chance of conversion from prebipolar to bipolar states and therefore contribute to BD development [70]. BDNF regulates neuronal survival during brain development [71] and may be involved in individual responses to antidepressants [72] and lithium [73]. Researchers have reported an association between a common functional single nucleotide polymorphism at codon 66 of the BDNF, called the val66 allele, and development of BD [69,74]. Furthermore, subanalyses of BD cohorts that were not originally found to be associated with the val66 allele reveal overtransmission of the val66 allele in patients with rapid cycling BD [75,76]. This finding is interesting given that the phenotypic expression of pediatric-onset BD often involves rapid-cycling between mood states [77]. In addition, the val66 polymorphism has been associated early in the onset of BD development [68], and with an earlier age of onset of BD [78]. The BDNF polymorphisms may affect the function of various brain areas involved with attention and emotion regulation. The relationships between candidate genes and BD phenotypes, medication responses, rapid-cycling subtypes and ages of onset illustrate the vulnerabilities to aberrant development.

Other potential gene candidates in the adult literature include catechol-*O*-methyl transferase (*COMT*), D-amino-acid oxidase activator (*DAOA*) and neuregulin (*NRG1*) [79]. Relevant to pediatric populations are genetic mechanisms that have been proposed to mediate an earlier age of BD illness onset. Faraone and colleagues reported on three areas associated with age of illness onset in a genome scan of 539 people from 97 families, on chromosomes 12p, 14, and 15q [80]. These and other data suggest the possibility of genetic anticipation in pediatric BD, where the appearance of a familial disorder in the next generation occurs at an earlier age and/or with greater severity than the previous generation [17,81,82]. Anticipation has been reported for various neurological conditions such as Fragile X [83] and monogenic Huntington's disease [84], but this hypothesis is more controversial for complex, polygenic illnesses such as BD [85–87]. Anticipation in monogenic illnesses is commonly due to unstable trinucleotide repeat expansions, but this explanation for anticipation has not been established in polygenic disorders due, in part, to the fact that cohorts with polygenic disorders are insufficiently observed over several generations [88]. In summary, although genetic mechanisms for BD may provide promise for early detection of youth at high-risk for the disorder [89], further studies across generations and examining associations between genetic risk and age of BD illness onset are warranted.

In combination, the above phenomenological and neurobiological research has demonstrated that BD is a brain-based disorder involving emotion dysregulation, which can be affected by, and in turn impacts, developmental trajectories in children. Given that BD is highly heritable, individuals are presumed to be vulnerable to this disorder at conception, yet peak symptom emergence generally occurs during adolescence. Knowing when during development certain brain structures are particularly vulnerable to environmental or genetic influences would aid in developing effective interventions for this disorder [45]. Future studies on children who have not yet developed emotion dysregulation but are at familially high risk for developing BD will further elucidate the predeterminants and developmental factors involved in symptom progression and long-term prognosis of this disorder.

Hypothesis 2: BD disrupts cognitive development & interferes with academic progress

Several studies have demonstrated that children and adolescents with BD have impairments in cognitive and academic functioning. Up to

30–40% of children and adolescents with BD have difficulties with math or reading, and some may even have lower verbal and performance IQs relative to children with ADHD or no disorder [14]. Onset of bipolar illness during adolescence has also been found to negatively impact academic achievement, on time for completion of high school and expected progression into college [90]. Compared with adolescents with major depression or no psychiatric illness, adolescents with BD may also have deficits in mathematical ability [91]. Such impairments may result in an increased need for and use of specialized educational services [92] and impact other societal domains, such as caregiver burden and work performance [93]. If BD disrupts cognitive development, there should be evidence that certain domains of cognition are impaired. In addition, it would be important to clarify if mood symptoms or other associated factors such as ADHD lead to cognitive impairments in BD. Finally, demonstration of brain structural or functional changes corresponding to cognitive dysfunction in BD would also provide evidence for BD-related impairments in cognitive development.

Studies have indeed reported specific patterns of impairment in pediatric BD, including deficits in executive functioning, working memory, verbal memory [94] and attention [95]. Recent studies in adults with BD have also demonstrated that long-term neurocognitive impairment is related to clinical and functional status [96–98]. However, these patterns have not yet been clearly linked to academic difficulties experienced by children with BD. The closest examination of this link was done in one study relating neurocognitive deficits to parent-reported academic difficulties [14]. This study showed that children (7–17 years old) with BD had poorer neurocognitive performance on executive functioning, attention, working memory, and verbal memory when they had a parent-reported history of reading or writing difficulties, regardless of the presence of ADHD.

Neurocognitive performance may or may not be related to the presence of mood symptoms or exposure to psychotropic medications. Certainly, frequent mood swings and adverse effects from medications used to treat BD can affect a child's attendance, concentration, motivation, and energy level in school. In a neuropsychological evaluation of children with BD, 28 unmedicated and 28 medicated, compared with 28 demographically matched healthy controls, impairments in attention, executive functioning, working memory, and verbal learning were found in subjects with BD, regardless of illness or medication state [99]. The cognitive deficits found in this study thus appear to be trait-like characteristics of BD [99], predating full bipolar development, suggesting the importance of screening for cognitive deficits in populations at risk for developing BD.

ADHD commonly co-occurs with pediatric BD, with rates of ADHD of up to 85% in young people with BD [100]. Neuropsychological studies examining whether cognitive impairment in pediatric BD is due to ADHD have shown mixed results. A study of 28 subjects with BD alone versus 27 subjects with BD plus ADHD found no difference between these two groups in neuropsychological function or academic difficulties [14]. Another study of 57 young people with BD compared with 46 healthy controls found that after controlling for the effects of comorbid ADHD, young people with BD showed deficits in sustained attention, working memory, and processing speed similar to adults with BD [101]. A third study comparing 12 subjects with only BD, 12 subjects with BD plus ADHD, 30 subjects with ADHD only, and 41 healthy controls, found ADHD-only and combined groups to be most impaired in the domains of processing and naming speed, working memory and response inhibition [102]. Apart from poorer working memory, there were no differences between the pediatric BD only and normal control groups [102]. The first two studies implicate BD-associated cognitive dysfunction independent of ADHD, while the third study suggests that the presence of ADHD symptoms may be an independent risk factor for cognitive impairment and resulting academic dysfunction in pediatric BD.

Structural and functional imaging data described in the previous section demonstrate why BD may lead to cognitive impairments independent of mood symptoms, exposure to medications, or ADHD. Interferences in attention, working memory, and higher-order executive functioning have been shown to occur in the presence of abnormalities in the anterior cingulate and dorsolateral prefrontal cortices. In addition, deficits in motor inhibition, which may be related to impulsivity and irritability in BD, have corresponded to decreased activation in the striatum and in the right ventral prefrontal cortex in unmedicated children with BD [103]. In combination, these

findings demonstrate that abnormalities in neural circuitry correspond to neurocognitive impairments in pediatric BD.

Regardless of the sample diagnostic variability of the studies described above, they all demonstrate that cognitive impairments are present in BD. A proper educational setting would be integral to the therapeutic plan for children with BD to facilitate academic progress. Parents and clinicians may collaborate with school personnel to determine the appropriate educational plan for the child with BD, with accommodations to be considered for transitions to new teachers and new schools, return to school from vacations and absences, and for any change in medication, which can all result in increased symptomatology and declining school performance. A determination should be made regarding whether an individualized educational plan (IEP) is needed, and if input from the clinician on the IEP team would be useful to develop an appropriate academic curriculum for the child. Further studies examining the therapeutic benefit of pharmacological and educational interventions to reverse cognitive impairments associated with BD are needed.

Hypothesis 3: BD causes impairments in psychosocial development

Twin and family studies suggest high heritability of BD, but as with other complex polygenic disorders and the fact that not all individuals with BD have a family history of BD, environmental factors must also play a role in the impact of BD on development. Family, social or financial stress, exposure to physical or sexual abuse, or co-occurring anxiety or substance abuse, are among many environmental factors that have societal impacts [104], and may leave affected individuals with significant impairments in various domains of functioning. Researchers who have explored the impact of psychosocial stress on the onset and progression of BD [105,106], have concluded that psychosocial factors are important targets for early intervention and intensive treatment. What follows is a discussion of the impact of untreated BD symptoms on a child's psychosocial development and the relevant neural circuitry that may be involved.

As discussed above, several studies, including the National Comorbidity Survey Replication [107], have demonstrated long delays between the onset and diagnosis and treatment of patients with BD. These delays may in part be due to stigma associated with psychiatric illness, or due to the challenges related to diagnosing developmentally dynamic symptom clusters. Many argue that despite such challenges, interventions should be aggressive owing to the high risk for poor outcome associated with early-onset BD [1,105]. Despite advancements in pharmacological interventions for BD, problems related to mood symptom relapse, medication nonadherence, and comorbid conditions such as substance abuse, continue to impact its long-term morbidity and mortality [28]. Adverse environments, such as low maternal–child warmth, high maternal–child tension, and high paternal–child tension have been found in families of children with BD [108]. Negative life events, sleep problems, and social dysfunction have also been associated with poor outcome for adults with BD [109].

Any sort of lifetime adversity may be relevant to the onset, recurrence, and progression of mood episodes, having cumulative or deleterious effects [105]. In a recent review of longitudinal studies of children and adolescents with an early onset of symptoms, Birmaher and colleagues provide evidence that BD significantly affects healthy psychosocial development in children [110]. BD is associated with high rates of recurrent symptoms and hospitalizations, and increases the risk for suicidal behaviors and completed suicide, substance abuse, and legal problems [110]. Combined with the dynamic and chronic course of symptoms, these factors may each interfere with healthy psychosocial development and could have potentially lethal consequences.

The marked psychosocial impairments described above have been, in part, examined experimentally using cognitive neuroscience and functional neuroimaging techniques. One paradigm studying measures of social cognition found that compared with healthy controls, children with BD had impaired awareness of appropriate language for various social situations and an impaired ability to accurately identify emotional facial expressions [111]. This study was followed up with an fMRI study demonstrating that cognitive misperceptions of emotional faces by children with BD (mean age: 14.2 years) correspond to increased brain activation in the amygdala–striatum–ventral prefrontal cortex circuit, with particularly significant activation in the left amygdala [112]. Misinterpretation of social cues and associated social dysfunction in BD are easily inferred when neutral facial expressions are viewed as hostile and fear-inducing.

Furthermore, the neural circuitry involved with social misperceptions here overlaps with the same limbic circuit implicated in emotion dysregulation described above.

Owing to the high risk for poor prognostic outcomes, psychosocial interventions to target problems that may be inadequately treated by pharmacotherapy alone may add benefit and lead to improved course and outcome.

Early intervention & prevention

With the realization that BD onset in childhood greatly impacts normal brain, emotional, cognitive, and psychosocial development, it may be particularly important to consider schemes for early intervention and prevention. By intervening early in the development of BD, the evolution to fully expressed BD in children and adolescents and its associated morbidities may be prevented [89,113]. For example, a particular group of children who might be targeted for early intervention are offspring of parents with BD, who have an increased risk for developing BD themselves. Such children are vulnerable to developing ADHD and mood disorders such as depressive disorders [114,115], or subthreshold BD, also referred to as a spectrum of milder bipolar disorders [27], which may precede or elevate the risk for developing bipolar I disorder. Individuals at high risk for developing BD may also be exposed to antidepressants or psychostimulants, which may precipitate, exacerbate [116], or accelerate the onset of mania [117]. Strategies designed to identify high-risk symptom complexes and prevent the full development of BD might result in avoidance of inappropriate interventions that may precipitate mania. Early identification and screening by primary care providers by directly eliciting symptoms of mania could prevent onset or progression of BD and result in more favorable long-term outcomes [34].

Unfortunately, there are only a few studies that have investigated the benefits of early intervention. Pharmacological studies for children and adolescents with nonbipolar I mood disorders and a familial risk for BD [118–122] aim to intervene using medications that may have neuroprotective or neurogenic properties. Although these studies vary methodologically, they represent important early efforts to intervene on children and adolescents at familial risk for BD that could improve their long-term outcomes. Additional pharmacological as well as psychotherapeutic studies in these high-risk populations are sorely needed.

Treatment: pharmacotherapy

Meanwhile, optimal clinical suspicion, an early diagnosis and adequate management of this chronic mood disorder may lessen its impact on the quality of life children and their families. There has been a recent surge in pharmocological data, which should aid in such management. Numerous case reports, open-label trials and chart reviews have described the effectiveness of various pharmacological agents for this population; however, only a few relevant double-blind placebo controlled (DBPC) studies have been published, and therefore off-label use of agents to treat pediatric BD and its associated disorders is common. Recently, the American Academy of Child and Adolescent Psychiatry (AACAP) published guidelines for the treatment of pediatric BD, endorsing lithium, divalproex and the atypical antipsychotics as optimal first-line agents [123]. In addition, these guidelines recommend that clinicians initiate medications that are already Food and Drug Administration (FDA) approved for the treatment of BD in adults. Lithium (for ages ≥12 years) and risperidone (for ages ≥10 years) are the only medications currently approved by the FDA for mania in children and adolescents, despite the fact that no large-scale DBPC studies of lithium or risperidone have yet been published in children and adolescents with BD.

Anticonvulsant therapies such as divalproex have documented efficacy in open-label studies of pediatric mania [124–126]. However, a recently completed large placebo-controlled study of extended-release divalproex for pediatric mania did not demonstrate efficacy for mania in children and adolescents [201]. Given the positive efficacy data in open-label studies, it is not clear whether this was a negative or a failed study. Possible reasons for study failure include short study duration, a different mechanism of action of the extended-release preparation compared with immediate-release divalproex for acute mania, or achievement of inadequate serum levels for the study population. Side effects associated with divalproex include weight gain, sedation, tremor, hepatotoxicity, thrombocytopenia, and polycystic ovarian disease. It is recommended that patients on divalproex be monitored for baseline liver function tests, complete blood counts, pregnancy status, and valproate levels at least every 6 months [123].

Atypical antipsychotics are beginning to demonstrate efficacy in large randomized controlled trials for acute mania in children and

adolescents. A DBPC study of olanzapine for children and adolescents with manic or mixed episodes (n = 161, ages 13–17 years), reported a significantly greater reduction in manic symptoms in patients taking olanzapine compared with those assigned to placebo [127]. Several large studies that have yet to be published have demonstrated positive results for other atypical antipsychotics in the treatment of pediatric mania. In a 3-week multicenter DBPC trial on the use of risperidone in children and adolescents (n = 166, ages 10–17 years) with bipolar I disorder, response rates with medication ranged from 59–63% separating from a 26% placebo response rate, thus demonstrating efficacy in decreasing manic or mixed symptoms [202]. Pediatric patients with mania also responded more favorably to quetiapine versus placebo ($p < 0.001$ with 600 mg dose) after a 3 week DBPC trial in pediatric mania (n = 277, ages 10–17 years) [128]. Finally, aripiprazole, a partial dopamine agonist, has also demonstrated efficacy in a 4 week DBPC trial of children and adolescents with bipolar I disorder in a manic or mixed episode (n = 302, ages 10–17 years) [129]. In summary, there are now several controlled trials supporting the efficacy of atypical antipsychotics in the treatment of acute mania in pediatric populations.

Efficacy data for atypical antipsychotics must be balanced by an understanding of the safety profiles of these medications. The incidence of extrapyramidal symptoms or neuroleptic malignant syndrome is often lower with atypical antipsychotics than with the conventional antipsychotics, but may still occur with atypical agents and should be monitored. These medications can cause significant weight gain in youth, with subsequent metabolic problems that may increase risk of Type II (non-insulin dependent) diabetes mellitus and metabolic syndrome [130]. When starting a child or adolescent on an atypical antipsychotic, it is recommended to obtain a personal and family history of obesity, diabetes, dyslipidemia, and cardiovascular disease [130]. Furthermore, clinicians should monitor blood pressure and fasting lipids and glucose beginning at the initial appointment, 3 months after the initial appointment, and then annually. A body mass index (BMI) should be calculated every 3 months. If there is relative weight gain of 5% compared with baseline weight during the first 3 months of treatment, consideration should be given to discontinuing or switching to another agent. Clinicians should also discuss lifestyle and dietary measures with patients and their families, and seek nutritional advice if needed [130]. In addition, oral antihyperglycemics, such as metformin, may also be effective to reduce the risk of weight gain and metabolic dysfunction in pediatric patients on atypical antipsychotics [131].

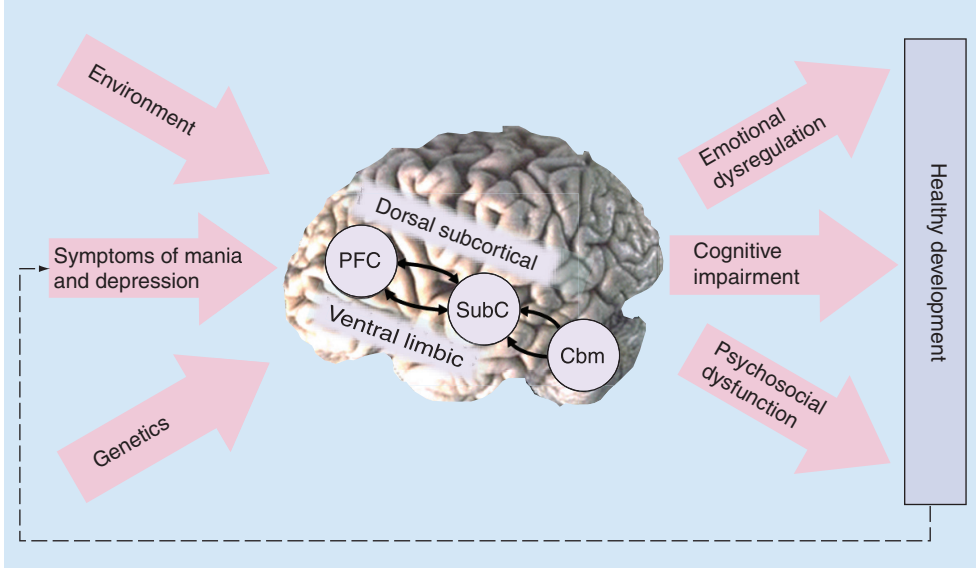
Although there are limited longitudinal clinical trials to determine the impact of pharmacological treatments on various domains of pediatric development, preliminary data have shown that adolescents can achieve syndromic recovery from bipolar illness 12 months following inpatient hospitalization [32]. Unfortunately, nonadherence to treatment is a clinical challenge and may limit the statistical power of treatment efficacy studies in pediatric BD [132]. Additional research on interventions targeting morbidities associated with BD such as suicidality, impaired functioning at school, and substance use is needed.

Treatment: psychosocial interventions

Psychosocial treatment alongside pharmacotherapy for children with BD has been recommended, a logical companion in light of the profound effects of a child's environment on brain development. Psychoeducation and the inclusion of cognitive–behavioral techniques and skills [133] to intervene on environmental factors have been proposed as important components of such psychosocial interventions for BD. Psychoeducation aims to teach patients and their families regarding BD, its course, prognosis and treatment, and can be performed by primary care physicians and mental health providers alike. The goal of cognitive–behavioral therapy (CBT) is to modify everyday thoughts and behaviors to influence emotions in a positive way. Psychoeducation and CBT can be used in individual or group therapeutic settings.

Various psychosocial interventions have been shown to be effective for adults with BD. Studies have shown that psychoeducation, bipolar-specific CBT, family therapy, and interpersonal social rhythm therapy may significantly improve the overall wellbeing, treatment adherence, and functioning of adults with BD [134]. Researchers have recently begun to study the effectiveness of adjunctive psychosocial interventions for children and adolescents with BD. Treatments currently being developed include MultiFamily Psychoeducation Groups [135], Family Focused Therapy for Adolescents [136], and a modified CBT combined with family therapy [137]. These have all shown initial success in decreasing symptom severity and preventing relapse in children with

Figure 1. Schematic representation of selected vulnerabilities and insults to healthy development in pediatric bipolar disorder.



The dorsal subcortical circuit includes the dorsolateral aspects of the PFC and SubC structures including the thalamus and basal ganglia. The ventral-limbic circuit includes the ventromedial prefrontal and orbital cortices (PFC) and SubC structures including the amygdala, hippocampus, striatum and thalamus. The Cbm also provides inputs into SubC structures via the cerebellar vermis.
Cbm: Cerebellum; PFC: Prefrontal cortex; SubC: Subcortical.

BD. Current clinical guidelines recommend that all individuals with BD receive a combination of both medication and psychotherapy [123,138].

Conclusion

The literature examined for this review demonstrates the profound impact of BD on emotional, cognitive, and social domains of pediatric development. All of these domains contribute to altering the developmental trajectories of children affected by BD, which, in turn, may further perpetuate bipolar symptoms in a cyclical fashion (**Figure 1**). During the past decade, investigators have made progress toward the goal of understanding the onset and course of BD in children and adolescents. Studies using diagnostic instruments and rating scales have validated the existence of BD in pediatric populations. Moreover, there has been initial progress in identifying specific biological markers for BD. Emerging data suggest that children and adolescents with BD are characteristically different from adults with BD, and in children BD is principally characterized by core disturbances in emotion regulation and attention. Structural, functional and genetic data suggest that the emotion dysregulation associated with BD may interfere with healthy brain development. Moreover, cognitive deficits in BD occur regardless of illness state, medication exposure, or ADHD, and include deficits in working and verbal memory functions, attention, and executive functioning. BD-related cognitive impairment may interfere with normal academic functioning and usually requires school intervention. Finally, BD is associated with impairments in social cognition, high rates of recurrent symptoms, hospitalizations, psychosis, an increased risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, which all interfere with psychosocial development. Early identification and combined pharmacological and psychosocial interventions are cornerstones for treating children with BD and improving their long-term outcomes.

Future perspective

Despite the progress in understanding the impact of BD in pediatric development, future longitudinal controlled studies are needed to examine the effects of specific mood states in individuals with BD, to develop rational treatment strategies in children with and at-risk for developing BD, and to determine the neurodevelopmental trajectories of this disorder. With additional investigations clarifying the developmental underpinnings of BD, patients may be more accurately diagnosed and more effectively treated.

In 10 years, the field will have progressed in obtaining data relating to the genetic, neurobiological, and environmental determinants and consequences of bipolar illness. More information regarding risk factors leading to the development of BD will be available as studies on genetically high-risk subjects prior to the onset of illness will be performed. Information pertaining to the efficacy and safety of pharmacological and psychosocial interventions to prevent and treat symptoms of emotion dysregulation will continue to grow, so that the clinical management of pediatric BD will be fully evidence-based and targeted to improve functioning and optimize healthy child development.

Financial & competing interests disclosure

Dr Singh does not have any current financial disclosures. Dr Chang has disclosed the following financial relationships: Consultant: Abbott, AstraZeneca, GlaxoSmith-Kline, Eli Lilly and Otsuka; Advisory Board: Abbott and Eli Lilly; Speakers' Bureau: Abbott and AstraZeneca; Research Support Recipient: AstraZeneca, Eli Lilly, Otsuka and National Institute of Mental Health. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Hypothesis 1: Bipolar disorder symptom expression leads to emotion dysregulation, which impacts healthy brain development.

- Bipolar disorder (BD) is principally characterized by core disturbances in emotion regulation and attention, which manifests differently across the lifespan.
- Structural, functional, and genetic data suggest that emotion dysregulation associated with BD may interfere with healthy brain development.

Hypothesis 2: BD disrupts cognitive development & interferes with academic progress

- Cognitive deficits in BD occur regardless of illness state, medication exposure, or attention-deficit hyperactivity disorder, and include deficits in working and verbal memory functions, attention, and executive functioning.
- BD-related cognitive impairment may interfere with normal academic functioning and requires school intervention.

Hypothesis 3: BD causes impairments in psychosocial development

- BD is associated with high rates of recurrent symptoms, hospitalizations, and psychosis, and increases the risk for suicidal behaviors and completed suicide, substance abuse and legal problems, which all interfere with psychosocial development.
- Children and adolescents with BD have impairments in social cognition.

Prevention & early intervention

- Studies on children at familial high risk for developing BD have shown improvements in symptoms with pharmacological treatment.

Treatment: pharmacological

- The Food and Drug Administration (FDA) has approved lithium (for ages ≥12) and risperidone (for ages ≥10 years) for use in pediatric BD.
- There are several emerging double-blind placebo-controlled trials demonstrating the efficacy of atypical antipsychotics for the treatment of acute mania in pediatric populations. However, children and adolescents should be carefully monitored for adverse reactions to these and other pharmacological agents.

Treatment: psychosocial interventions

- Psychoeducation provided by pediatricians and mental health providers may be helpful for families affected by BD.
- Cognitive–behavioral and family-focused therapies are important adjuncts to pharmacological treatments.

Conclusion

- During the past decade progress has been made to understand the onset and course of BD in children and adolescents.
- Specific biological markers for BD have been proposed and more developmentally sensitive diagnostic criteria are applied when making a diagnosis.
- Future research may elucidate the developmental trajectories of individuals affected by BD who are diagnosed and treated early.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Post RM, Kowatch RA: The health care crisis of childhood-onset bipolar illness: some recommendations for its amelioration. *J. Clin. Psychiatry* 67, 115–125 (2006).
2. Grant BF, Stinson FS, Hasin DS *et al.*: Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry* 66, 1205–1215 (2005).
3. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M: National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch. Gen. Psychiatry* 64, 1032–1039 (2007).
4. Blader JC, Carlson GA: Increased rates of bipolar disorder diagnoses among US child, adolescent and adult inpatients, 1996–2004. *Biol. Psychiatry* 62, 107–114 (2007).
5. Soutullo CA, Chang KD, Diez-Suarez A *et al.*: Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. *Bipolar Disord.* 7, 497–506 (2005).
6. Perlis RH, Miyahara S, Marangell LB *et al.*: Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol. Psychiatry* 55, 875–881 (2004).
7. Leverich GS, Post RM, Keck PE Jr *et al.*: The poor prognosis of childhood-onset bipolar disorder. *J. Pediatr.* 150, 485–490 (2007).

•• **Discusses predictors of poor outcome according to the retrospective reports of a sample of 480 adult outpatients with bipolar disorder.**

8. Geller B, Luby J: Child and adolescent bipolar disorder: a review of the past 10 years. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 1168–1176 (1997).
9. Geller B, Zimerman B, Williams M *et al.*: Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 10, 157–164 (2000).
10. Geller B, Zimerman B, Williams M *et al.*: Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. *J. Child Adolesc. Psychopharmacol.* 10, 165–173 (2000).
11. Goldstein TR, Birmaher B, Axelson D *et al.*: History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. *Bipolar Disord.* 7, 525–135 (2005).
12. Axelson D, Birmaher B, Strober M *et al.*: Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch. Gen. Psychiatry* 63, 1139–1148 (2006).
13. Romero S, Delbello MP, Soutullo CA, Stanford K, Strakowski SM: Family environment in families with versus families without parental bipolar disorder: a preliminary comparison study. *Bipolar Disord.* 7, 617–622 (2005).
14. Pavuluri MN, MM O'Connor, Harral EM *et al.*: Impact of neurocognitive function on academic difficulties in pediatric bipolar disorder: a clinical translation. *Biol. Psychiatry* 60, 951–956 (2006).

• **Investigates the degree to which neuropsychological deficits contribute to academic problems to aid in the recognition and intervention for school achievement difficulties in pediatric bipolar disorder. A sample of 55 children and adolescents with bipolar disorder with and without attention-deficit/hyperactivity disorder (ADHD) were tested with a computerized neurocognitive battery and standardized neuropsychological tests.**

15. Wilens TE, Biederman J, Millstein RB, Wozniak J, Hahesy AL, Spencer TJ: Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 38, 680–685 (1999).
16. Masi G, Perugi G, Millepiedi S *et al.*: Developmental differences according to age at onset in juvenile bipolar disorder. *J. Child Adolesc. Psychopharmacol.* 16, 679–685 (2006).
17. Geller B, Tillman R, Bolhofner K, Zimerman B, Strauss NA, Kaufmann P: Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *Arch. Gen. Psychiatry* 63, 1130–1138 (2006).

•• **Examines morbid risk of developing bipolar I disorder in first-degree relatives in a sample of prepubertal and early-adolescent bipolar I disorder phenotype, ADHD, and healthy control probands, as well as imprinting, sibling recurrence risk, and anticipation by controlled, blind, direct interview.**

18. Geller B, Zimerman B, Williams M *et al.*: DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J. Child Adolesc. Psychopharmacol.* 12, 11–25 (2002).
19. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS: Defining clinical phenotypes of juvenile mania. *Am. J. Psychiatry* 160, 430–437 (2003).
20. Wozniak J, Biederman J, Kwon A *et al.*: How cardinal are cardinal symptoms in pediatric bipolar disorder? An examination of clinical correlates. *Biol. Psychiatry* 58, 583–588 (2005).
21. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL: Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J. Affect. Disord.* 51, 81–91 (1998).
22. Carlson GA, Meyer SE: Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: complexities and developmental issues. *Dev. Psychopathol.* 18, 939–969 (2006).
23. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL: Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord.* 7, 483–496 (2005).
24. Luby J, Belden A: Defining and validating bipolar disorder in the preschool period. *Dev. Psychopathol.* 18, 971–988 (2006).
25. Luby J, Tandon M, Nicol G: Three clinical cases of DSM-IV mania symptoms in preschoolers. *J. Child Adolesc. Psychopharmacol.* 17, 237–243 (2007).
26. Schraufnagel CD, Brumback RA, Harper CR, Weinberg WA: Affective illness in children and adolescents: patterns of presentation in relation to pubertal maturation and family history. *J. Child Neurol.* 16, 553–561 (2001).
27. Birmaher B, Axelson D, Strober M *et al.*: Clinical course of children and adolescents with bipolar spectrum disorders. *Arch. Gen. Psychiatry* 63, 175–183 (2006).
28. Geller B, Tillman R, Craney JL, Bolhofner K: Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch. Gen. Psychiatry* 61, 459–467 (2004).
29. Biederman J, Faraone SV, Wozniak J *et al.*: Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J. Psychiatr. Res.* 39, 611–622 (2005).
30. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M: Recovery and relapse in adolescents with bipolar affective illness: a five-year

naturalistic, prospective follow-up. *J. Am. Acad. Child Adolesc. Psychiatry* 34, 724–731 (1995).

31. Chang K: Adult bipolar disorder is continuous with pediatric bipolar disorder. *Can. J. Psychiatry* 52, 418–425 (2007).
32. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM: Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am. J. Psychiatry* 164, 582–590 (2007).

•• **First published prospective report assessing symptomatic, syndromic, and functional outcomes and the effect of medication adherence on outcome in adolescents following initial hospitalization for mania.**

33. Geller B, Tillman R, Bolhofner K: Proposed definitions of bipolar I disorder episodes and daily rapid cycling phenomena in preschoolers, school-aged children, adolescents, and adults. *J. Child Adolesc. Psychopharmacol.* 17, 217–222 (2007).
34. Scheffer RE: Childhood onset bipolar disorder: a role for early recognition and treatment. *J. Pediatr.* 150, 459–460 (2007).
35. Chang K, Adleman N, Wagner C, Barnea-Goraly N, Garrett A: Will neuroimaging ever be used to diagnose pediatric bipolar disorder? *Dev. Psychopathol.* 18, 1133–1146 (2006).
36. Strakowski SM, DelBello MP, Sax KW *et al.*: Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch. Gen. Psychiatry* 56, 254–260 (1999).
37. DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM: Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord.* 6, 43–52 (2004).
38. Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, Strakowski SM: Voxel-based study of structural changes in first-episode patients with bipolar disorder. *Biol. Psychiatry* 61, 776–781 (2007).
39. Yakovlev PI, Lecours A: The myelogenetic cycles of regional maturation in the brain. In: *Regional Development of the Brain in Early Life.* Minowski A (Ed.). Blackwell, Oxford UK, 3–65 (1967).
40. Machado CJ, Bachevalier J: Non-human primate models of childhood psychopathology: the promise and the limitations. *J. Child Psychol. Psychiatry* 44, 64–87 (2003).
41. Giedd JN, Blumenthal J, Jeffries NO *et al.*: Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* 2, 861–863 (1999).
42. Luna B, Thulborn KR, Munoz DP *et al.*: Maturation of widely distributed brain function subserves cognitive development. *Neuroimage* 13, 786–793 (2001).
43. Rubia K, Overmeyer S, Taylor E *et al.*: Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci. Biobehav. Rev.* 24, 13–19 (2000).
44. Alexander GE, Goldman PS: Functional development of the dorsolateral prefrontal cortex: an analysis utlizing reversible cryogenic depression. *Brain Res.* 143, 233–249 (1978).
45. Giedd JN, Schmitt JE, Neale MC: Structural brain magnetic resonance imaging of pediatric twins. *Hum. Brain Mapp.* 28, 474–481 (2007).

•• **Examines the relationship between genetic and nongenetic factors on human brain anatomy during pediatric development using MRI applied to a large sample of healthy pediatric monozygotic and dizygotic twins.**

46. Chang K, Adleman NE, Dienes K, Simeonova DI, Menon V, Reiss A: Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. *Arch. Gen. Psychiatry* 61, 781–792 (2004).
47. Strakowski SM, Delbello MP, Adler CM: The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol. Psychiatry* 10, 105–116 (2005).
48. Cecil KM, DelBello MP, Sellars MC, Strakowski SM: Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. *J. Child Adolesc. Psychopharmacol.* 13, 545–555 (2003).
49. Mills NP, Delbello MP, Adler CM, Strakowski SM: MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am. J. Psychiatry* 162, 1530–1532 (2005).
50. Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A: Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 565–573 (2005).
51. Blumberg HP, Kaufman J, Martin A *et al.*: Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch. Gen. Psychiatry* 60, 1201–1208 (2003).
52. Post RM, Weiss SR: A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. *Mol. Neurobiol.* 13, 33–60 (1996).
53. Post RM: Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci. Biobehav. Rev.* 31, 858–873 (2007).
54. Chang K, Adleman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T: Decreased N-acetylaspartate in children with familial bipolar disorder. *Biol. Psychiatry* 53, 1059–1065 (2003).
55. Olvera RL, Caetano SC, Fonseca M *et al.*: Low levels of N-acetyl aspartate in the left dorsolateral prefrontal cortex of pediatric bipolar patients. *J. Child Adolesc. Psychopharmacol.* 17, 461–473 (2007).
56. Davanzo P, Yue K, Thomas MA *et al.*: Proton magnetic resonance spectroscopy of bipolar disorder versus intermittent explosive disorder in children and adolescents. *Am. J. Psychiatry* 160, 1442–1452 (2003).
57. Moore CM, Biederman J, Wozniak J *et al.*: Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: a proton magnetic resonance spectroscopy study of the anterior cingulate cortex. *J. Affect. Disord.* 99, 19–25 (2007).
58. Dickstein DP, Leibenluft E: Emotion regulation in children and adolescents: boundaries between normalcy and bipolar disorder. *Dev. Psychopathol.* 18, 1105–1131 (2006).
59. Blumberg HP, Donegan NH, Sanislow CA *et al.*: Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. *Psychopharmacology (Berl.)* 183, 308–313 (2005).
60. Blumberg HP, Martin A, Kaufman J *et al.*: Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. *Am. J. Psychiatry* 160, 1345–1347 (2003).
61. Smoller JW, Finn CT: Family, twin and adoption studies of bipolar disorder. *Am. J. Med. Genet. C. Semin. Med. Genet.* 123, 48–58 (2003).
62. Cardno AG, Marshall EJ, Coid B *et al.*: Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch. Gen. Psychiatry* 56, 162–168 (1999).
63. Coolidge FL, Thede LL, Young SE: Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: a preliminary investigation. *Dev. Neuropsychol.* 17, 273–287 (2000).
64. Craddock N, Dave S, Greening J: Association studies of bipolar disorder. *Bipolar Disord.* 3, 284–298 (2001).

65. Etain B, Mathieu F, Rietschel M *et al.*: Genome-wide scan for genes involved in bipolar affective disorder in 70 European families ascertained through a bipolar type I early-onset proband: supportive evidence for linkage at 3p14. *Mol. Psychiatry* 11, 685–694 (2006).
66. Tomas C, Canellas F, Rodriguez V *et al.*: Genetic linkage study for bipolar disorders on chromosomes 17 and 18 in families with a high expression of mental illness from the Balearic Islands. *Psychiatr. Genet.* 16, 145–151 (2006).
67. Caspi A, Sugden K, Moffitt TE *et al.*: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301, 386–389 (2003).
68. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr: Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am. J. Psychiatry* 161, 1698–700 (2004).
69. Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL: The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am. J. Hum. Genet.* 71, 651–5 (2002).
70. Howe M, Karchemskiy A, Yee J, Beenhakker J, Hallmayer J, Chang K: Prospective longitudinal study of offspring at risk for bipolar disorder: Three-Year Follow-up. In: *53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry.* San Diego, CA, USA (2006).
71. Poo MM: Neurotrophins as synaptic modulators. *Nat. Rev. Neurosci.* 2, 24–32 (2001).
72. D'Sa C, Duman RS: Antidepressants and neuroplasticity. *Bipolar Disord.* 4, 183–194 (2002).
73. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM: Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. *Neuropharmacology* 43, 1173–1179 (2002).
74. Sklar P, Gabriel SB, McInnis MG *et al.*: Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. *Mol. Psychiatry* 7, 579–593 (2002).
75. Green EK, Raybould R, Macgregor S *et al.*: Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. *Br. J. Psychiatry* 188, 21–25 (2006).
76. Muller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL: Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: Family-based association study. *Br. J. Psychiatry* 189, 317–323 (2006).
77. Geller B, Sun K, Zimerman B, Luby J, Frazier J, Williams M: Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. *J. Affect. Disord.* 34, 259–268 (1995).
78. Chang K, Howe M, Karchemskiy A, Wagner C, Beenhakker J, Hallmayer J: Effect of BDNF polymorphisms on age at onset and hippocampal volume in pediatric bipolar disorder. In: *53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry.* San Diego, CA, USA (2006).
79. Farmer A, Elkin A, McGuffin P: The genetics of bipolar affective disorder. *Curr. Opin. Psychiatry* 20, 8–12 (2007).
80. Faraone SV, Glatt SJ, Su J, Tsuang MT: Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. *Am. J. Psychiatry* 161, 625–630 (2004).
81. Visscher PM, Yazdi MH, Jackson AD *et al.*: Genetic survival analysis of age-at-onset of bipolar disorder: evidence for anticipation or cohort effect in families. *Psychiatr. Genet.* 11, 129–137 (2001).
82. Grigoroiu-Serbanescu M, Wickramaratne PJ, Hodge SE, Milea S, Mihailescu R: Genetic anticipation and imprinting in bipolar I illness. *Br. J. Psychiatry* 170, 162–166 (1997).
83. Sutherland GR, Haan EA, Kremer E *et al.*: Hereditary unstable DNA: a new explanation for some old genetic questions? *Lancet* 338, 289–292 (1991).
84. Ridley RM, Frith CD, Crow TJ, Conneally PM: Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *J. Med. Genet.* 25, 589–595 (1988).
85. Lange KJ, McInnis MG: Studies of anticipation in bipolar affective disorder. *CNS Spectr.* 7, 196–202 (2002).
86. Goossens D, J Del-Favero, van Broeckhoven C: Trinucleotide repeat expansions: do they contribute to bipolar disorder? *Brain Res. Bull* 56, 243–257 (2001).
87. O'Donovan M, Jones I, Craddock N: Anticipation and repeat expansion in bipolar disorder. *Am. J. Med. Genet. C. Semin. Med. Genet.* 123, 10–17 (2003).
88. Picco MF, Goodman S, Reed J, Bayless TM: Methodologic pitfalls in the determination of genetic anticipation: the case of Crohn disease. *Ann. Intern. Med.* 134, 1124–1129 (2001).
89. Chang K, Howe M, Gallelli K, Miklowitz D: Prevention of pediatric bipolar disorder: integration of neurobiological and psychosocial processes. *Ann. NY Acad. Sci.* 1094, 235–247 (2006).
90. Quackenbush D, Kutcher S, Robertson HA, Boulos C, Chaban P: Premorbid and postmorbid school functioning in bipolar adolescents: description and suggested academic interventions. *Can. J. Psychiatry* 41, 16–22 (1996).
91. Lagace DC, Kutcher SP, Robertson HA: Mathematics deficits in adolescents with bipolar I disorder. *Am. J. Psychiatry* 160, 100–104 (2003).
92. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB: Pediatric bipolar disorder: phenomenology and course of illness. *Bipolar Disord.* 6, 305–313 (2004).
93. Dore G, Romans SE: Impact of bipolar affective disorder on family and partners. *J. Affect. Disord.* 67, 147–158 (2001).
94. McClure EB, Treland JE, Snow J *et al.*: Memory and learning in pediatric bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 461–469 (2005).
95. Dickstein DP, Treland JE, Snow J *et al.*: Neuropsychological performance in pediatric bipolar disorder. *Biol. Psychiatry* 55, 32–39 (2004).
96. Altshuler LL, Bearden CE, Green MF, van Gorp W, Mintz J: A relationship between neurocognitive impairment and functional impairment in bipolar disorder: a pilot study. *Psychiatry Res.* (2007) (Epub ahead of print).
97. Gruber SA, Rosso IM, D Yurgelun-Todd: Neuropsychological performance predicts clinical recovery in bipolar patients. *J. Affect. Disord.* (2007) (Epub ahead of print).
98. Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P: Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disord.* 9, 93–102 (2007).
99. Pavuluri MN, Schenkel LS, Aryal S *et al.*: Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. *Am. J. Psychiatry* 163, 286–293 (2006).

100. Singh MK, DelBello MP, Kowatch RA, Strakowski SM: Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. *Bipolar Disord.* 8, 710–720 (2006).
101. Doyle AE, Wilens TE, Kwon A *et al.*: Neuropsychological functioning in youth with bipolar disorder. *Biol. Psychiatry* 58, 540–548 (2005).
102. Rucklidge JJ: Impact of ADHD on the neurocognitive functioning of adolescents with bipolar disorder. *Biol. Psychiatry* 60, 921–928 (2006).
103. Leibenluft E, Rich BA, Vinton DT *et al.*: Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. *Am. J. Psychiatry* 164, 52–60 (2007).
104. Jolin EM, Weller EB, Weller RA: The public health aspects of bipolar disorder in children and adolescents. *Curr. Psychiatry Rep.* 9, 106–113 (2007).
105. Post RM, Leverich GS: The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev. Psychopathol.* 18, 1181–1211 (2006).
106. Kim EY, Miklowitz DJ, Biuckians A, Mullen K: Life stress and the course of early-onset bipolar disorder. *J. Affect. Disord.* 99, 37–44 (2007).
107. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC: Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62, 603–613 (2005).
108. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K: Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *J. Am. Acad. Child Adolesc. Psychiatry* 39, 1543–1548 (2000).
109. Johnson SL, McMurrich S: Life events and juvenile bipolar disorder: conceptual issues and early findings. *Dev. Psychopathol.* 18, 1169–1179 (2006).
110. Birmaher B, Axelson D: Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev. Psychopathol.* 18, 1023–1035 (2006).
111. McClure EB, Treland JE, Snow J *et al.*: Deficits in social cognition and response flexibility in pediatric bipolar disorder. *Am. J. Psychiatry* 162, 1644–1651 (2005).
112. Rich BA, Vinton DT, Roberson-Nay R *et al.*: Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc. Natl Acad. Sci. USA* 103, 8900–8905 (2006).
- **Examined neural mechanisms mediating face processing in bipolar youths versus controls using event-related functional MRI. While viewing emotional aspects of faces (hostility, subjects' fearfulness) versus nonemotional aspects (nose width), youth with bipolar disorder perceived greater hostility in neutral faces and reported more fear when viewing them. Correspondingly, patients had greater activation in the left amygdala, accumbens, putamen and ventral prefrontal cortex when rating face hostility, and greater activation in the left amygdala and bilateral accumbens when rating their fear of the face.**

113. Lewinsohn PM, Seeley JR, Klein DN: Bipolar disorders during adolescence. *Acta Psychiatr. Scand. Suppl.* 47–50 (2003).
114. Strober M, Carlson G: Predictors of bipolar illness in adolescents with major depression: a follow-up investigation. *Adolesc. Psychiatry* 10, 299–319 (1982).
115. Geller B, Fox LW, Clark KA: Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *J. Am. Acad. Child Adolesc. Psychiatry* 33, 461–468 (1994).
116. Baumer FM, Howe M, Gallelli K, Simeonova DI, Hallmayer J, Chang KD: A pilot study of antidepressant-induced mania in pediatric bipolar disorder: Characteristics, risk factors, and the serotonin transporter gene. *Biol. Psychiatry* 60, 1005–1012 (2006).
117. Soutullo CA, DelBello MP, Ochsner JE *et al.*: Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. *J. Affect. Disord.* 70, 323–327 (2002).
118. Findling RL, Frazier TW, Youngstrom EA *et al.*: Double-blind, placebo-controlled trial of divalproex monotherapy in the treatment of symptomatic youth at high risk for developing bipolar disorder. *J. Clin. Psychiatry* 68, 781–788 (2007).
119. Geller B, Cooper TB, Zimerman B *et al.*: Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J. Affect. Disord.* 51, 165–175 (1998).
120. DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM: A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. *J. Clin. Psychiatry* 68, 789–795 (2007).
121. Chang KD, Dienes K, Blasey C, Adleman N, Ketter T, Steiner H: Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J. Clin. Psychiatry* 64, 936–942 (2003).
122. Saxena K, Howe M, Simeonova D, Steiner H, Chang K: Divalproex sodium reduces overall aggression in youth at high risk for bipolar disorder. *J. Child Adolesc. Psychopharmacol.* 16, 252–259 (2006).
123. McClellan J, Kowatch R, Findling RL: Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 107–125 (2007).
- **Reviews literature on the assessment and treatment of pediatric bipolar disorder, and provides guidelines that mirror those of an expert panel of child psychiatrists published 2 years earlier.**

124. Kowatch RA, Suppes T, Carmody TJ *et al.*: Effect size of lithium, divalproex sodium and carbamazepine in children and adolescents with bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 39, 713–720 (2000).
125. Findling RL, McNamara NK, Youngstrom EA *et al.*: Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 409–417 (2005).
126. Scheffer RE, Kowatch RA, Carmody T, Rush AJ: Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am. J. Psychiatry* 162, 58–64 (2005).
127. Tohen M, Kryzhanovskaya L, Carlson G *et al.*: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am. J. Psychiatry* 164, 1547–1556 (2007).
128. DelBello M, Findling R, Earley W, Acevedo L, Stankowski J: Efficacy of quetiapine in children and adolescents with bipolar mania. In: *American Academy of Child and Adolescent Psychiatry Annual Meeting.* Boston, MA, USA (2007).
129. Chang K, Nyilas M, Aurang C *et al.*: Efficacy of aripiprazole in children (10–17 years old) with Mania. In: *American Academy of Child and Adolescent Psychiatry Annual Meeting.* Boston, MA, USA (2007).
130. Correll CU, Carlson HE: Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 45, 771–791 (2006).

- **Report provides a selective review of the endocrine and metabolic effects of psychotropic medications in pediatric populations, with a focus on monitoring and management strategies.**

131. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA: A randomized double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am. J. Psychiatry* 163, 2072–2079 (2006).
132. Drotar D, Greenley RN, Demeter CA *et al.*: Adherence to pharmacological treatment for juvenile bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 831–983 (2007).
133. Lofthouse N, Fristad MA: Psychosocial interventions for children with early-onset bipolar spectrum disorder. *Clin. Child Fam. Psychol. Rev.* 7, 71–88 (2004).
134. Miklowitz DJ: An update on the role of psychotherapy in the management of bipolar disorder. *Curr. Psychiatry Rep* 8, 498–503 (2006).
135. Fristad MA, Gavazzi SM, Mackinaw-Koons B: Family psychoeducation: an adjunctive intervention for children with bipolar disorder. *Biol. Psychiatry* 53, 1000–1008 (2003).
136. Miklowitz DJ, George EL, Axelson DA *et al.*: Family-focused treatment for adolescents with bipolar disorder. *J. Affect. Disord.* 82(Suppl 1), S113–S128 (2004).
137. Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ: Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: development and preliminary results. *J. Am. Acad. Child Adolesc. Psychiatry* 43, 528–537 (2004).
138. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M: Treatment guidelines for children and adolescents with bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 213–235 (2005).

Websites

201. An outpatient study of the effectiveness and safety of depakote ER in the treatment of mania/bipolar disorder in children and adolescents. (2007). www.clinicaltrials.gov/ct2/show/NCT00067262
202. FDA approves risperdal for two psychiatric conditions in children and adolescents. (2007). www.fda.gov/bbs/topics/NEWS/2007/NEW01686.html