Bipolar disorder in children: assessment in general pediatric practice

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Purpose of review
Pediatricians are increasingly confronted with the mental health needs of children. Given the unanticipated role, well-described diagnostic guidelines and treatment protocols are essential: but often lacking. Identification of bipolar disorder in children, a condition which lacks diagnostic criteria consensus, presents a particular challenge. Despite this, it is generally regarded as a condition associated with considerable morbidity and mortality. Extended delays to treatment, typical for the condition, contribute to significantly reduced adult functionality.

Recent findings
Most children with bipolar disorder exhibit a subsyndromal course of illness. This has prompted many investigative groups to explore whether such a presentation is developmental or unique. Despite the ongoing debate, there has been a rapid increase in the rate of diagnoses. Concurrently, breakthroughs in neurology, neuroimaging, and genetics have called into question the existing conceptually based psychiatric constructs altogether. New research approaches which reflect these advances are more likely to lead to evidence-based diagnosis and treatment. Such an example is a novel phenotype called Fear of Harm (FOH). A new research perspective resulted in the unification of a broad range of symptoms from bipolar disorder as well as many of the co-occurring disorders. When considered as a whole, the syndrome maps on to a known neural pathway and has led investigators to a putative biomarker.

Summary
If given the right information and tools, pediatricians are uniquely positioned to interrupt the decline caused by mental illnesses. Importantly, the newly defined FOH syndrome includes clinical symptoms which are frequently first brought to the attention of pediatricians. Although these symptoms are not exclusive to the mood disorder, they could alert pediatricians to the need for further evaluation.

Keywords
behavioral phenotypes, early recognition, fear of harm, pediatric bipolar disorder, prodromal symptoms

FOREWORD

From time to time as the opportunity arises, Current Opinion in Pediatrics will invite and publish short, scholarly commentaries on subjects of importance to clinical pediatrics. The subjects of these commentaries may emerge from the pages of the journal as current controversies or from the world of child health as important new initiatives or breakthroughs not otherwise covered in recent issues. Suggestions for commentaries are invited.

Richard B. Johnston, Jr, MD, Editor

INTRODUCTION

Increasingly, pediatricians have been thrust into the role of gatekeeper, diagnostician, and treating physician for the mental healthcare of children [1]. A particularly difficult situation arises in regard to the presentation of bipolar disorder in children, a condition for which there is no diagnostic consensus but which is widely recognized by researchers and medical practitioners as a significant and common mental health disorder [2–4]. Early onset of the condition is associated with a worse course of illness [5,6■], including a high risk of suicide [3,7,8], increased likelihood for substance abuse [3,9], lability of mood state, and high psychiatric and medical comorbidity [10]. One study suggests that

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KEY POINTS

- Pediatric bipolar disorder, a condition for which there is no current consensus on the diagnostic criteria, is widely recognized by researchers and medical practitioners as a common, serious mental health disorder.

- Bipolar disorder which onsets in childhood confers a higher risk for suicide, psychosis, and violence, and has a more severe course of illness with higher rates of relapse, hospitalization, and psychosocial impairment than adult-onset bipolar disorder. It exerts a profound and costly impact on family and mental healthcare systems.

- The high rates of comorbid psychiatric conditions, attention-deficit disorder with hyperactivity (ADHD), oppositional defiant disorder, conduct disorder, autism spectrum disorder, obsessive-compulsive disorder, and other anxiety disorders, often confound diagnosis and result in significant delay in treatment, and a far more deleterious progression of the illness.

- A common, novel, evidence-based phenotype of bipolar disorder, termed FOH, has a developmental trajectory of symptoms and a rapid method of early assessment of prominent prodromal symptoms, which are often first brought to the attention of the pediatrician.

- Through screening and early identification of these prodromal symptoms, pediatricians can play a critical role in the impact of prognosis and outcome of this serious psychiatric disorder.

bipolar disorder in children may be the most impairing condition presented to the pediatrician [3].

Children as young as 3 years old have met full criteria for the disorder [11]. The early and frequent intrusion of symptoms during crucial periods deprives children of normal psychosocial development [12]. The toll is evidenced by the low scores on many quality-of-life dimensions [3,13,14].

Although many of these children are able to carry themselves well, novel or stressful situations or environmental stimuli can trigger overexcited, fearful, or rageful behavior. The aggressive behaviors, which include personal injury, suicide attempts, and serious physical attacks on others, particularly primary caretakers and younger siblings, make it difficult to manage such children at home and school.

Between 1995 and 2003, the rate of bipolar diagnoses among children increased 40-fold [4]. Although the increase may seem alarming, prior to 2001 there was no classification available for a subthreshold presentation of the condition: the profile most commonly exhibited by the children

[15–17]. Further, the 2003 prevalence rate is consistent with the rates of bipolar spectrum disorders in adults [18]. Nevertheless, inconsistencies with the application of the diagnosis perpetuate concerns over its appropriate designation [19▪,20▪].

Given the severity of the illness, it is important that concerns of overdiagnosis do not thwart early identification. Reports of adults whose onset is early in life indicate a more severe course of illness including increased suicidality, more severe mood lability and polarity, higher rates of comorbidity, a lower quality of life, and greater functional impairment [21–23,24▪,25]. Despite the severity of the symptoms associated with the early onset of bipolar disorder, delay in treatment is inversely correlated with the age of onset [23] and varying studies put average delay to diagnosis between 5 and 16 years [20▪,23,26]. When left undiagnosed, it may be an important risk factor for substance use disorders, early cigarette smoking, school failure, contact with the juvenile justice system, and increased suicide risk [8,15,27], not to mention continued negative neuronal changes [6▪]. Importantly, early identification and treatment have been shown to reduce the negative impact of the condition [13].

CRITICAL ISSUES IN THE DIAGNOSIS OF BIPOLAR DISORDER IN CHILDREN

Identification of bipolar disorder in childhood is challenged by high rates of co-occurring psychiatric conditions, which include attention-deficit disorder with hyperactivity, depression, oppositional defiant disorder, conduct disorder, obsessive-compulsive disorder, Tourette's syndrome, autism spectrum disorder, and other anxiety disorders [5,28–30]. Further complication derives from the apparent similarity between difficult, but developmentally normal, behaviors and those which may indicate pathology.

However, a fundamental obstacle to diagnosis derives from the very lack of consensus regarding the criteria for the condition in children [31]. The Diagnostic and Statistical Manual for Mental Disorders (DSM) has always described bipolar disorder as an episodic illness, the cardinal feature of which is mania [32]. According to the DSM, mania is either a persistently elevated mood or a persistently irritable mood with co-occurring elevated behaviors. In the disorder, well-defined episodes of mania alternate with periods of wellness and episodes of depression. Differentiation between bipolar I and bipolar II depends upon minimum duration of the manic episode: 7 and 4 days, respectively [33].

Yet, data has suggested a developmentally different, and typically subsyndromal, presentation of the disorder in young children [5,15,21,34]. Many

studies of bipolar disorder in children have observed numerous brief episodes of elated or irritable mood lasting hours to days or long sustained irritability without episodes [16,35]. While the pediatric presentation may seem quite different from the adult one, it should be noted that most adults who meet criteria for bipolar I or II spend up to half of their lives in a symptomatic but subsyndromal state [36–38]. While diagnostic focus has always prioritized the presence of episodic behavior, the importance of episodicity to the condition has never been proven. Additionally, approximately half of adults with bipolar disorder report an early onset of symptoms [5,22].

In 2001, the classification of Bipolar Disorder-Not Otherwise Specified (BD-NOS) was created as a 'working diagnosis' in order to further study children who are severely impaired from mood disturbance but who do not meet full criteria for bipolar disorder [39]. Although the BD-NOS classification has made possible the diagnosis, treatment, insurance coverage, and accommodation of many children, it has not led to any research breakthroughs which would unify opinion on the diagnostic criteria of mania in children and its role in bipolar disorder.

Broadly speaking, at this time most clinical investigators support the opinion that mania in childhood is associated with a chronic course of highly impairing affective symptoms, severely irritable mood, and a mixed presentation of depression, mania, and, often, psychotic features. It is also associated with comorbid substance abuse disorders, disruptive disorders, anxiety disorders, and particularly attention-deficit hyperactivity disorder [15,17,40]. Finally, bipolar disorder in children is recognized as an illness with strong genetic influence: early-onset bipolar disorder is associated with greater familial loading than adult onset and greater heritability than other psychiatric illnesses [5,41].

Regardless of the ongoing discussion regarding the criteria for pediatric mania, the recent decision to include a new classification called disruptive mood dysregulation disorder (DMDD) into the next iteration of the DSM, in effect, closes the debate. Investigators who delineated DMDD concluded that nonepisodic irritability is a developmental precursor to a depressive or anxiety disorder rather than to a bipolar disorder [42–44]. Accordingly, they proposed DMDD as an alternative classification for children who exhibit chronic irritability marked with explosive anger. DMDD has been described as a diagnostic home for a severely ill population of children [45] and has been introduced to the public as a corrective action which improves diagnostic accuracy.

An important consequence of the approval of DMDD is that it preserves the requirement of episodic mania for a bipolar diagnosis. Children with chronic irritability or rapid cycling of mood, who would currently qualify for a BD-NOS diagnosis, will no longer do so. Instead, they will be given a diagnosis of DMDD, and, as with depression and anxiety, first-line treatment would include serotonin reuptake inhibitors and stimulants. This treatment approach is contraindicated for a bipolar disorder, which requires initial mood stabilization [40,46,47].

A PARADIGM SHIFT IN PSYCHIATRIC DIAGNOSIS

In spite of the apparent diagnostic clarity purported by the approval of DMDD, recent shifts in psychiatric research suggest that delineation of the severe syndrome exhibited by so many children is far from resolved.

It is important to bear in mind that DMDD is a phenotype derived from, and justified by, its relationship to other DSM classifications and principles [44,45,48,49]. Despite the decades of familiarity and use, only a few of the disorders described in the DSM are validated. Further, high rates of comorbidity suggest that the nosology suffers from improperly defined boundaries [50,51▪].

Although DSM constructs have improved reliability within the field of psychiatry, their conceptual foundation has come under increasing scrutiny [6▪,50,52]. Leadership at the National Institute of Mental Health recently stated that the 'categories do not reflect the burgeoning knowledge base about genetics, neural circuits, and behavior relevant to mental disorders' [53].

Rather than continue to conceptualize disorders in the categorical manner of DSM, it has often been suggested that adherence to a dimensional perspective, in which overlapping symptoms, reflective of specific mental functions and biological substrates, would be more productive [50,52,54–60]. However, until recently, this type of analysis had not been achievable.

While the independent research community is just beginning a transformation in this direction, The National Institute for Mental Health has already launched a major effort which formalizes the approach. A new research initiative called the Research Domain Criteria Project moves away from research based upon DSM classifications and their underlying principles and toward 'new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures' [61▪].

A successful application of this approach can be seen in a 2004 study of obsessive-compulsive behavior. Like many other DSM disorders, obsessive-compulsive disorder is regarded as a heterogeneous condition. Factor-analytic studies by Mataix-Cols *et al.* [62] identified four temporally stable symptom dimensions which, when examined separately, revealed different activation patterns on functional MRI and mediation by relatively distinct components of frontostriatothalamic circuits. This study demonstrates that, when boundaries of a heterogeneous syndrome are in question, using a dimensional approach to arrive at more homogeneous subtypes for genotyping may be useful.

Undoubtedly, this transition will present challenges to diagnostic continuity. One can expect that the important standardization made possible by DSM will fall into a period of transitional chaos as the field learns what to let go of and what to use in its stead.

A DIMENSIONAL EXPLORATION OF BIPOLAR DISORDER: FEAR OF HARM

Like obsessive-compulsive disorder, bipolar disorder is a heterogeneous condition. Similar to the clarification that resulted in the Mataix-Cols study discussed above, delineation of dimensions of behavior led to the identification of a clinically homogeneous phenotype associated with specific physiological features and a particular neural pathway [63].

The new phenotype is called Fear of Harm (FOH). Research which delineated FOH relied upon a database of over 6500 symptom profiles of children at risk for, or with a diagnosis of, bipolar disorder [63]. Those profiles were collected through The Child Bipolar Questionnaire, an instrument which captures degree of severity data on 65 items drawn from DSM symptom criteria for mania, depression, and other conditions comorbid to bipolar disorder such as anxiety, sleep, and behavior disorders [64,65].

Early studies ($n = 1620$) clarified a trait termed 'fear-of-harm' in which, for children within the study population, fearful, aggressive obsessions associate with severe injury to self and others [66].

Concurrently, a series of factor-analytic studies was conducted using Child Bipolar Questionnaire items ($n = 2795$). This process produced clusters of symptoms which associate more often with each other than with others: each cluster describes a 'dimension' of behavior. One of those dimensions suggested, and was termed, FOH.

Concordance analysis to determine the heritability of the resulting dimensions ($n = 260$ sib-pairs and 260 non-sib pairs) found the FOH dimension to

Table 1. Key factors of the fear of harm phenotype – symptoms derived from Child Bipolar Questionnaire

Aggression (Territorial)[a]
Q32) Has irritable mood states
Q44) Is intolerant of delays
Q45) Relentlessly pursues own needs and is demanding of others
Q46) Is willful and refuses to be subordinated by others
Q47) Argues with adults
Q48) Is bossy towards others
Q49) Defies or refuses to comply with rules
Q50) Blames others for his/her mistakes
Q5I) Is easily angered in response to limit setting
Q52) Lies to avoid consequences of his/her actions
Q53) Has protracted, explosive temper tantrums
Q54) Has difficulty maintaining friendships
Q55) Displays aggressive behavior towards others

Harm to Self and Others
Q56) Has destroyed property intentionally
Q57) Curses viciously, uses foul language in anger
Q58) Makes moderate threats to others or self
Q59) Makes clear threats of violence to others or self
Q60) Has made clear threats of suicide
Q61) Is fascinated with gore, blood, or violent imagery

Anxiety
Q I) Displays excessive distress when separated from family
Q2) Exhibits excessive anxiety or worry

Self-Esteem
Q37) Complains of being bored
Q40) Experiences periods of self-doubt and poor self-esteem
Q41) Feels easily criticized and/or rejected
Q42) Feels easily humiliated or shamed

Psychosis/Parasomnias/Sweet Cravings/Obsessions (PPSO)
Q62) Has acknowledged experiencing auditory and/or visual hallucinations
Q8) Has night terrors and/or nightmares
Q 9) Wets bed
Q I0) Craves sweet-tasting foods
Q63) Hoards or avidly seeks to collect objects or food
Q64) Has concern with dirt, germs, or contamination

Sleep/Arousal
Q3) Has difficulty arising in the AM QS) Has difficulty settling at night
Q6) Has difficulty getting to sleep
Q7) Sleeps fitfully and/or awakens in the middle of the night

[a]The term territorial is used to describe the nature of aggressive symptoms associated with this factor; typically defensive in reaction to limit setting, deprivation or perceived threat as opposed to other forms of aggressive behaviors.

be considerably more significant than all the other dimensions examined, including mania and depression [67].

Identification of this salient, clinically important, and evidently highly heritable trait prompted further analysis in order to delineate the full-dimensional profile associated with it. The dimensions, and the symptoms which describe them, can be seen in Table 1. This profile presents a unique behavioral syndrome that has aptly been named the FOH phenotype [63].

The utility of this research approach, in which delineation of a syndrome is anchored to a highly heritable trait, is borne out by the fact that it quickly led investigators to an evolutionarily ancient and important neuropathway in the brain, one which is involved in the interaction of homeostatic systems. The disruption of this pathway accounts for the broad range of symptoms of the phenotype [63]. From this information, treatment selection followed and the continued exploration of a putative biomarker regarding thermoregulation continues. To date, a pilot study ($n = 50$) which uses that treatment has demonstrated a significant reduction or abolishment of symptoms primary to the illness in 96% of the participants [68▪▪].

FEAR OF HARM: BEHAVIORAL CHARACTERISTICS

Analysis indicates that, among children at risk for, or with a community diagnosis of, bipolar disorder, the population divides into thirds of no-FOH, low-FOH, and high-FOH. Compared with children in the no or low FOH groups, children with high FOH have significantly higher indices of severity of mania and depression [63], and clearly fall within the domain of classical manic depression [69,70]. Course of illness analysis indicates that presence of the FOH trait associates with the most severe form of the illness, including early age of onset, frequent hospitalizations, significant social impairment, and school problems [63].

In addition to the symptoms commonly associated with bipolar disorder, Table 1 reveals the many symptoms included in FOH which are either currently associated with conditions comorbid to bipolar disorder or not previously associated with any mental disorder.

Although some important features of the phenotype are difficult to discern within the brief window of a pediatric consultation, other prominent symptoms, such as sleep disturbances, attentional difficulties and aggression, or anxiety, are commonly first brought to the attention of a pediatrician. As these symptoms have not previously been

identified as parts of a single syndrome, it is likely that they have always been considered separately. As such, they would be regarded as developmental concerns or primary symptoms of other psychiatric disorders. Medications appropriate for those diagnostic decisions often delay proper diagnosis and may exacerbate the mood disorder, both of which lead to poorer outcome [15,30].

The intention of this article is to alert the members of the pediatric community that the common complaints described below may represent features of a specific syndrome. Suspicion should increase if there is a known family history of mental illness, particularly mood disorders and alcoholism.

FOH: SLEEP CYCLE PROBLEMS

Sleep and arousal disturbances are prominent features of FOH: particularly delayed sleep-onset, sleep fragmentation, and morning sleep inertia [71,72] (P. Murphy, unpublished observation). Children suffer frequent, recurrent nightmares that often contain images of gore and mutilation and themes of pursuit, bodily threat, and parental abandonment. Other symptoms include both hypnogogic and hypnopompic hallucinations and parasomnias such as night terrors, bruxism, and enuresis: some of the most common symptoms related to disturbances of sleep and arousal presented to a pediatrician [63].

This set of symptoms is indicative of both primary sleep problems and sleep perturbations secondary to altered circadian and ultradian rhythms of sleep, wakefulness, and temperature [73–76]. Preliminary data indicate anomalies in circadian and temperature rhythms which could explain the difficulties with sleep onset and offset, and may ultimately prove to be a biomarker for the condition (P. Murphy, unpublished observation).

FOH: ANXIETY AND AGGRESSION

Anxiety and inappropriate aggression are other common parental concerns and defining characteristics of the FOH phenotype. These behaviors showed up repeatedly in important dimensions throughout the series of factor analyses (Table 1). The dimension of territorial aggression characterizes the behavior which is aggressive, defiant, or explosive, but, importantly, which is defensively triggered in reaction to limit setting, deprivation, or perceived threat. The FOH dimension includes items of suicidal and overt threat, use of foul language, and destruction of property as well as a fascination with gore and violent imagery. Finally, the anxiety dimension is associated with severe separation anxiety and worry.

FOH: ATTENTION DEFICITS

Distractibility or difficulty sustaining attention is a common impetus for parents to seek treatment for their children who are performing poorly in school. Although often diagnosed under the rubric of attention-deficit disorder (with or without hyperactivity), these symptoms are also common to bipolar disorder or FOH. Misdiagnosis can lead to treatments that are often contraindicated and may worsen the course of illness.

Recent research [77] has found that the following neuropsychological measures distinguish the groups:

(1) Wechsler Intelligence Scale for Children: children with bipolar disorder (FOH) have a higher Verbal IQ than Performance IQ. This is not a trait feature of attention-deficit disorder.
(2) Conners' Continuous Performance Test:
   (a) Children with bipolar disorder (FOH) demonstrated impaired preparatory processes, a significant conservative response bias, and poor speed of performance on sequenced grapho-motor acts.
   (b) Children with attention-deficit disorder performed poorly on repetitive motor tasks.

FOH: THERMOREGULATORY SIGNS AND SYMPTOMS

Although not listed in Table 1, other symptoms which could help the pediatrician to recognize the presence of FOH include physiological symptoms and behaviors consistent with body temperature dysregulation, a deficit which investigators believe to be central to the disorder and likely derives from difficulty dissipating heat from the body. Children with FOH often complain of being too 'hot'. Mothers may have noted this from infancy and commonly describe their children as being 'like little furnaces'. Common observations include the pinna of the ears turning beet red, pronounced facial flushing, profound sweating before and during sleep, sweating despite neutral ambient temperatures, and significant tolerance to the cold exemplified by under-dressing in cold weather [63].

FOH: HOW TO DIAGNOSE IT

The FOH syndrome is more specifically delineated than most other classifications. Therefore, simple reference to the list of dimensions provides rather clear guidance to its identification. In particular, the four dimensions of territorial aggression, harm to self and others, self-esteem, and psychosis/ parasomnias/sweet craving/obsessions correctly predicted the FOH group with 96% accuracy [63]. Additionally, familiarity with the research articles that describe the phenotype (Refs. [35–39] below) will sharpen awareness of its presence.

Finally, because the FOH dimensions derive from Child Bipolar Questionnaire items, the instrument itself is uniquely suited to screen for the presence of the condition. More information about the use of this instrument can be found at http://www.jbrf.org/the-child-bipolar-question-naire-for-families-use/.

CONCLUSION

Bipolar disorder is increasingly recognized by researchers and medical practitioners as a significant pediatric mental health concern. However, the lack of consensus regarding its presentation in children has obstructed early diagnosis and intervention. The authors suggest that the difficulties which surround the confusion and controversy are directly related to the underlying inadequacies of the current diagnostic nosology to provide evidence-based descriptions of mental disorders generally and bipolar disorder specifically. Under such a system, variations which challenge the longitudinal consistency of previously agreed upon diagnoses are bound to erupt.

Seen through a new research perspective that employs a dimensional analysis, a clearer view of the illness emerges. Importantly, it includes symptoms which are often brought to the attention of a pediatrician or general practitioner and which can readily be identified within a consultation setting. When armed with the knowledge that these symptoms may represent the elements of a single syndrome, members of the pediatric community could make a profound contribution to the intervention of this life-altering condition which exerts such a substantial burden on the individual, the family, and society.

Conflicts of interest

Dr Papolos is a nonvoting member of the Board of Directors of JBRF. He receives royalties from Broadway Books for the book, 'The Bipolar Child'. He has not received consulting fees or support from pharmaceutical manufacturers in the last 4 years.

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