IRRITABILITY IN PEDIATRIC MANIA

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Summary

Although the study of pediatric bipolar disorder (BPD) and childhood mania is of increasing interest, clinical criteria for diagnosing the illness in children continue to be debated. The role of irritability is central to this controversy. Of particular importance is whether irritable mood (as opposed to euphoria/grandiosity) is sufficient to diagnose pediatric mania, and if mania is characterized by episodic (as opposed to chronic) irritability. This article discusses these issues in an effort to clarify the associations among irritability, mania, and pediatric BPD. In addition, although the term irritability is used frequently, there are few clearly operationalized definitions of irritability and few validated and reliable measures to assess it. We also discuss the pathophysiology of irritability and provide a developmental perspective. Finally, we discuss pharmacological and psychotherapeutic strategies for treating irritability in pediatric mania.

Key Words: Irritability – Mania – Bipolar Disorder – Mood Dysregulation – Children – Frustration

Declaration of interest: None

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The role of irritability in pediatric bipolar disorder (BPD) is, in many ways, central to the controversy surrounding the appropriate diagnosis of this illness. While epidemiological studies document a low prevalence of childhood BPD (Costello et al. 1996, Lewinsohn et al. 1995), clinical studies suggest that pediatric BPD may be a significant problem among children presenting for care (Wozniak et al. 1995a). Rates of clinical diagnosis of BPD in youth are increasing rapidly (Youngstrom et al. 2005), and pediatric BPD is of growing interest to the general public and research community (Lofthouse and Fristad 2004).

Despite this heightened focus, disagreement remains regarding the presentation of BPD in children. While some contend that episodes, and perhaps euphoria, should be required for the diagnosis of mania, others claim that severe irritability is sufficient, even if that irritability has a chronic, non-episodic presentation and occurs without euphoria (Biederman et al. 1998a, Geller et al. 1998c). Thus, the controversy surrounding pediatric BPD focuses on the importance of euphoric versus irritable mood, and on an episodic versus chronic presentation. Defining the role of irritability in mania is critical to identifying how to make the diagnosis in children; this in turn will enhance effective assessment and treatment of pediatric BPD.

In this paper, we will discuss the presentation of irritability in childhood mania, irritability's importance as a diagnostic criterion of BPD, its potential role in the pathophysiology of BPD, and how the presence of irritability influences treatment.

Defining Irritability

Despite its frequent use in the field of childhood psychopathology, irritability remains a rather undefined concept. Typical synonyms used to define it include grumpy, grouchy, easily frustrated, angry, aggressive, or defiant. As this list suggests, irritability can take many forms and its presentation may differ from child to child. Leibenluft et al. (Leibenluft et al. 2003a) defined irritability as "an emotional state characterized by having a low threshold for experiencing anger in response to negative emotional events. Anger, in turn, can be defined as a dysphoric state associated with aggressive impulses." It is important to note that this definition conceptualizes irritability as involving both affective and behavioral dysfunction. Most often, it is the behavioral consequences of irritability which result in functional impairment.

This definition of irritability also highlights the

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critical role of a stimulus in eliciting the dramatic, exaggerated response from the irritable child. What a nonirritable child could let "roll off his back", the irritable child "can't let go". Thus, a nonirritable child might produce a response which, while potentially negative and disruptive, is nevertheless tempered and manageable in both its intensity and duration. In contrast, the irritable child may respond to a benign or minimally noxious stimulus or event in an immediate and excessive manner that results in marked environmental disruption.

This theory is consistent with Davidson's (Davidson 1998) suggestion that differences in emotional responsivity reflect differences in "affective chronometry". That is, emotional reactivity follows a temporal course in response to a particular stimulus. Differences in the onset, intensity, and duration of this emotional response determine individual variability in affective regulation and emotional stability or lability. Thus, a benign stimulus is more likely to elicit a negative emotional response from a highly irritable child than from a calm one. In response to a negative stimulus, a highly irritable child is more likely to respond instantaneously, and with far greater arousal and rage than a healthy child. Further, irritable children are more likely to reach their peak anger more quickly and remain at that peak for a longer period of time. Thus, in psychopathological states, the irritable response is immediate and intense, while recovery is slow.

Developmental Considerations

To add to the complexity of defining irritability, it is important to note that periods of irritability are present in psychiatrically healthy children, and changes in irritability are normal aspects of emotional maturation and personality formation (Birmaher et al. 1996, Costello et al. 2002). Parents of infants and toddlers note that mood lability is commonplace and continues through school age and adolescence, with a gradual dissipation through early adulthood. The increased presentation of irritability in earlier years may reflect maturation of emotion regulation skills (Kochanska et al. 2000) and the maturation of executive attention (Posner and Rothbart 1998). That is, as children develop, their ability to tolerate frustration improves, in part because older children re-direct their attention away from frustrating stimuli and can maintain a focus on relatively distal goals while in a frustrating context. Reductions in irritable mood with development may also reflect the fact that children are more reactive to environmental stressors than are adults (Gould et al. 1994, Pine et al. 2002). Finally, as children age, they become increasingly aware of their peers and the impact of their behavior on social relationships. This pressure to "fit in" is an additional impetus to regulate their outward expressions of frustration and/or anger.

In sum, irritability can be conceptualized as a multi-faceted emotional state characterized by a low threshold for experiencing anger in response to negative emotional events and stimuli; this anger produces behavioral outbursts, often marked by aggression. Severe irritability is noted for its rapid onset, substantial intensity, and prolonged duration. Developmental contributors include younger children's relatively immature emotion regulation skills, their poorer skill in controlling attention as a means of controlling affect, and their greater reactivity to emotional stimuli in the environment.

Measuring Irritability

Given the multidimensionality of irritability, it is not surprising that tools designed to assess it use a variety of terms and descriptors. Evaluation of irritability is often a component of a more global assessment of psychiatric status and overall functioning. Evaluation may consist of a clinical interview, diagnostic structured interview, and/or parent and/or child-report severity scales.

Questions typically assess the presence of irritability using an operationalized synonym, describing either a related mood state or behavior. For example, standardized structured interviews including the Kiddie-Schedule for Affective Disorders (KSADS) (Kaufman et al. 1997) and Diagnostic Interview Schedule for Children (DISC) (Costello et al. 1985) inquire about irritability using phrases such as "anger; crankiness; bad temper; short-tempered; resentment or annoyance; easily lose temper; touchy or easily annoyed;" as well as "cranky; angry toward people you had no reason to; talk back; temper tantrum", respectively. The Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al. 1995) assesses the intensity, frequency, and duration of irritability using a variety of questions, such as "Do things get on his/her nerves easily?", "Does s/he get annoyed more easily than most people?", "Does s/he get angry very often?", and "What happens when s/he doesn't get what s/he wants or something upsets him/her?". A strength of most structured interviews is that they assess irritability using multiple questions and within different diagnostic categories (i.e. Major Drepressive Disorder, MDD; Oppositional Defiant Disorder, ODD); this allows for the pooling of responses from different domains of emotional and behavioral dysfunction, and thus a more comprehensive assessment.

Rating scales also tend to assess irritability using operationalized synonyms. For example, the Children's Depression Rating Scale (CDRS) (Poznanski et al. 1984) uses the descriptors "grumpy, crabby, talked back, sassy, wouldn't do something your parents asked you to do". The Child Behavior Checklist (CBCL) (Achenbach 1991) has a single irritability item: "stubborn, grumpy, irritable". The reliability and validity of assessments that use a single, vs. multiple, items to assess irritability has not been tested. However, it may be difficult for one item to assess this multidimensional construct, which can be characterized in terms of frequency, intensity, duration, and presenting form (i.e. verbal versus physical aggressiveness, destructiveness, etc).

Rating scales that focus on irritability are the Overt Aggression Scale (OAS) (Vitiello and Stoff 1997), and the Aberrant Behavior Checklist (ABC) (Marshburn and Aman 1992). The OAS, often used in treatment trials, assesses observable verbal and physical aggression,

with strong reliability and validity. However, this questionnaire fails to document milder, yet often impairing, irritable symptoms. Similarly, the ABC, designed for use in children with Pervasive Developmental Disorder (PDD), has an irritability subscale comprised of 15 items focused on overt irritable aggression, such as property destruction and self injury. Future work is needed to develop tools to assess the affective (as opposed to behavioral) aspects of irritability, and to better evaluate the relationship between irritability and specific forms of childhood psychopathology.

Neural correlates of irritability

Attempts to identify the neural mechanisms associated with irritability have tended to focus on either the emotional (i.e. frustration) or behavioral (i.e. aggression) aspects of the symptom.

As noted above, irritability can be defined as an emotional state characterized by having a low threshold for experiencing anger in response to negative emotional events. Such negative emotional events often involve the failure to attain anticipated rewards. For this reason, the neural correlates of reward and punishment are informative in understanding irritability. Brain regions that mediate the anticipation of, and response to, rewards include midbrain dopamine systems, particularly the ventral striatum (Schultz et al. 2000). Specifically, omission of reward is associated with decreased dopaminergic activity in this region (Mirenowicz and Schultz 1996), which is thought to foster learning and behavioral adaptation. A functional magnetic resonance imaging (fMRI) study found that omission of an expected reward was associated with increased activation of the right anterior insula, right ventral prefrontal cortex (VPFC), and anterior cingulate cortex (ACC) (Abler et al. 2005). The anterior insular cortex and VPFC have also been implicated in the regulation and inhibition of distress and negative affect (Hariri et al. 2000), so activation of these regions may also be associated with the experience of irritability.

Other neural studies have focused on a behavioral component of irritability: aggression. Two primary forms of aggression have been identified: premeditated and reactive. Premeditated aggression is predatory and planned, whereas reactive aggression, like irritability, is an unplanned, spontaneous, and/or impulsive response to threatening or frustrating stimuli. While irritability and reactive aggression are not synonymous, there is substantial overlap between the two.

Studies indicate that the medial hypothalamus and dorsal half of the periaqueductal gray (PAG) mediate reactive aggression (Gregg and Siegel 2001, Panksepp 1998), while the amygdala, orbital frontal cortex (OFC), and medial frontal cortex (MFC) play a more modulatory role (Blair and Charney 2003). More specifically, reactive aggression is thought to be related to decreased activation of the OFC and MFC (Anderson et al. 1999, Raine et al. 1998) when frustrated. The finding of OFC involvement in reactive aggression is consistent with its role in computing expected rewards and mediating responses to the failure to receive anticipated contingencies (Rolls 2000). The OFC may also be involved in modulating the response to frustration, in particular negative emotional expressions that might curtail aggression (Blair et al. 1999, Sprengelmeyer et al. 1998).

Animal studies implicate multiple neurotransmitters in aggression, including dopamine (acting via the D-2 receptor), norepinephrine (acting via alpha-2 adrenergic receptors), GABA, serotonin, glutamate (acting via NMDA receptors), and peptides (Siegel et al. 1999). In humans and animals, attenuated levels of serotonin are associated with aggression, both external (Virkkunen et al. 1995) and self-directed (van Heeringen 2001), as well as impulsivity (Birmaher et al. 1990, Filley et al. 2001).

In sum, the brain regions mediating irritable mood may include the anterior insula, VPFC, and ACC. Aberrant patterns of activation of these appear to be most strongly associated with the affective and behavioral components of irritability and behavioral regulation.

As we now turn to a discussion of the relationship between irritability and pediatric bipolar disorder, it is interesting to note the substantial overlap between the neural regions associated with irritability and aggression and those associated with the pathophysiology of pediatric BPD. Specifically, research indicates that children with BPD, as compared to controls, have greater activation of the insula when viewing negatively valenced pictures (Chang et al. 2004), decreased volume (Dickstein et al. 2005b, Wilke et al. 2004) and hyperactivation of the frontal cortex when viewing negatively valenced pictures (Chang et al. 2004), and volumetric deficits (Kaur et al. 2005, Wilke et al. 2004) and hyperactivation of the ACC when viewing positively valenced pictures (Chang et al. 2004).

Irritability in pediatric BPD

The role that irritability should play in the diagnosis of pediatric BPD has spawned considerable debate. While some argue that irritability alone (i.e. in the absence of euphoria) is sufficient to warrant a BPD diagnosis, others contend that euphoria is the cardinal symptom required for a mania diagnosis. In addition, disagreement over the nature of irritability in pediatric mania reflects debate if the presentation of irritability in childhood BPD is primarily chronic or episodic.

Irritability, euphoria, and pediatric BPD

Some researchers argue that the irritability of mania is qualitatively and quantitatively distinct from other forms of irritability, and is thus a useful symptom for identifying childhood mania (Biederman et al. 2004, Biederman et al. 2005, Mick et al. 2005, Wozniak et al. 2005). Indeed, according to the Diagnostic and Statistical Manual, 4th Edition (DSM-IV) (American Psychiatric Association 1994), *episodic* irritability, in the absence of elated mood, meets criteria for mania when it occurs with four of the seven criteria "B" symptoms (i.e. grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased goal-directed activity, and excessive pleasure seeking/risky behavior) (see below for further discussion of the episodic vs. chronic distinction).

In contrast, others claim that euphoric mood is the cardinal symptom for pediatric BPD diagnosis (Geller et al. 1998c, Geller et al. 2003, Pavuluri et al. 2004). They note that, as opposed to irritability, euphoric mood or grandiosity is unique to mania: it does not overlap with any other mood or behavioral disorder. Supporters of this view contend that requiring euphoria for the diagnosis of BPD makes it feasible to distinguish irritable children with Attention Deficit Hyperactivity Disorder (ADHD) from those with mania (Geller et al. 1998c), and that pathological euphoria can be differentiated from normative giddiness, by its intensity, duration, and frequency. Mania is further distinguished from other mood states by the presence of unique behavioral and cognitive deficits (i.e. grandiosity, decreased need for sleep, increased goal-directed activity, and excessive pleasure seeking) not seen with other moods (Geller et al. 1998c, Geller et al. 2002). Thus, one point of view is that the sustained presentation of a highly elevated and expansive mood state is a pathognomonic feature of BPD that differentiates it from all other psychopathology (Leibenluft et al. 2003b).

Interestingly, although there is divergent opinion as to the diagnostic utility of irritability in pediatric mania, researchers agree on the high prevalence of irritability amongst children with mania, i.e. in the range of 71%-98% (Biederman et al. 2005, Birmaher et al. 2002, Geller et al. 1998c, Wozniak et al. 1995a). Thus, irritability is very prominent whether or not euphoria is required for the bipolar diagnosis. In evaluating research on pediatric BPD, the inclusion criteria should be carefully considered, since different criteria may yield different results. Further, diagnoses reached using research criteria may vary from those given in clinical practice; one study found that only 40% of children who receive a clinical diagnosis also meet research criteria for BPD (Pogge et al. 2001).

While the prevalence of irritability in mania is well documented, the relationship between the two remains rather undefined. Research is beginning to address core questions regarding the characterization of irritability in mania and how this compares to other child psychopathologies or adult mania.

Is irritability more common in pediatric BPD that in other childhood diagnoses? Few studies have used identical assessment techniques to compare irritability across different childhood psychopathologies. In addition to BPD, irritability is common in unipolar depression (i.e. MDD), anxiety disorders, ODD, conduct disorder (CD), ADHD, and PDD. In fact, for BPD, MDD, ODD, and generalized anxiety disorder, irritability is a diagnostic symptom listed by the DSM-IV.

Geller and colleagues (Geller et al. 2002) compared children with ADHD to those with BPD, and found that irritability was more common in the BPD group than the ADHD sample. However, since irritable mood was prominent in both samples (BPD: 98%, ADHD: 72%), the authors concluded that the between-group difference was not clinically meaningful and was not useful for differential diagnosis. It is important to note that this study required euphoria during mania and allowed for episodes consisting of ultradian rapid cycling (i.e. $\geq$1 cycle/day lasting $\geq$ 4 hours). Nevertheless, this study, one of the few direct comparisons of irritability in different childhood psychopathologies, suggests that irritability is not more uniquely related to pediatric BPD than ADHD. Additional direct comparisons between BPD and other childhood psychopathologies, using identical assessment techniques, are needed to further determine if irritable mood is more prevalent in pediatric BPD than in other psychiatric illnesses.

In addition to issues of prevalence, it will be important to determine the developmental progression of irritability as it relates to pediatric BPD and co-occurring childhood pathologies. Not only are comorbid disorders common in pediatric BPD (Biederman et al. 1999), but most BPD youth will receive an alternate psychiatric diagnosis prior to their BD diagnosis (Carlson et al. 2002, Tillman et al. 2003). Further, because irritability is a prominent symptom in most of these earlier diagnoses, this means that irritability in a bipolar child may initially present as a symptom of a disorder that precedes the diagnosis of BPD. For example, externalizing disorders, such as ODD or CD, have been found to predict a BD diagnosis at follow-up (Biederman et al. 1996, Biederman et al. 2001, Kim-Cohen et al. 2003), and having a diagnosed behavior disorder prior to the onset of BPD may relate to poorer functional outcome (Carlson et al. 2002). Premorbid mood disorders in which irritability is frequently present, such as MDD or anxiety, are also common in youth eventually diagnosed with BPD and may indicate those at increased risk for developing BPD (Johnson et al. 2000, Wilens et al. 2003). Bringing behavior and mood problems together, studies find that individuals with a CBCL profile of elevated attention problems, aggressive behavior, and anxious-depressed mood, are likely to meet criteria for pediatric BPD (Faraone et al. 2005, Hudziak et al. 2005), although the specificity of this finding is unclear (Youngstrom et al. 2004). In sum, given that irritability is highly prevalent in the conditions that often precede BPD (i.e. ADHD, ODD, CD, anxiety, depression), it is possible that irritability will first emerge in association with disorders other than BPD. It is unclear if the quality of this irritable presentation changes as the child develops and bipolar symptoms become evident. Well designed prospective longitudinal studies will increase our ability to determine the role of irritability itself in predisposing a child with psychiatric illness to eventually developing BPD.

Is irritability in pediatric BPD more severe than in other childhood psychopathologies? Many researchers suggest that irritability is the most debilitating symptom in pediatric BPD (Biederman et al. 2000, Carlson et al. 2003, Geller et al. 1998c, Wozniak et al. 1995a). Despite differing criteria used for diagnosing BPD, many researchers have described the irritability during pediatric mania as characterized by severe, intense tantrums that occur in response to relatively benign triggers and result in excessive aggression and destruction (Carlson et al. 1998, Chang et al. 2000, Geller et al. 2002, Kowatch et al. 2005, Scheffer and Niskala Apps 2004). Aggression may in fact be the most common reason for psychiatric hospitalization in manic children (Wozniak et al. 1995a). However, we are aware of just one study that has directly compared irritability across childhood psychopathologies, which suggested that severe irritability is more common in children with BPD than in those with ADHD (Mick et al. 2005). However,

severe irritability was assessed using a single question with the qualifier "super" to describe the irritability, and most children with severe irritability were not diagnosed with BPD. Clearly, more research is needed to determine if irritability in mania is in fact more impairing than in other childhood disorders.

Does the irritability in childhood mania differ from that in adult mania? Although it is commonly said that irritability is more prevalent and severe in manic children than adults, to our knowledge no prospective study directly compares child and adult samples using the same criteria for mania and the same measurement tool for irritability. A recent comparison of children vs. adults with DSM-IV BPD found that youth were significantly more likely than adults to present with irritable mood during their manic episode (83% vs. 74%) (Jerrell and Shugart 2004). However, this study was a retrospective chart review, and it is unclear whether or not a difference of 9% is clinically meaningful. A recent 35-year longitudinal study suggested that early onset bipolar patients are more likely to experience irritability than later onset patients (Kennedy et al. 2005). However, the early onset group included subjects ages 16-40 years. Thus, the developmental progression of irritability in BPD remains unknown.

In sum, many questions regarding irritability in childhood mania remain unanswered. While most researchers agree it is both prevalent and impairing, empirical studies have yet to clarify if irritability in pediatric BPD is in fact more common or severe than in other childhood psychopathologies or adult BPD.

Episodic versus chronic irritability in BPD

In addition to disagreement regarding the role of irritability, as opposed to euphoria, in the diagnosis of pediatric BPD, controversy also centers on whether pediatric BPD, and its associated irritability, is characterized by a chronic course or by distinct episodes (Biederman et al. 1998b, Geller et al. 1998c, Leibenluft et al. 2003c, Leibenluft et al. 2003a). Some contend that the mania seen in bipolar children, particularly when defined by the presence of irritability, has a chronic presentation. Others contend that the mania in children is rapid cycling, with "episodes" lasting as short as a few minutes or as long as months if not years. Finally, still others argue that, comparable to adult BPD, children can present with discrete episodes of mania which comply with DSM criteria for hypomania ($\geq$ 4 days) and mania ($\geq$ 7 days).

To address this controversy, Leibenluft et al. (Leibenluft et al. 2003c) suggested a classification system differentiating children with strictly-defined BPD (i.e. narrow phenotype) from those with chronic irritability and hyperarousal (i.e. severely mood dysregulated children, or the "broad phenotype" of pediatric BPD) (Leibenluft et al. 2003c). Narrow phenotype bipolar disorder (NP-BD) patients have a lifetime history of at least one distinct episode of mania or hypomania meeting DSM-IV duration criteria, and including elevated mood and/or grandiosity along with at least three DSM-IV criterion "B" mania symptoms (Geller et al. 2002).

In contrast, severely mood dysregulated (SMD) patients exhibit chronic, non-episodic irritability, accompanied by hyper-reactivity to emotional stimuli (i.e. explosive tantrums at least three times weekly), and hyper-arousal (including at least three of the following: insomnia, intrusiveness, pressured speech, flight of ideas/racing thoughts, distractibility, psychomotor agitation) (Leibenluft et al. 2003c). Symptoms have to begin prior to age 12, and be chronic i.e., present for at least one year, without remission of two months or longer. Symptoms have to cause severe impairment (i.e. hospitalization, repeated grade, marked family discord) in at least one setting (home, school, peers), and mild impairment (i.e. poor academic performance, school disciplinary problems, disrupted family activities) in another. Euphoric mood or distinct episodes lasting $\geq$ 4 days are exclusionary (Leibenluft et al. 2003c). Research is being conducted to determine whether SMD may be a pre-pubertal presentation of BPD, a "bipolar spectrum" illness (Johnson et al. 2000), or a subtype of ADHD, ODD, and/or depression.

It is important to note how NP-BD and SMD children differ in the presentation of irritability. Irritability, specifically chronic irritability, is the central symptom of SMD. In addition, SMD children present with marked hyper-reactivity to environmental stimuli, which, theoretically, may be the behavioral consequences of low frustration tolerance and irritability. In contrast, whereas irritability is not required for the NP-BD diagnosis, it may be present; indeed, data show that 77% of narrow phenotype children have prominent irritability (Bhangoo et al. 2003). However, while irritability may be present and even impairing in NP-BD children, episodic euphoria and/or grandiosity defines this sample. Thus, chronic irritability is the cardinal feature of SMD, but in NP-BD children, mania, as defined by episodes of elated mood, is the diagnostic requirement. By comparing SMD and NP-BD samples, we are able to compare children with chronic irritability (but without a history of classic mania) to those with classic mania, characterized by episodic euphoria and, often, irritability.

Is episodic irritability distinct from chronic irritability? Is it one more characteristic of BPD in children? Recent data are beginning to answer these questions.

Empirical Investigations

Epidemiologic and clinical evidence suggests that chronic and episodic irritability are distinct constructs which may be differentially related to pediatric BPD vs. other childhood psychopathology. Additional research is now examining potential pathophysiological differences in children with chronic versus episodic irritability, using structural MRI techniques and paradigms which evoke irritability.

Bhangoo and colleagues (Bhangoo et al. 2003) compared children, diagnosed with BPD by community clinicians, with chronic versus episodic symptoms. In the episodic sample, symptoms occurred during discrete episodes lasting at least four days and representing a distinct change from the child's baseline. The chronic sample's mood symptoms were constant and lacked discernable episodes. Children with chronic and episodic presentations had comparable rates of irritability (episodic: 82%; chronic: 77%). Also, the groups

did not differ in the mean number of medications (episodic: 3.29 ± 1.38; chronic: 3.45 ± 1.84) or psychiatric hospitalizations (episodic: 1.59 ± 2.23; chronic: 1.17 ± 1.22).

However, the groups differed in other symptomatology. DSM mania symptoms all occurred significantly more frequently in the episodic group. Further, the episodic group was significantly more likely to have a parent with BPD. Also, the episodic group was found to have significantly greater rates of suicide attempts, perhaps suggesting greater impairment. The chronic group exhibited higher rates of violence toward others. In sum, episodic irritability was associated with mania-like symptoms, whereas chronic irritability was associated with behavior disorder-like symptoms.

A second comparison of irritability (Leibenluft et al. 2006) used a randomly selected subset (N=776) of the Children in the Community Dataset (Cohen et al. 1993, Pine et al. 1998). Subject were assessed at baseline (mean age 13.8 ± 2.6 years) and then 2 (mean age 16.2 ± 2.8 years) and 9 years later (mean age 22.1 ± 2.7 years). Psychiatric diagnoses were made using the DISC (Costello et al. 1985), and items from the DISC were used to determine the severity of chronic and episodic irritability. Results indicated that episodic and chronic irritability were longitudinally stable and distinct constructs. That is, the intra-individual correlation between irritability measures obtained in early and late adolescence was 0.79 for episodic irritability and 0.56 for chronic irritability. However, the correlation between episodic and chronic irritability at the same time point was lower: 0.26 for early adolescence and 0.34 for late adolescence. In addition, at the 2 year follow-up assessment (i.e. adolescence), whereas episodic irritability at the first assessment was associated with later mood disorders (i.e. BPD and anxiety disorders), chronic irritability at the first assessment was associated with disruptive behavior disorders (i.e. ADHD and ODD). At the 9 year follow-up assessment (i.e. early adulthood), whereas episodic irritability at the first assessment was still associated with BPD, chronic irritability at the first assessment was associated with MDD.

Preliminary data from another longitudinal study may be consistent with these findings. Brotman and colleagues (Brotman et al. 2006) analyzed data from the Great Smoky Mountains longitudinal epidemiological study (N=1,420 children). Based on items from the CAPA (Angold et al., 1995), the authors identified which children ages 9-19 met criteria for SMD, strict BPD, and other psychiatric disorders. In the SMD sample, the most common DSM-IV Axis I diagnoses were ADHD (26.9%), CD (25.9%), and ODD (24.5%), i.e. behavior disorders often associated with chronically irritable presentations. SMD in childhood (mean age 10.6 ± 1.4) was associated with an increased risk for a depressive disorder in young adulthood (mean age 18.3 ± 2.1). Thus, this study again suggests that a chronically irritable presentation in childhood may be either a developmental presentation of, or a risk factor for, depression.

Expanding upon these studies, recent work suggests that chronic and episodic irritability may be mediated by different pathophysiologies. As previously discussed, frontal regions, in particular the ACC (Chang et al. 2004, Kaur et al. 2005, Wilke et al. 2004) and the inferior frontal gyrus (Chang et al. 2004), have been implicated in the pathophysiology of pediatric BPD and in reward-related decision-making and behavior (Koski and Paus 2000, Pochon et al. 2002), and thus may be involved in the pathophysiology of irritability. A recent structural volumetric analysis using voxel-based morphometry (VBM) evaluated cortical gray matter differences in NP-BD, SMD, and healthy control youth (Dickstein et al. 2005a). Preliminary results found that, compared to both SMD and control samples, the NP-BD sample had increased right medial frontal gyrus volume in the vicinity of the ACC and in the superior frontal gyrus. Thus, there is preliminary evidence of volumetric differences between NP-BD and SMD samples in neural regions associated with reward-related behavior and cognition.

Related to these results, a recent magnetic resonance spectroscopy (MRS) study (Davanzo et al. 2003) compared youth with BPD and those with intermittent explosive disorder, which has a clinical presentation similar to that of SMD. This study found that the BPD sample had decreased ACC myo-inositol, as compared to those with intermittent explosive disorder and healthy controls. ACC myo-inositol is of interest because it is a second-messenger metabolite thought to be relevant to lithium's anti-manic mechanism of action (Moore et al. 1999). Thus, as with the VBM study, this study indicates that children with episodic irritability and those with chronic irritability may differ in the ACC region.

Perhaps most germane to the current discussion, a recent study (Rich et al. 2006a) suggests that the neurological mechanisms of episodic versus chronic irritability may differ. Twenty-one SMD, 35 NP-BD, and 26 controls completed the affective Posner task (Derryberry and Reed 1994, Perez-Edgar and Fox 2005) which systematically manipulates emotional context while subjects perform an orientation task. By rigging the feedback subjects received regarding their performance, we were able to induce frustration and thus study the affective, behavioral, and psychophysiological (event-related potentials, ERPs) correlates of irritability. We compared performance on the non-emotional baseline context to the emotional, frustrating context.

As predicted, compared to controls, both patient groups reported significantly greater arousal following punishment on the frustration task. However, despite the similar affective response, SMDs and NP-BDs differed in their behavioral and psychophysiological performance. Specifically, the pattern of deficits displayed by the SMD sample was consistent with those typical of children with ADHD: poorer accuracy and lower N1/P1 ERP amplitude (a measure of visual information processing at the initial stages of attention (Mangun and Hillyard 1991)), independent of emotional context. In contrast, the NP-BD sample showed slower reaction time and lower P3 amplitude (a measure of allocation of attention (Steger et al. 2000)), but only during the frustration task. These results indicate that children with chronic and episodic irritability may have comparable subjective responses to frustration, but they may have different behavioral manifestations and psychophysiological mechanisms mediating their symptoms.

In sum, disagreement remains regarding the presentation of irritability in pediatric mania and its diag-

nostic utility. The question of whether irritability is particularly severe in children with BPD has received minimal empirical investigation. Differentiating chronic versus episodic irritability provides a means by which to begin to study the presentation of irritability in pediatric BPD and other disorders. Though the relationship between irritability and mania in children remains largely undefined, it is agreed that irritability is a prominent characteristic of childhood mania. For this reason, the successful treatment of irritability is likely to support the successful treatment of mania.

Clinical implications

Treating Bipolar Irritability

As with treatment of pediatric bipolar disorder in general, the treatment of irritability is likely to include psychopharmacological interventions, psychotherapeutic interventions, or, optimally, a combination of the two. Treatment studies assess outcome in highly divergent ways; that is, while most examine overall functioning, others assess rates of hospitalization, treatment adherence, social functioning, or specific symptoms. Relatively few studies explicitly use irritability as an outcome measure. Given the theoretical overlap between irritability and aggression, many studies examine rates of aggression and may use this to assess irritability and anger. Thus, it is useful to include studies of aggression when examining treatment efficacy for irritability.

The selection of treatment interventions for irritability in children with BPD should follow a thorough clinical evaluation. Treatment will vary based upon the presenting type of irritability. If the child's irritability is associated with mood episodes, either euphoric or dysphoric, that irritability would be consistent with a DSM-IV conceptualization of pediatric BPD. Treatment of this child should follow guidelines consistent with the treatment of BPD: addressing the overriding (manic) mood state and *then* additional impairing symptoms, including those of comorbid disorders and irritability (Kowatch et al. 2005). Conversely, if the child has chronic irritability without episodic mood states, i.e. consistent with a SMD presentation, that child does not present with symptoms consistent with a DSM-IV diagnosis of BPD. In that case, following treatment guidelines consistent with this child's DSM diagnoses, e.g., ADHD, MDD, or ODD/CD, may be most efficacious. However, studies have not addressed the topic of treating a chronically irritable, hyper-reactive, and hyperaroused child. For this reason, care should be taken when deciding upon the best course of intervention, determining target symptoms, defining therapy goals, and establishing the guidelines for prospective monitoring by parents.

Medication

Medication is often the first course of intervention with a bipolar child, with the goal to provide an immediate reduction in symptom severity. Stabilization via medication may also better prepare the child to benefit from psychotherapeutic interventions (Fristad et al. 2003, Miklowitz et al. 2003a, Pavuluri et al. 2004). Despite the widespread use of medication in pediatric BPD, there are few double-blind, placebo-controlled studies of medication in the illness (Frazier et al. 2001, Geller et al. 1998a, Geller et al. 1998b). Further, although irritability and impulsive aggression (which may reflect irritable mood) are thought to be prevalent in BPD children, few prospective studies have examined the efficacy of pharmacological treatment for these symptoms.

Recent treatment guidelines for youth with BPD include two algorithms which differ based upon the presence or absence of psychosis (Kowatch et al. 2005). For the child with BPD-I, manic or mixed, without psychosis, monotherapy with traditional mood stabilizers (i.e. lithium, divalproex, carbamazepine) and atypical antipsychotics (i.e. olanzapine, quetiapine, risperidone) is advised. Trials of combinations of mood stabilizers or atypical antipsychotics are recommended where there is a partial, or no response (see Kowatch et al. 2005 for a more complete discussion). For treatment-refractory cases, clozapine for children and adolescents, and electroconvulsive therapy (ECT) for adolescents only, is advised. In the second algorithm, where psychosis is present, the guidelines suggest a combination of a traditional mood stabilizer and atypical antipsychotic. If there is no response, combination treatment with three medications is recommended. Again, clozapine and/or ECT is advised as a final treatment option.

While these algorithms suggest treatment options for pediatric BPD, the pharmacological treatment of irritability and aggression in bipolar youth is far less defined. In an open-label case series of children aged 5-16 with affective symptoms consistent with bipolar disorder, 8 of 11 children had therapeutic responses (including reduced aggression) to low-dose treatment with risperidone (although 7 of the 8 responders were taking additional medications) (Schreier 1998). Another study of a 6-week course of divalproex in 14 adolescents hospitalized for a manic or mixed episode (Delbello et al. 2004) found a significant reduction in irritability and aggression scores. Thus divalproex, and perhaps risperidone, may be effective in reducing irritability and aggression in bipolar youth. Consistent with this, in adults with BPD, previous work indicates that valproate may be more effective than lithium in treating aggression during mixed mania (Bowden et al. 1994), though lithium is more effective than placebo, and the differences between valproate and lithium may reflect Type II error (Swann et al. 2002).

Since children with SMD do not meet DSM-IV criteria for mania, the extent to which the above discussion of pharmacological treatment algorithms can be applied to them is unclear. However, a retrospective chart review of 46 children and adolescents with impulsive aggression and irritability admitted to an acute inpatient psychiatric hospital examined the efficacy of divalproex in treating the symptoms of SMD (Barzman et al. 2005). After a two-week psychiatric hospitalization, there was a significant reduction in aggression and hostility symptoms. This study has a number of limitations, including potential therapeutic effects of the inpatient milieu, the use of concomitant medications, and the retrospective design

Much of the rationale for using certain medications to treat irritability in bipolar youth comes from studies that examine the treatment of irritability and/or aggression in children with other psychiatric illnesses. Lithium has been shown to reduce aggression in youth with CD (Campbell et al. 1995, Malone et al. 1994, Malone et al. 2000), though one study failed to find lithium to be effective in this population (Rifkin et al. 1997). Studies indicate that aggression in youth with disruptive behavior disorders is reduced by treatment with atypical antipsychotics including haloperidol (Campbell et al. 1984) and risperidone (Findling et al. 2000), as well as mood stabilizers, such as divalproex (Donovan et al. 2000, Steiner et al. 2003), although another study found valproate to be ineffective in reducing irritability in a sample of aggressive children with PDD (Hellings et al. 2005). However, in children with autism, risperidone significantly reduced aggressive behavior (McCracken et al. 2002) and irritability (Shea et al. 2004). In children with ADHD and CD, stimulants appear to decrease physical and verbal aggression (Connor et al. 2002, Klein et al. 1997).

Given that the irritability seen in BPD may reflect depressive symptoms, and selective serotonin reuptake inhibitor antidepressants (SSRIs) have demonstrated efficacy in treating depression in youth (Emslie et al. 2002, Emslie and Mayes 2001) as well as irritability and aggression in depressed adults (Walsh and Dinan 2001), there is evidence to support the treatment of bipolar irritability using SSRIs. However, the treatment of irritability in youth with SMD or BPD is complicated by recent "black box" warnings regarding SSRIs, and concerns that SSRIs, and stimulants, may be contraindicated for children with BPD (and perhaps SMD as well) due to the potential risk for inducing mania. SSRI-induced mania has been reported in 0-3.7% of adults with BPD (Nemeroff et al. 2001, Peet 1994, Young et al. 2000). However, these studies vary in duration of follow up (see Altshuler et al. 2003 for a review), and the rates of mania induction are comparable to those reported in bipolar adults treated with placebo (2.3-4.2%) (Nemeroff et al. 2001, Peet 1994). Though far fewer studies have examined the safety of SSRIs for use with bipolar children, some results seem to support the careful and judicious use of SSRIs in children with BPD. For example, the use of antidepressants in children hospitalized for MDD and psychosis resulted in four times *less* mania after 1-2 years than in similarly ill children not treated with antidepressants (DelBello et al. 2003). In addition, the careful use of SSRIs in conjunction with mood stabilizers, in particular when mood stabilizers are used first, may improve functioning in children with BPD without increasing the risk of mania (Wagner 2004).

There is also concern that stimulants may induce mania in children with BPD, or at risk of developing BPD (Carlson and Kelly 2003, DelBello et al. 2001, DelBello and Geller 2001). However, data from the large Multi-Modal Treatment of ADHD (MTA) study found that ADHD youth with some manic symptoms (in particular, severe irritability) responded robustly to methylphenidate and were not more likely to have an adverse response (Galanter et al. 2003). Further, in youth with BPD and ADHD, stimulants, added to divalproex sodium after manic symptoms had resolved, were both safe and effective (Scheffer et al. 2005). In sum, studies do not seem to indicate that SSRIs or stimulants are contraindicated in children with BPD, although caution should be used and each case monitored carefully. Fewer data are available to guide the treatment of children with SMD, but again the available data do not indicate that stimulants are necessarily contraindicated.

Psychotherapy

As with pharmacotherapy, controlled studies of psychotherapy in bipolar youth are limited in number. Controlled studies demonstrate that interventions incorporating techniques from child- and family-focused cognitive-behavioral therapy (CBT) may improve the function of youth with BPD (Fristad et al. 2003, Pavuluri et al. 2004). Psychoeducationally-based family therapies have also been shown to improve compliance with medication treatment in bipolar adults (Miklowitz 1996) and result in overall improved family environment, greater positive attitudes, and increased social support for BPD children (Fristad et al. 2002). Although no study has explicitly examined irritability as an outcome measure, the "Rainbow Program", a child- and family-focused CBT for bipolar children 8 to 12 years old, has been shown to significantly reduce aggression (Pavuluri et al. 2004).

As discussed by Goldberg-Arnold and Fristad (Goldberg-Arnold and Fristad 2002), goals of psychotherapy with bipolar youth are to 1) improve the child and parent's understanding of bipolar disorder, its symptoms, and treatment options; 2) improve symptom management; 3) improve coping skills to better deal with negative moods as well as improve communication and problem solving, and; 4) improve peer and family relationships.

Most therapeutic interventions begin with a psychoeducational approach. A better understanding of the illness addresses common misperceptions and provides the base on which latter therapeutic interventions can build. The goal of psychoeducation is to teach parents and children about BPD: its potential causes (biological, neurological, and genetic underpinnings), its symptoms and course (often with an emphasis on this longitudinal nature of the disorder), and treatment options (Fristad et al. 2003, Miklowitz et al. 2003a, Pavuluri et al. 2004). Of course, this psychoeducational approach will be far clearer when working with a narrow phenotype patient, to whom studies on bipolar disorder clearly apply. Given the controversy surrounding chronic irritability and its place along the bipolar spectrum, it is challenging to educate the patient and family when the nature of the illness itself is unclear. For this reason, with the SMD child, a psychoeducational approach that focuses on the symptoms, rather than the diagnosis *per se*, may be more applicable.

A key component in the treatment of irritability is increasing the child's understanding of mood states and improving his/her ability to label his/her emotions. This includes discussing what it means to be irritable, frustrated, and angry, and learning to identify these emotions, including the affective, behavioral, and even physiological signs of anger. Connecting environmen-

tal triggers to the child's irritability, and then irritability to anger and aggression, helps the child to recognize how different situations impact his/her mood and actions. By identifying triggers, the child becomes aware of potentially stressful situations and can decide how to cope with them proactively and adaptively.

Since studies indicate that BPD children are at high risk for learning disabilities (Wozniak et al. 1995b), and that approximately half require academic accommodations (Dickstein et al. 2005c), frustration with schoolwork is likely to be a significant source of irritability in the bipolar child. Targeting academic triggers, both at school and at home (e.g. when doing homework) will therefore be highly beneficial in reducing irritability.

Further, given data showing that bipolar children have marked social deficits (Geller et al. 2000, Rudolph et al. 1994), it is important to address problematic social skills in order to reduce a potential source of frustration. Research indicates that bipolar children misinterpret emotional facial displays (McClure et al. 2005), and that they may be particularly prone to misattributing negativity to otherwise benign or even happy facial expressions (Rich et al. 2006b, Rich et al. 2005). Thus, focusing on improving the interpretation of facial expressions may help to improve social functioning and reduce irritability.

Once particular triggers for irritability and anger have been discussed, psychotherapeutic interventions focus on identifying strategies for increasing emotion regulation and impulse control. Coping skills, most notably anger management, focus on developing specific techniques for preventing or reducing irritability, anger, and aggression. These can include calming strategies such as deep breathing, counting to 10, using soothing self-statements, and self-control statements and thoughts. In addition, alternate and enjoyable activities may help the child cope with irritability by providing a distractor and a positive, reinforcing environment.

Rather than instructing the child, the therapist should work with the child to develop coping strategies with which the child is comfortable and is likely to achieve mastery. It is critical that these strategies be ones that the child will use in his/her natural environment. The development of a variety of skills is important so that the child has several coping options that are appropriate for different environments: school, with peers, and at home. Some skills may be observable by others (i.e. engaging in an enjoyable activity, removing oneself from a stressful environment), but some strategies can be done inconspicuously (i.e. breathing, coping statements). Once coping strategies are identified, the child should practice employing them. Role playing and in vivo practice are critical to insure mastery of the skills and likelihood that the child will actually use these skills when becoming frustrated or irritable.

Working with parents is exceptionally important. Standard behavioral management techniques, comparable to those used in children with disruptive behavior disorders, may be efficacious in irritable bipolar children. These may include identifying age-appropriate consequences and punishment procedures, such as time-out, response cost as consequence for negative behaviors, and a home token economy system. It is also important to provide parents with techniques for giving effective commands and reinforcing rules (Wells et al. 2000), including remaining calm and responding with a measured tone of voice and neutral facial expression (Pavuluri et al. 2004). Parents should learn to recognize when it is appropriate to intervene during the outbursts, as opposed to waiting until the rage subsides (Pavuluri et al. 2004). In addition, providing the parent with a set of techniques for managing his/her own stress, both in everyday life as well as during acute periods when their child becomes particularly irritable and/or aggressive, is highly beneficial (Pavuluri et al. 2002). Finally, given the high prevalence rates of psychiatric illness in parents of bipolar children, treating the parent's mood disorder may be required.

In addition to working with parents and children separately, sessions including the family as a whole can be helpful (Fristad et al. 2002, Miklowitz et al. 2000). Using role-playing and behavioral rehearsal, family members learn to reduce conflict and augment the positive nature of family interactions. Family interventions often focus on communication enhancement, including improving active listening skills, effective delivery of positive and negative feedback, and learning ways to seek changes in other's behaviors. An additional focus of family therapy is improving problem-solving skills by learning how to appropriately define and label problems, brainstorm solutions, evaluate pros and cons of alternative solutions, identify the option most likely to be successful, and implement the identified solution (Miklowitz et al. 2003b).

In addition to CBT, group, and family based interventions, interpersonal social rhythm therapy (IPSRT) (Frank et al. 2000) may be applicable to pediatric BPD. In bipolar adults, studies show that events which alter daily routine (especially those associated with sleep deprivation) are associated with increased risk for mania (Malkoff-Schwartz et al. 1998). Data show that sleep deprivation may precipitate mania (Leibenluft et al. 1996, Wehr 1992), and sleep regularity reduces mood lability (Wehr et al. 1998). IPSRT seeks to minimize the effects of life stressors on individuals' schedules and their mood. Given that in children with BPD, irritability is often preceded by stressors, and irritability is often related to changes in a child's routine, a modified, developmentally appropriate version of IPSRT may aid in the reduction of irritability in bipolar youth. In fact, the "Rainbow Program" of child- and family-focused CBT for bipolar children includes a discussion of the importance of routine in its psychoeducational section (Pavuluri et al. 2002). Modified IPSRT could help bipolar children and their families understand the relationship between stressors and the onset of mood disorders, identify triggers for disruption of social routines, and develop plans to maintain a predictable daily routine even in the face of daily pressures and emerging symptoms. As additional studies examine psychotherapy in bipolar youth, IPSRT may be worthy of investigation.

Issues related to comorbid conditions should also be considered. Given the high rates of comorbidity between pediatric BPD and anxiety, ADHD, ODD, and CD (Biederman et al. 1998b, Dickstein et al. 2005c, Geller and Luby 1997, Kovacs and Pollock 1995,

Lewinsohn et al. 1995), it is important to consider the extent to which irritability reflects a co-occurring condition. In general, is advisable to first stabilize the symptoms of BPD before focusing on a comorbid diagnosis (Kowatch et al. 2005). The effective treatment of pediatric BPD, its associated irritability, and problems related to comorbid conditions, is likely to reflect the integration of multiple forms of psychotherapy which have, individually, demonstrated efficacy.

Conclusion

In conclusion, while the relationship between pediatric mania and irritability, as well as pediatric bipolar disorder as a whole, have increasingly become the focus of research in the past decade, continued study is greatly needed. While clinical lore holds that the irritability seen in childhood mania is particularly pervasive and severe, more so than in adult mania or other forms of childhood psychopathology, few studies have investigated these issues. While research finds that irritability is a common symptom in youth with BPD, the diagnosis of BPD in children remains a source of debate in part because of continued disagreement regarding the role of irritability in pediatric BPD; specifically, if irritability (as opposed to euphoric mood) is diagnostically sufficient, and whether irritability in mania is predominantly chronic or episodic. Emerging data indicates that these two presentations of irritability are in fact distinct constructs and may have differing longitudinal outcomes and pathophysiological substrates. While more study is needed to clarify ideal treatment strategies for irritability in mania, the few completed studies indicate that irritability and aggression in bipolar youth may be reduced following treatment with divalproex and perhaps risperidone, as well as group- and family-based psychoeducational and cognitive-behavioral therapies. The continued clarification of irritability in childhood mania will greatly aid in elucidating the nature of pediatric bipolar disorder.

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