Revista Brasileira de Psiquiatria. 2013;35:S32–S39
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doi:10.1590/1516-4446-2013-S107

UPDATE ARTICLE

Irritability in children and adolescents: past concepts, current debates, and future opportunities

Fernanda Valle Krieger,[1,2,3] Ellen Leibenluft,[4] Argyris Stringaris,[3] Guilherme V. Polanczyk[1,2,5]

[1]*Department of Psychiatry, Universidade de São Paulo (USP), São Paulo, SP, Brazil.* [2]*National Science and Technology Institute for Developmental Psychiatry for Children and Adolescents (INCT), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).* [3]*Institute of Psychiatry, King's College London, London, UK.* [4]*Emotion & Development Branch, National Institute of Mental Health (NIMH), Department of Health and Human Services (HHS), USA.* [5]*Department of Psychiatry, Medical School and Research Support Center on Neurodevelopment and Mental Health, USP, São Paulo, SP, Brazil.*

Irritability is defined as a low threshold to experience anger in response to frustration. It is one of the most common symptoms in youth and is part of the clinical presentation of several disorders. Irritability can present early in life and is a predictor of long-term psychopathology; yet, the diagnostic status of irritability is a matter of intense debate. In the present article, we address two main components of the debate regarding irritability in youth: the misdiagnosis of chronic irritability as pediatric bipolar disorder, and the proposal of a new diagnosis in the DSM-5, disruptive mood dysregulation disorder, whose defining symptoms are chronic irritability and temper outbursts.

Keywords: Irritability; disruptive behavior; mood; dysregulation; children; adolescents

Introduction

Irritability is defined as a low threshold to experience anger in response to frustration. It is one of the most common symptoms in youth and is part of the clinical presentation of several disorders. Irritability can present early in life and is a predictor of long-term psychosocial adversity; yet, the diagnostic status of irritability is a matter of intense debate.[1] In the present article, we present a review of two aspects of irritability in children and adolescents: 1) The historical and theoretical background of the debate regarding the association of irritability with youth bipolar disorder (BD) and its role in the dramatic increase in the rates of this disorder reported in recent years; 2) The proposal of a new diagnostic category in the DSM-5 called disruptive mood dysregulation disorder (DMDD), with chronic irritability and temper outbursts as the defining symptoms. Because the conceptualization of this entity is a work in progress, we reviewed up-to-date clinical and epidemiological data on DMDD.

The controversy about irritability and youth bipolar diagnosis

Mental disorders are the result of maladaptive trajectories throughout development.[2] Approximately 80% of adult mental disorders begin during childhood and adolescence. In some cases, the same disorder is found in different stages of development (homotypic continuity); whereas in others the clinical phenotype changes with development (heterotypic continuity).[3] In recent years, researchers have focused on identifying the developmental trajectories of psychopathology, in the hope that this could help clarify relevant aspects of etiology, course, prognosis, prevention, and therapeutic strategies.[4] BD is a mood disorder that causes high levels of functional impairment. Retrospective studies showed that in 50% of cases BD begins during adolescence. Therefore, the developmental trajectory of BD is of great interest for researchers and clinicians.[5]

Between the mid 1990s and early 2000s in the United States, there was a dramatic increase in the rate of diagnosis of BD in children and adolescents, paralleling a discussion in the professional literature about the presentation of BD in youth.[6] The proportion of bipolar diagnosis of all psychiatric inpatient discharges in the United States rose from 10 to 34% in children and from 10 to 49% in adolescents in 8 years. In 1996, there were 1.3 discharges with a bipolar diagnosis per 10,000 children and adolescents in the general population, whereas in 2004 the ratio was 7.3 per 10,000, a five-fold increase. In outpatient settings, the increase was approximately 40-fold during that period.[7] It is possible that youth BD was previously underdiagnosed, explaining the increase in the rates. However, another plausible explanation is a change in the way the diagnostic criteria were applied, leading to misdiagnosis of other conditions under the label of BD.

BD is characterized by episodes of mania or hypomania, i.e., a distinct period of abnormally and persistently elevated, expansive, or irritable mood (A symptoms) accompanied by a number of cognitive, behavioral, and physical symptoms (B symptoms) such as grandiosity, decreased need for sleep, pressure of speech, increased

Correspondence: Fernanda Valle Krieger, Instituto de Psiquiatria, Universidade de São Paulo, Rua Dr. Ovídio Pires Campos, 785, 1° andar, sala 1C015, CEP 05403-903, São Paulo, SP, Brazil.
E-mail: fvkrieger@gmail.com

goal-directed activities, flight of ideas, distractibility, and psychomotor agitation. The concurrent presence of A and B symptoms configures an episode of mania or hypomania; the difference between the two depends on the intensity and duration of symptoms.[8] Specifically, the controversy in pediatric BD was focused on chronic, nonepisodic irritability as a developmental presentation of BD.[9] Although the core definition of BD comprises an episode, some researchers have suggested that mania in youth presents as a nonepisodic, persistent, chronic, and severe irritability.[10-12] This shift in the concept of bipolar illness has obvious implications in nosological classification, prevalence, therapeutic approaches, and prognosis. For instance, accepting youth BD as chronic and nonepisodic leads to overlap of symptoms with other disorders. For instance, distractibility, increased goal-directed activities, pressure of speech, and psychomotor agitation occur both in mania and attention deficit hyperactivity disorder (ADHD). The episodicity of the presentation was useful to differentiate BD and ADHD, because while irritability is not a diagnostic criterion for ADHD, temper outbursts and deficits in emotional regulation (chronic irritability) are often seen in this entity. Thus, defining BD in youth as chronic may then result in many children with ADHD and irritability receiving the diagnosis of BD, increasing the rates of comorbidity. Therefore, the nonepisodic hypothesis of youth BD kindled interest and concern among researchers, stimulating research in the field.[13]

The considerations above show that the presentation of irritability - chronic or episodic - is crucial for understanding its psychopathological meaning, particularly because the constructs of episodic and chronic irritability are separable and remain stable over time.[14] For instance, the correlation of episodic irritability between early and late adolescence is 0.79, whereas that of chronic irritability, is 0.56. However, the correlation between episodic and chronic irritability is much lower, 0.34 in early and 0.26 in late adolescence.[15] Thus, chronic and episodic irritability seldom overlap but are each relatively stable over time. Furthermore, the two constructs present different associations with age: episodic irritability has a linear association, whereas chronic irritability presents a curvilinear trajectory, with a peak in mid-adolescence. In addition, longitudinal associations are also diverse between the two phenotypes: episodic irritability in early adolescence is associated with generalized anxiety disorder (GAD), simple phobia, and mania in late adolescence and only mania in early adulthood, whereas chronic irritability in early adolescence is associated with disruptive disorders in late adolescence and only with major depressive disorder (MDD) in early adulthood.[15]

In 2003, Leibenluft et al. proposed a systematization of critical aspects of the youth bipolar debate, thus prompting research on the field[16]: 1) narrow phenotype, including those patients who meet the full DSM-IV diagnostic criteria for (hypo)mania, with hallmark symptoms of elevated mood and duration criterion (7 days for mania; 4 days for hypomania); 2) (hypo)mania not otherwise specified, featuring those who exhibit clear episodes with elation as the hallmark symptom, but duration between 1-3 days; 3) irritable (hypo)mania, in which patients have a clear episode with irritability but not elated mood as the main symptom; and 4) broad phenotype, also called severe mood dysregulation (SMD), characterized by chronic, nonepisodic illness, and severe irritability.

Since then, several studies have established differences between the classical episodic bipolar phenotype (BD) and those exhibiting chronic irritability and temper outbursts (SMD). Whereas both groups show similar levels of impairment on the Children's Global Assessment Scale (BD 51.1±10; SMD 47.4±9, both indicating moderate impairment), the BD group presents higher rates of familial BD.[17] To address the issue of whether children with SMD would develop episodes of mania, longitudinal analyses have been conducted. Irritability in adolescence predicted MDD (odds ratio [OR] = 1.33, 95% confidence interval [95%CI] 1-1.78), generalized anxiety disorder (OR = 1.72, 95%CI 1.04-2.87), and dysthymia (OR = 1.81, 95%CI 1.06-3.12). Youth irritability did not predict BD at follow-up.[18] Conversely, those with classical BD, including an episodic course and elated mood, had up to 50 times more chance to develop a manic episode than those with SMD (i.e., chronic irritability) in a three-year follow-up (BD 58/93 subjects - 62%; SMD 1/84 subjects - 1.2%).[19] In addition, neuropsychological and imaging data gave further contributions to the differentiation between BD and chronic irritability.[20-22]

In short, there is definite evidence for a well-circumscribed entity characterized by episodic elated and/or irritable mood and well-defined associated symptoms that can be diagnosed as BD.[23] This entity needs to be identified clearly and treated appropriately because of a high probability of poor outcomes throughout life.[24] Conversely, patients identified as having chronic irritability should not be treated as exhibiting a developmental manifestation of BD. Because the goal of this review is pediatric irritability, we now move from the controversy surrounding BD to focus on data addressing specifically chronic irritability and emotional dysregulation in children. We characterize clinical pictures whose main symptoms are persistent irritability and temper outbursts that are impairing in both the short and long term. We also discuss functional burden, family history, neuropsychological findings, and nosological uncertainties. We conclude addressing therapeutic strategies.

Chronic irritability, temper outbursts, and disruptive mood dysregulation disorder

Irritability is defined as above, i.e., a deficit in emotional regulation. Developmentally appropriate anger-related behaviors tend to reflect frustration in expectable contexts, whereas chronic irritability is inappropriate to the situation, i.e., stimuli that could be manageable elicit intense responses manifested by reactive verbal and/or physical aggression towards the perceived object of threat or frustration. Deficits in emotional regulation are

highly associated with psychopathology and one of the most important predictors of mental disorders in cross-sectional and longitudinal studies.[25] Despite the impact of emotional dysregulation on child and adolescent psychopathology, it has no definite nosological home in the current classificatory systems. Some efforts have been made, but the phenotypic presentation of impairing emotional dysregulation is still open and is an empirical question. Currently, there are at least four different ways to classify this group of children.

Firstly, SMD was proposed as a phenotypic differentiation from BD. The diagnostic criteria comprised abnormal mood (anger or sad, at least half of the day, most days), frequent temper outbursts (three times/week), and hyperarousal symptoms (three or more: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, and intrusiveness). Symptoms must cause severe impairment in one setting (i.e., home, school, peers) and mild impairment in a second setting, must begin before 12 years of age and be present for at least 12 months, without symptom-free periods exceeding 2 months (Table 1). The research on SMD focused on the differentiation from BD, and neuropsychological and imaging data comparing the two entities clarified its boundaries.[26,27] Furthermore, research on SMD stressed the importance of chronic irritability for developmental psychiatry and suggested its adoption by the DSM-5. In an epidemiological sample, lifetime prevalence for SMD

Table 1 Diagnostic criteria: SMD vs. DMDD

SMD	DMDD
1. Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week.	A. The disorder is characterized by severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation. 1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages or physical aggression towards people or property. 2. The temper outbursts are inconsistent with developmental level.
2. Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness.	B. Frequency: the temper outbursts occur, on average, three or more times per week.
3. Abnormal mood (specifically anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable by people in the child's environment (e.g., parents, teachers, peers).	C. Mood between temper outbursts: 1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry. 2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).
4. The symptoms noted in 2-4 above are currently present and have been present for at least 12 months without any symptom-free periods exceeding 2 months.	D. Duration: criteria A-C have been present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months without the symptoms of criteria A-C.
5. The symptoms are severe in at least one setting (i.e., violent outbursts, assaultiveness at home, school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.	E. Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least one setting.
6. Aged 7-17, with the onset of symptoms before age 12.	F. The diagnosis should not be made for the first time before age 6 or after age 18.
	G. The onset of criteria A through E is before age 10. H. There has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of the three of the B criteria of mania (i.e., grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation. I. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better accounted for by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, dysthymic disorder).* The symptoms are not due to the effects of a drug or to a general medical or neurological condition.

DMDD = disruptive mood dysregulation disorder; SMD = severe mood dysregulation.
* Note: This diagnosis cannot co-exist with oppositional defiant disorder or bipolar disorder, though it can co-exist with attention deficit hyperactivity disorder and substance use disorders. Individuals meeting criteria for both DMDD and oppositional defiant disorder should only be given the diagnosis of DMDD. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of DMDD should not be assigned.

was 3.3%. Around 70% of SMD youth had a concomitant axis I diagnosis, ADHD (27%), conduct disorder (CD) (36%), and oppositional defiant disorder (ODD) (25%). Moreover, those who met criteria for SMD at first wave (mean age 10.6±1.4 years) were significantly more likely to be diagnosed with a depressive disorder (OR = 7.2, 95%CI 1.3-38.8) at follow-up (mean age 18.3±2.1 years) than youth who never met criteria for SMD.[28]

Secondly, the DSM-5 working group excluded the hyperarousal criterion from SMD, since it overlapped with ADHD symptoms,[29] and proposed a new diagnostic category called DMDD (Table 1). There is still little evidence on DMDD and studies mostly construct the phenotype based on other DSM-IV symptoms. Recently, Copeland et al., using two community samples, suggested prevalence rates of DMDD between 0.8 to 3.3%, with higher rates in preschool aged and male individuals. In the same study, DMDD significantly co-occurred with all common psychiatric disorders. The highest levels of co-occurrence were with depressive disorders (OR between 9.9 and 23.5) and ODD (OR between 52.9 and 103.0). Only one case of DMDD overlapped with mania. The likelihood of DMDD occurring alone ranged from 8% to 38% (for comparison, conduct disorder occurred alone 64% of the time, and depression occurred alone in 36.6%). Besides, youth with DMDD experienced higher levels of all social impairments and had elevated rates of recent suspension compared with those without DMDD criterion. These individuals were more likely to come from impoverished families.[30]

In another study with a clinically referred sample - n=706, aged 6-12 years, who participated in the Longitudinal Assessment of Manic Symptoms (LAMS) - high levels of overlap with other disorders were also described.[31] At intake, the DMDD phenotype was present in 26% of patients. Nearly all subjects with DMDD (96%) met criteria for ODD/CD and 77% met criteria for both ODD and ADHD. Compared with those without the phenotype, DMDD subjects presented higher rates of disruptive behavior disorders, dysthymia, and ADHD as well as higher scores on Young Mania Rating Scale (YMRS), Children Depression Rating Scale (CDRS), and ODD and CD subscales of the Child and Adolescent Symptom Inventory. At a 12-month follow-up, only 53% of those meeting criteria for DMDD at intake continued to meet criteria. Of those meeting criteria at any assessment (intake, 12-month, and 24-month follow-up), 52% did it at only one assessment, 30% at two, and 20% at all three time points. A diagnosis of DMDD at any time-point was significantly associated with a diagnosis of ODD/CD (71% of those with ODD also had DMDD vs. 3% without ODD, $p < 0.0001$) and ADHD (44% of those with ADHD also had DMDD vs. 23% without ADHD, $p < 0.0001$), but there was no association with any depressive disorder, any anxiety disorder, or BD. There was no specific association between DMDD and family history of mental disorders. The authors concluded that the DMDD phenotype could not be clearly delimited from ODD and CD and it showed limited longitudinal diagnostic stability.

Thirdly, the Irritable dimension within the ODD diagnosis is characterized by temper outbursts, annoyance, and touchiness.[32] Similar to SMD, the Irritable dimension shows strong association with emotionality.[33,34] However, even though both share the same core features, the assumption of SMD/DMDD as a specifier of ODD (Irritable dimension) was considered insufficient to describe the phenotype clinically. The DSM-5 Task Force argued that a syndrome characterized by chronic irritability, temper outbursts, and association with depressive disorders should be labelled under a mood section rather than a section on disruptive disorders, like ODD. In a British sample, the Irritable dimension of ODD was the only predictor of emotional disorders (anxiety and/or depression) compared to the other ODD dimensions of oppositionality, headstrong, and hurtful.[32] The association between Irritable dimension of ODD and internalizing disorders was replicated in distinct samples and age groups.[35-37] Longitudinal data from the British national survey (n=7,912) showed that the Irritable dimension of ODD predicted emotional disorders at follow-up, particularly distress disorders (depression and anxiety).[18] Findings of shared genes between the Irritable dimension of ODD and depressive disorders provided further support of a developmental association between them.[38] Moreover, the Irritable dimension of ODD showed a strong association with maternal depression.[39] The DSM-5 subtyped ODD into three dimensions (1. Angry/Irritable Mood; 2. Argumentative/Defiant Behavior; 3. Vindictiveness),[32] excluding the possibility of comorbidity between DMDD and ODD. If ODD and DMDD co-occur, DMDD should be the diagnosis given.

Fourthly, irritability as a dimension phenotype cutting across diagnoses. This concept is in agreement with the Research Domain Criteria of the National Institutes of Mental Health (NIMH), which suggests that psychopathological mechanisms and new treatment targets should be studied across diagnostic boundaries.[40] Furthermore, this perspective is consistent with the presence of chronic irritability and temper outbursts in a wide range of disorders, such as ADHD, ODD, and ASD.[41,42] Indeed, Wakschlag et al. found that around 80% of preschool-aged children have temper loss, but only 8% have it daily.[43] Using Item Response Theory (IRT), the authors psychometrically validated Temper loss as a dimensional continuum ranging from normative misbehaviors to problem indicators. Thus, quality as well as frequency would contribute to a severity continuum. Indicators of concern include daily tantrums, lasting more than 5 minutes, physical aggression during the tantrum, the occurrence of a tantrum with nonparental adults, and the presence of tantrums without a trigger. Although these results were in preschoolers, thus too young for either the SMD or DMDD diagnoses, they provide support for a dimensional conceptualization.

Regardless of the classification applied, emotional dysregulation has been described as a common component of many developmental psychopathologies and a strong predictor of both disruptive and mood syndromes.[44] Although empirical evidence supports emo-

tional dysregulation as a continuum and a critical domain of research, clinical decisions remain dependent upon diagnostic categories. Driven by the concern regarding BD misdiagnosis and focused on clinicians' use, the DSM-5 deliberations point towards the adoption of DMDD. One can conclude at this time that not enough scientific data about these children are available to create a new diagnosis. However, we should agree on the importance of this problem and the need to expand the efforts to understand the complex construct of irritability.[45]

In short, clinical assessment of a child presenting with irritability and temper outbursts should always start with active investigation of episodicity. Is it possible to determine when the symptoms began? Have there been significant changes relative to the child's usual baseline behavior? Did the changes occur in response to life events? Have associated symptoms occurred along with irritability? Is it possible to distinguish a clear episode of irritable mood and its associated symptoms? In the case of episodicity, proper assessment for BD should be carried on. On the contrary, if irritability is considered chronic, clinical investigation should turn towards emotional dysregulation-based diagnoses (Figure 1). DMDD phenotype should be considered if the child is described as always irritable and angry, it is difficult to determine when symptoms began (probably early in life), and temper outbursts occur frequently. It is important to evaluate triggering events, duration and intensity of outbursts as well as settings where they usually occur (home, with family, and peers). Children with the DMDD phenotype present irritable or angry mood between outbursts, characterized as sensitive to day-to-day frustration and ordinary changes. In almost all cases, these children will present with another diagnosis, ODD being by far the most common (however, as specified above, when the comorbidity between ODD and DMDD occur, the latter should be given preference). Besides, ADHD and anxiety disorders also commonly co-occur. Of note, family history of psychopathology should be actively assessed.

Research on measurement of irritability has been limited. The Affective Reactivity Index (ARI), a scale that contains six symptom items and one impairment item about irritability, has been created to address this gap. The scale focuses on three aspects of irritability over the last 6 months: threshold for an angry reaction, frequency of anger feelings/behaviors, and duration of such feelings/behaviors. The ARI has excellent internal consistency and external validation and can be used at both research and clinical settings.[46]

Therapeutic strategies for chronic irritability

Taken together, evidence of functional impairment, early onset, high morbidity, and wide spread comorbidity make

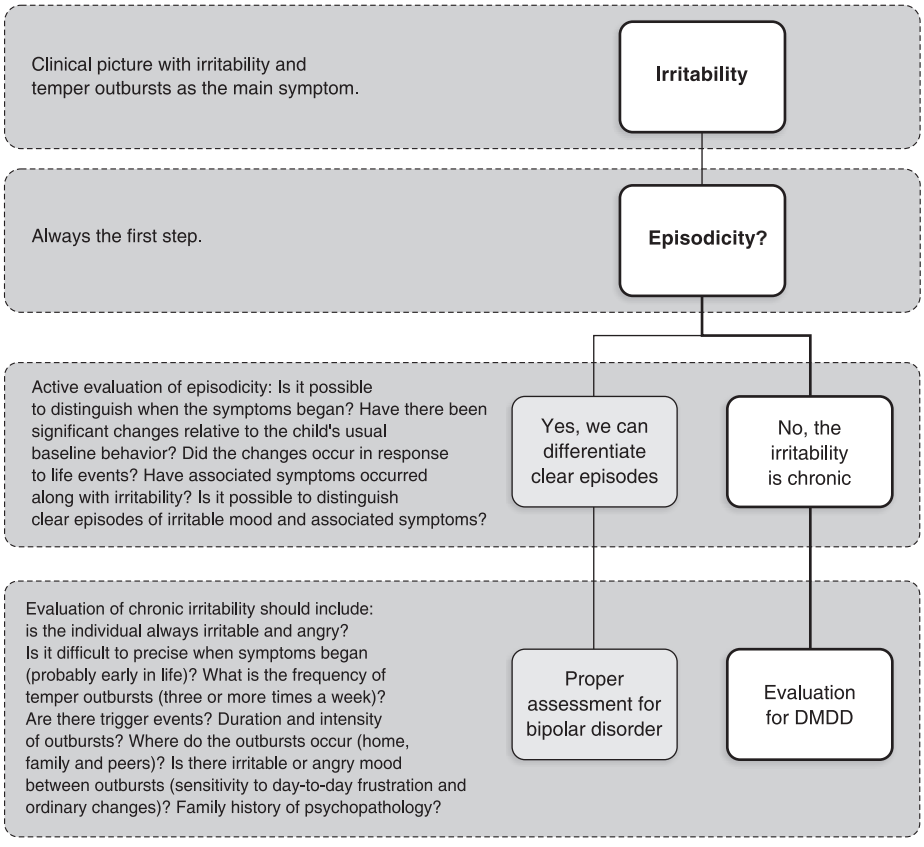


Figure 1 Assessment of irritability in children and adolescents

emotional dysregulation a critical target for intervention. Although little research has focused on the treatment of SMD/DMDD, parent training and cognitive behavioral therapy has shown promising results. Scott et al. evaluated whether children presenting the irritable dimension of ODD would be more sensitive to the positive effects of a parenting program than those without such a profile.[47] One hundred and twelve children, between 4-6 years, were randomized to the intervention (n=61) or control group (n=51). Parental intervention covered promotion of desirable child behavior through play, praise, rewards, handling misbehavior, applying consequences, and time out. Post hoc analyses indicated that treatment effect was moderated by emotional dysregulation. Although too young for meeting diagnostic criteria for either SMD or DMDD, preschool children with emotional dysregulation were more sensitive to changes in parenting and showed significantly stronger treatment effect than those without the phenotype.

Along these lines, Waxmonsky et al. proposed a group-based psychosocial treatment integrating evidence-based techniques of behavioral modification, anger management, and CBT programs to target oppositional behaviors and mood symptoms for children with ADHD plus SMD (mean age: 8.7±2 years).[48] The 9-week intervention included parent sessions paralleled with child sessions and promoted joint application of learned skills for the whole family. Treatment had a large effect on the CDRS (Cohen's d 1.17), YMRS (Cohen's d 0.81), and improved Child Global Assessment Scale (CGAS: pretreatment 47.86±7.5; posttreatment 66.43±10.7). These findings provide preliminary evidence for behavioral cognitive interventions. Moreover, the inclusion of the parents in the intervention seems crucial for treatment effectiveness.

Addressing pharmacological options for the treatment of emotional dysregulation, the only placebo-controlled trial in children with SMD found no benefit of lithium over placebo.[49] An open label trial using low doses (mean 1.2±0.5 mg) of risperidone in children and adolescents with SMD showed significant reductions in irritability scores (Aberrant Behavior Checklist-Irritability at baseline 25.89, standard error [SE] 2.7, and at week 8 11.28, SE 3.06, $p < 0.001$).[50] Risperidone was also effective in reducing duration of rage outbursts in inpatient settings (baseline 44±20 min, last dose 25±12 min).[51] Indeed, risperidone is FDA approved for the treatment of irritability in patients with autism spectrum disorders, although irritability in autism may not be the same as the one found in typically developing children. However, such findings should be seen with caution, especially because of the potential damaging side effects of antipsychotics in youth.

In addition, some studies show support for the use of stimulants in patients exhibiting ADHD plus SMD symptoms. A study examining the effect of stimulants in children with ADHD and SMD found the association to be safe and to reduce externalizing symptoms.[52] Studies examining emotional liability in ADHD provide additional support for the use of stimulants in this population.[53] A randomized controlled trial, conducted by the NIMH mood disorders team using citalopram plus methylphenidate in children with SMD, is under way. The rationale for use selective serotonin reuptake inhibitors (SSRIs) in children with SMD is the clear link between this phenotype and depressive disorders. The concern of using antidepressants in these children is no longer valid, since the boundaries with BD are well established. There is, however, a clear need for further studies on treatment strategies in children presenting with chronic irritability and temper outbursts. Furthermore, as comorbidity seems to be the rule, trials addressing therapeutic strategies according to comorbid disorders are much needed.

Conclusion

Irritability has been surrounded by controversy in child and adolescent psychiatry. First, the debate was driven by the boundaries between chronic irritability and bipolar diagnosis. Once the boundaries with BD were clarified, the debate turned to the proposal of a new diagnosis category, whose main symptom is emotional dysregulation. Although evidence suggests a dimensional distribution across the pediatric population, the DSM-5 indicates the adoption of DMDD as a new category entity. The associations of emotional dysregulation phenotypes are wide and include both internalizing and externalizing disorders, but are mainly linked to depressive disorders. Finally, treatment evidence includes cognitive behavioral therapy, especially parental intervention, but there is a pressing need for research on adjunctive pharmacological treatment.

Acknowledgements

This study was supported by a PhD scholarship received by the first author from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil.

Disclosure

Fernanda Valle Krieger has served as a speaker to Shire Pharmaceuticals. Guilherme V. Polanczyk has served as a speaker and/or consultant to Eli-Lilly, Novartis, Janssen-Cilag, and Shire Pharmaceuticals; has developed educational material to Janssen-Cilag; receives authorship royalties from Manole Editors; and has received unrestricted research support from Novartis. The other authors report no conflicts of interest.

References

1 Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011;168:129-42.
2 Sroufe LA, Rutter M. The domain of developmental psychopathology. Child Dev. 1984;55:17-29.
3 Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry. 2003;60:709-17.
4 Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009;66:764-72.

5 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593-602.

6 Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biol Psychiatry. 2007;62:107-14.

7 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. 2007;64:1032-9.

8 American Psychiatric Association. Diagnostic and statistical manual of mental disorders - DSM-IV-TR®. 4th ed. Arlington: American Psychiatric Publishing; 1994.

9 Leibenluft E, Charney DS, Pine DS. Researching the pathophysiology of pediatric bipolar disorder. Biol Psychiatry. 2003;53:1009-20.

10 Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry. 1995;34:867-76.

11 Biederman J, Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children. J Am Acad Child Adolesc Psychiatry. 1998;37:1091-6; discussion 1096-9.

12 Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. J Affect Disord. 2004;82:S45-58.

13 Carlson GA, Meyer SE. Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: complexities and developmental issues. Dev Psychopathol. 2006;18:939-69.

14 Leibenluft E, Blair RJ, Charney DS, Pine DS. Irritability in pediatric mania and other childhood psychopathology. Ann N Y Acad Sci. 2003;1008:201-18.

15 Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J Child Adolesc Psychopharmacol. 2006;16:456-66.

16 Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry. 2003;160:430-7.

17 Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, et al. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. Am J Psychiatry. 2007;164:1238-41.

18 Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry. 2009;166:1048-54.

19 Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, et al. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. J Am Acad Child Adolesc Psychiatry. 2010;49:397-405.

20 Adleman NE, Fromm SJ, Razdan V, Kayser R, Dickstein DP, Brotman MA, et al. Cross-sectional and longitudinal abnormalities in brain structure in children with severe mood dysregulation or bipolar disorder. J Child Psychol Psychiatry. 2012;53:1149-56.

21 Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. Am J Psychiatry. 2007;164:309-17.

22 Rau G, Blair KS, Berghorst L, Knopf L, Skup M, Luckenbaugh DA, et al. Processing of differentially valued rewards and punishments in youths with bipolar disorder or severe mood dysregulation. J Child Adolesc Psychopharmacol. 2008;18:185-96

23 Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. Am J Psychiatry. 2012;169:1247-55.

24 Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry. 2009;166:795-804.

25 McLaughlin KA, Hatzenbuehler ML, Mennin DS, Nolen-Hoeksema S. Emotion dysregulation and adolescent psychopathology: a prospective study. Behav Res Ther. 2011;49:544-54.

26 Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Pine DS, et al. Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. Biol Psychol. 2012;89:148-55.

27 Thomas LA, Brotman MA, Muhrer EJ, Rosen BH, Bones BL, Reynolds RC, et al. Parametric modulation of neural activity by emotion in youth with bipolar disorder, youth with severe mood dysregulation, and healthy volunteers. Arch Gen Psychiatry. 2012;69:1257-66.

28 Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry. 2006;60:991-7.

29 American Psychiatric Association. DSM-5 Development [Internet]. 2012 [cited 2013 Jun 17]. http://www.dsm5.org/

30 Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. Am J Psychiatry. 2013;170:173-9

31 Axelson D, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. J Clin Psychiatry. 2012;73:1342-50.

32 Stringaris A, Goodman R. Three dimensions of oppositionality in youth. J Child Psychol Psychiatry. 2009;50:216-23.

33 Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. J Am Acad Child Adolesc Psychiatry. 2009;48:404-12.

34 Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: findings from the Avon longitudinal study. J Am Acad Child Adolesc Psychiatry. 2010;49:474-83.

35 Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. J Abnorm Psychol. 2010;119:726-38.

36 Ezpeleta L, Granero R, de la Osa N, Penelo E, Domènech JM. Dimensions of oppositional defiant disorder in 3-year-old preschoolers. J Child Psychol Psychiatry. 2012;53:1128-38.

37 Drabick DA, Gadow KD. Deconstructing oppositional defiant disorder: clinic-based evidence for an anger/irritability phenotype. J Am Acad Child Adolesc Psychiatry. 2012;51:384-93.

38 Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. Am J Psychiatry. 2012;169:47-54.

39 Krieger FV, Polanczyk VG, Robert G, Rohde LA, Graeff-Martins AS, Salum G, et al. Dimensions of oppositionality in a Brazilian community sample: testing the DSM-5 proposal and etiological links. J Am Acad Child Adolesc Psychiatry. 2013;52:389-400.

40 Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748-51.

41 Skirrow C, McLoughlin G, Kuntsi J, Asherson P. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. Expert Rev Neurother. 2009;9:489-503.

42 Simonoff E, Jones CR, Pickles A, Happé F, Baird G, Charman T. Severe mood problems in adolescents with autism spectrum disorder. J Child Psychol Psychiatry. 2012;53:1157-66.

43 Wakschlag LS, Henry DB, Tolan PH, Carter AS, Burns JL, Briggs-Gowan MJ. Putting theory to the test: modeling a multidimensional, developmentally-based approach to preschool disruptive behavior. J Am Acad Child Adolesc Psychiatry. 2012;51:593-604.

44 Stringaris A, Goodman R. Mood lability and psychopathology in youth. Psychol Med. 2009;39:1237-45.

45 Axelson D. Taking disruptive mood dysregulation disorder out for a test drive. Am J Psychiatry. 2013;170:136-9.

46 Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, et al. The Affective Reactivity Index: a concise irritability scale for clinical and research settings. J Child Psychol Psychiatry. 2012;53:1109-17.

47 Scott S, O'Connor TG. An experimental test of differential susceptibility to parenting among emotionally-dysregulated children in a randomized controlled trial for oppositional behavior. J Child Psychol Psychiatry. 2012;53:1184-93.

48 Waxmonsky JG, Wymbs FA, Pariseau ME, Belin PJ, Waschbusch DA, Babocsai L, et al. A novel group therapy for children with ADHD and severe mood dysregulation. J Atten Disord. 2012 Feb 28. [Epub ahead of print]
49 Dickstein DP, Towbin KE, Van Der Veen JW, Rich BA, Brotman MA, Knopf L, et al. Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. J Child Adolesc Psychopharmacol. 2009;19:61-73.
50 Krieger FV, Pheula GF, Coelho R, Zeni T, Tramontina S, Zeni CP, et al. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. J Child Adolesc Psychopharmacol. 2011;21:237-43.
51 Carlson GA, Potegal M, Margulies D, Basile J, Gutkovich Z. Liquid risperidone in the treatment of rages in psychiatrically hospitalized children with possible bipolar disorder. Bipolar Disord. 2010;12:205-12.
52 Waxmonsky J, Pelham WE, Gnagy E, Cummings MR, O'Connor B, Majumdar A, et al. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. J Child Adolesc Psychopharmacol. 2008;18:573-88.
53 Rosler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World J Biol Psychiatry. 2010;11:709-18.