DISRUPTIVE MOOD DYSREGULATION DISORDER

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Florian Daniel Zepf, Caroline Sarah Biskup, Martin Holtmann, & Kevin Runions

Florian Daniel Zepf

Chair and Winthrop Professor of Child and Adolescent Psychiatry, Centre & Discipline of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy; University of Western Australia. Clinical Director & Head of Department of Specialized Child and Adolescent Mental Health Services. The University of Western Australia, Perth, Australia

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Although irritability and temper outbursts are by no means uncommon in the young, their chronicity and intensity beyond developmental norms can prove challenging for patients, parents, and those who work with children. Severe irritability is one of the most common reasons for presentation to mental health services (Stringaris, 2011), and emotional and behavioral dysregulation are commonly observed amongst young people referred to services. These symptoms can be present in a range of disorders including oppositional defiant disorder (ODD), attention-deficit/hyperactivity disorder (ADHD), bipolar and depressive disorders (Bertocci et al, 2014; Brotman et al, 2006; Stringaris & Goodman, 2009). The new diagnostic category of disruptive mood dysregulation disorder (DMDD) was introduced in DSM-5 to address this problem. Although DMDD has been controversial as indexed by discussions in the media as well as among clinicians and researchers, a growing body of evidence suggests that this condition has a distinct etiology, divergent developmental outcomes, and differences in neurobiology from pediatric bipolar disorder, ADHD, and ODD.

CLINICAL PRESENTATION AND DIAGNOSIS

DMDD as a diagnostic category was introduced after controversy about the diagnosis of pediatric bipolar disorder that had led to the identification of the syndrome, initially called "severe mood dysregulation". Severe mood dysregulation as a clinical phenotype was described by Leibenluft et al in 2003, who defined it as chronic (non-episodic) and severe irritability and hyperarousal without the euphoric and grandiose characteristics that are the hallmark of bipolar disorder. DMDD was introduced in DSM-5 to make available a diagnosis that would account for severe temper outbursts out of proportion to the context, that are not consistent with the child's developmental level, and that occur on average three or more times per week. A chart review study noted that patients with DMDD had a median of 4 temper tantrums per week (Tufan et al, 2016). Between tantrums, the child must show chronic irritability—angry outbursts, annoyance, and touchiness (Stringaris, 2011). Table E.3.1 summarizes the diagnostic criteria for DMDD, included in the depressive disorders chapter in DSM-5.

Unlike children and adolescents with bipolar disorder—who present with distinct periods of depressed mood and of mania or hypomania—patients with DMDD do not show well defined episodes. According to DSM-5, an *episode* is characterized by a *distinct period* of mood change distinguishable from the persons' usual mood, lasting at least one week for mania or four days for hypomania. These discrete episodes are separated by periods of euthymia or sub-syndromal symptoms. DMDD, on the contrary, requires persistency of the abnormal mood state. According to DSM-5, a diagnosis of DMDD cannot be made before 6 or after 10 years of age. Prior to the age of 6 temper outbursts are normal (Wakschlag et al, 2012) and the boundaries of clinically concerning temper tantrums are unclear. Importantly, DSM-5 criteria indicate that a DMDD diagnosis cannot be made concurrently with ODD, bipolar disorder, or intermittent explosive disorder.

Although this diagnostic category appears to have face validity, there is debate about its clinical validity and usefulness. A justification for introducing this diagnosis may have been to resolve the controversy and possible misuse of the pediatric bipolar disorder diagnosis, particularly in the US, and to codify the severe

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Caroline Sarah Biskup

Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, RWTH Aachen University Hospital, Aachen, Germany

Conflict of interest: none disclosed

Martin Holtmann

LWL-University Hospital for Child and Adolescent Psychiatry, Ruhr-University Bochum, Hamm, Germany

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Kevin Runions

Centre & Discipline of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy; School of Psychiatry & Clinical Neurosciences and School of Paediatrics & Child Health, The University of Western Australia, Perth, Australia; Telethon Kids Institute, Perth, Australia

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Table E.3.1 DSM-5 diagnostic criteria for disruptive mood dysregulation disorder

Severe recurrent temper outbursts in response to common stressors, which are: • On average, three or more times per week • Temper outbursts are inconsistent with developmental level • Between outbursts, mood is persistently irritable or angry, most of the day and nearly every day.
Onset of symptoms must be before the age of 10
Symptoms must have been present for 12 or more months
Symptoms must not be absent for three or more consecutive months
Children must be between 6 and 18 years of age
Symptoms should be present in at least two of three settings (home, school, social situations) and are severe in at least one setting
Symptoms are not better explained by another medical disorder, are not the manifestation of substance abuse or medical condition, criteria for manic/hypomanic episode have not been met for more than one day and behaviors do not occur solely during an episode of major depressive disorder

mood dysregulation construct (McGough, 2014). However, the concept has been criticized for lacking established diagnostic reliability and research evidence—much of what is known about DMDD is derived from studies examining severe mood dysregulation. It has been argued that DMDD should not be incorporated in ICD-11. In its place, it has been proposed to add a specifier to ODD indicating whether there is chronic irritability (Lochman et al, 2015).

Some researchers have used the Child Behavior Checklist (CBCL) (Achenbach, 1991) to capture a phenotype showing broad overlap between the behaviors observed in DMDD and severe mood dysregulation (e.g., Diler et al, 2009; Holtmann et al, 2008; Volk & Todd, 2007). This CBCL "dysregulation" profile encapsulates a mixed phenotype of severe behavioral and affective dysregulation, including irritability, aggression, "affective storms", hyperarousal, and mood instability. This profile is characterized by simultaneous extreme scores on the CBCL syndrome scales "anxious/depressed", "attention problems", and "aggressive behavior". Much of our current understanding of DMDD relies on inference from research on this construct.

EPIDEMIOLOGY

Most of what we know about DMDD has been inferred from research on severe mood dysregulation, although the upper age limit placed on its onset differs between DMDD (10 years) and severe mood dysregulation (12 years). A longitudinal study on severe mood dysregulation indicated that 97% of youths who met diagnostic criteria for this condition also met criteria for DMDD; the remainder only failed to meet the criteria due to an age of onset of 10 or 11 years (Deveney et al, 2015). Moreover, a diagnosis of severe mood dysregulation requires symptoms of hyperarousal, whereas DMDD does not, with the proviso that clinicians can assign a concurrent diagnosis of ADHD if warranted.

Severe irritability is one of the most common reasons for presentation to mental health services

A 3-month DMDD prevalence of 8.2% was observed in 6-year-old American children with no sex or ethnicity differences (Dougherty et al, 2014). A study by Copeland et al (2013) illustrates the prevalence of DMDD symptomology in a large epidemiological sample including preschool and school age cohorts. Among school age children, nearly half had shown severe temper outbursts during the 3 months prior to assessment. Applying the frequency criterion reduced the prevalence to 6-7%; applying the duration criterion dropped the rate to 1.5-2.8%. When all DMDD criteria were applied, prevalence was about 1%.

Research using the CBCL "dysregulation profile" results in comparable estimates of prevalence: 1-2% in epidemiological samples (Volk & Todd, 2007; Holtmann et al, 2007; Hudziak et al, 2005), 6-7% in child psychiatric clinical samples, and 13-20% in children with ADHD (Holtmann et al, 2008).

COURSE AND OUTCOME

Few studies have examined the stability of DMDD over time. Stability may be higher in childhood than adolescence: over 80% of children who meet criteria for DMDD at age 9 also met criteria when they were 6 years old (Dougherty et al, 2016). By contrast, a study of 200 adolescents diagnosed with severe mood dysregulation found that less than half met criteria at follow-up (Deveney et al, 2015).

Children diagnosed with DMDD at age 6 are at increased risk for depressive disorders and ADHD at age 9; the risk of disruptive behavior disorder symptoms was also elevated for these children (Doughterty et al, 2016). Childhood DMDD status also predicts subsequent peer relationship problems, increased peer exclusion and victimization (i.e., being bullied), and more use of relational aggression (Dougherty et al, 2016). In later childhood, DMDD diagnosis in 10 to 16 year olds predicted a range of subsequent problems in young adulthood (Copeland et al, 2014). Compared to non-cases and a psychiatric comparison group, those who met criteria for DMDD were at greater risk as young adults for serious illness, sexually transmitted diseases, other non-substance-related psychiatric disorders, nicotine use, police contact, poverty, not achieving a high school diploma, and no college attendance.

Although the DMDD diagnosis arose out of research on bipolar disorder (see Assessment and Differential Diagnosis, below) patients with DMDD or severe mood dysregulation do not show increased risk for later bipolar illness (Brotman et al, 2006; Stringaris et al, 2009), but have an increased risk of depressive disorder (Krieger et al, 2013)—thus the classification of DMDD in the depressive disorders chapter in DSM-5. This is also supported by studies concluding that children with severe temper outbursts seldom show symptoms of bipolar disorder (Roy et al, 2013, Mikita & Stringaris, 2013). Similarly, severe mood dysregulation is associated with depressive and anxiety symptoms in later adulthood (Brotman et al, 2006; Stringaris et al, 2009). Bipolar disorder is found less frequently in families of children with severe mood dysregulation than in families of children with bipolar disorder in both community and clinical populations (Brotman et al, 2007; Leibenluft, 2011). A 2-year follow-up of youths with severe mood dysregulation showed that they had lower rates of manic, hypomanic or mixed episodes than patients with bipolar disorder (Stringaris et al, 2010).

Long-term follow-up of children captured by the CBCL "dysregulation" profile suggests that young adults with a positive CBCL "dysregulation" profile in childhood are at increased risk for substance use, conduct and mood disorders, suicidal ideation, and suicide attempts but not for bipolar disorder. In addition, they showed a marked impairment in overall functioning (Althoff et al, 2010; Holtmann et al, 2011a). The CBCL "dysregulation" profile may be a valuable tool to identify patients with severe mood problems. High scores may indicate poor outcomes, such as substance use, suicidality, and functional impairment (Holtmann et al, 2011; Jucksch et al, 2011).

ASSESSMENT & DIFFERENTIAL DIAGNOSIS

As noted in the introduction, the core symptoms of DMDD – irritability and temper outbursts – are often present in individuals suffering from bipolar disorder, ADHD, and ODD among others. Moreover, DMDD commonly overlaps with other disorders. For example, Copeland et al (2013) noted a 63 to 92% overlap with other diagnoses; Fristad and her colleagues (2016) highlighted the high overlap of baseline demographic and clinical variables with Bipolar Disorder Not Otherwise Specified. Thus assessment and differential diagnosis of children with DMDD is difficult.

A chart review found an average age of onset of 4.9 years (Tufan et al, 2016). This study also provides insights into the diagnostic challenges: consensus could not be reached in more than 20% of patients. The more common reasons for this were whether symptoms occurred in more than one setting and whether there was anger or other negative moods between tantrums. Other sources of disagreement related to the frequency of tantrums, tantrum severity, and duration of symptoms. Holtmann and his colleagues (2011b) established that a 5-item subset from the Strengths & Difficulties Questionnaire could be a valid screening measure.

DMDD and Bipolar Disorder

The assignment of a bipolar disorder diagnosis to children and adolescents with chronic irritability but without distinct episodes of mania has been controversial. The debate is not only academic: broadening the diagnostic construct resulted in dramatic changes in clinical practice. For example, between 1993 and 2003 the number of adults diagnosed with bipolar disorder in the US doubled, but increased *40 times* in people younger than 20 years (Blader & Carlson, 2007; Moreno et al, 2007); this shift was accompanied by a large increase in the prescription of antipsychotic drugs to youth (Olfson et al, 2006). Data suggest that widening of the bipolar construct in the US was the explanation: for example, James et al (2014) noted a 70-fold difference in hospital discharges for bipolar disorder in the US and the UK, indicating different diagnostic practices.

According to the guidelines of the British National Institute for Health and Clinical Excellence, a diagnosis of bipolar disorder in children should only be made if the patient has a history of manic or hypomanic *episodes* in line with relevant diagnostic criteria, including duration and frequency of such episodes (Baroni et al, 2009). That is, bipolar disorder should not be diagnosed in the absence of episodes characterized by a distinct change in mood and concurrent

Who are the children with severe mood dysregulation?

"These explosive children are not new. A closer look at the traditional diagnoses that apply to this group of youth gives us further insight. Although there is no significant difference in the rates of ADHD between children with narrow phenotype bipolar disorder and those with severe mood dysregulation (60.6% and 86.7%, respectively), more than twice the number of children with severe mood dysregulation have oppositional defiant disorder (39.4% versus 83.3%) […] If we recast children with severe mood dysregulation as children with prominent combined ADHD and oppositional defiant disorder, we find we have considerable knowledge about them already. For instance, follow-up studies do not report inordinate rates of narrow phenotype bipolar disorder in children with ADHD plus oppositional defiant disorder. However, conduct disorder (CD) and later antisocial behavior/criminality and substance abuse are the unfortunate legacies of combined ADHD and oppositional defiant disorder" (Carlson, 2007).

changes in behavior and cognition. The traditional view, and the view represented in DSM-5, is that bipolar disorder can occur in pre-pubertal children but very rarely, becoming increasingly prevalent during adolescence, and that symptoms in the young are largely the same as in adults.

DMDD and the Disruptive Behavior Disorders

The presence of irritability and temper outburst have led some researchers and clinicians to argue that there is no clear demarcation between DMDD, ODD and conduct disorder (Axelson, 2013). Proponents of this view maintain that bipolar disorder is often misdiagnosed as, or co-morbid with, ADHD (Biederman et al, 1998). ADHD does seem to have a considerable symptom overlap with bipolar disorder in children and adolescents as can be seen in Figure E.3.1 (Zepf, 2009), though irritability in bipolar disorder is episodic, unlike in DMDD where it is chronic.

Click on the picture to view a brief video interview with Ellen Leibenluft MD on bipolar disorder in childhood summarizing the relationship between chronic irritability and chronic mood dysregulation problems, and how these problems differ from bipolar disorder in children

Lochman et al (2015) argue that ICD-11 should not incorporate the DMDD category, proposing instead to make a diagnosis of ODD and add a specifier indicating chronic irritability or anger instead. This argument is bolstered by findings that 92% of children aged 6-12 years in a general population sample who met DMDD criteria also met criteria for ODD, and 66% of those with ODD also had DMDD symptoms (Mayes et al, 2016). Deveney et al (2015) reported that over 80% of their sample of adolescents meeting criteria for severe mood dysregulation also met criteria for ODD or ADHD. However, other data indicate that DMDD and ODD show a more modest overlap (55%) and that DMDD predicts impairment over and above that due to ODD (Dougherty et al, 2014).

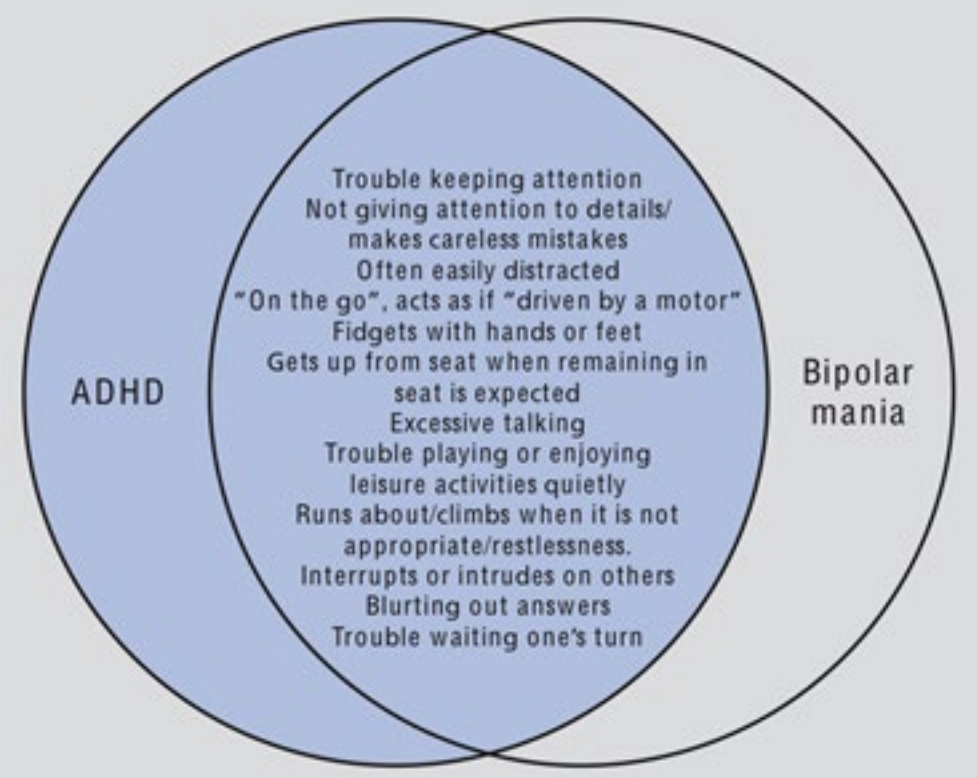
ETIOLOGY AND RISK FACTORS

The literature on developmental predictors of DMDD is in its infancy. Dougherty et al (2014) examined at age 3 predictors of DMDD at age 6. They noted that only temperamental "surgency" (a construct reflecting high levels of activity, reward seeking, low shyness, and impulsivity) and parental lifetime substance use disorder predicted DMDD status at age 6. In one study, participants with a CBCL "dysregulation" phenotype exhibited an increase in C-reactive protein and albumin concentrations, raising the possibility of an inflammatory diathesis (Holtmann et al, 2013).

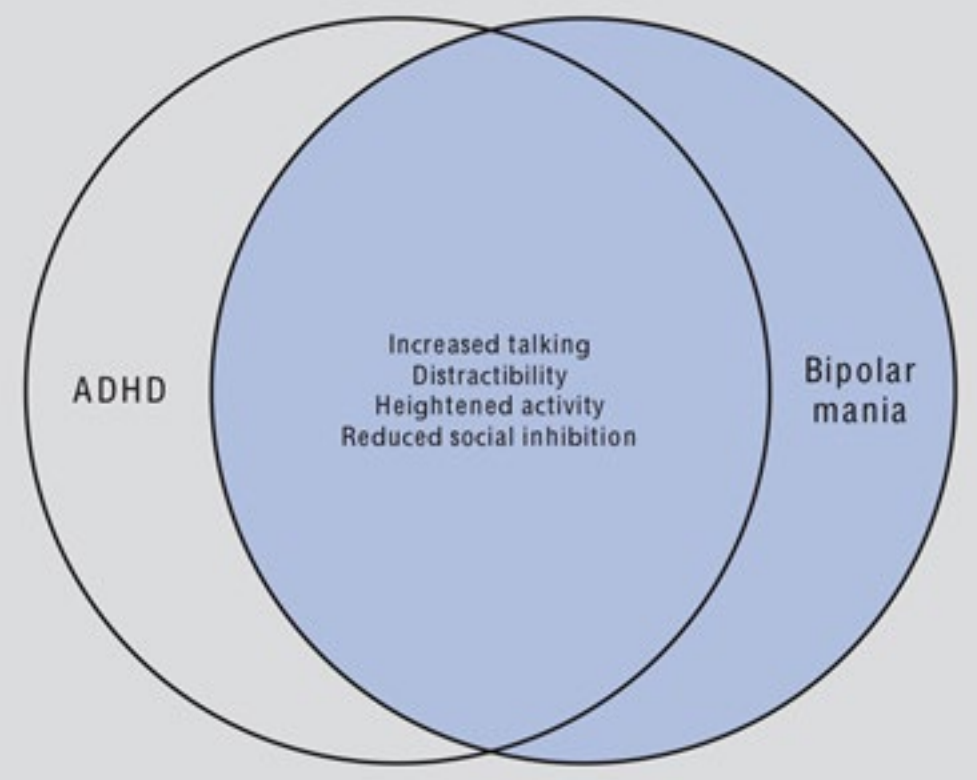
To date, few studies have been conducted shing light on family or other social or ecological factors that might contribute to the development of DMDD. The chart review by Tufan and colleagues (2016) indicated that over a three quarter of patients with DMDD had family histories involving parental mental health problems, including major depressive disorders, ADHD and anxiety disorder (56%, 25%, and 17% respectively). Although maternal depression has been linked to irritability in children with ODD (Krieger et al, 2013), no studies have found evidence for a role in DMDD of parental depression or other parental psychopathology (e.g., Axelson et al, 2012). Parents of children with DMDD have been shown to be more hostile and critical in their interactions with their children, but this may reflect bidirectional parent-child processes (Dougherty et al, 2014). A history of lifetime substance use disorder has also been implicated. Compared

Figure E.3.1: Diagnostic overlap in manic episodes and ADHD

DSM-IV symptoms of ADHD that can also be observed in a manic episode



DSM-IV symptoms of a manic episode that can also be observed in ADHD



Zepf, 2009, adapted with permission from Wingo & Ghaemi, ©2007, Physicians Postgraduate Press and Kent & Craddock, Journal of Affective Disorders, 73:211-221,©2003, with permission from Elsevier.

with children diagnosed with bipolar disorder not otherwise specified, children with DMDD are less likely to have a parent with bipolar disorder (Fristad et al, 2016).

Interpersonal trauma and exposure to traumatic events are widely acknowledged as being associated with affective dysregulation generally (Dvir et al, 2014), but to date no studies have examined trauma or related events including abuse and neglect as risk factors for DMDD. Child maltreatment and physical abuse are known risk factors for the sorts of affective processing biases observed with severe mood dysregulation and DMDD (see next section) (Leibenluft & Stoddard, 2013). However, empirical studies have not yet focused on whether these factors are particularly implicated in DMDD. Clearly, further research is needed to establish a better picture of the etiology of DMDD.

Social-Affective and Cognitive Neuroscience

There is a burgeoning body of research examining social and emotional information processing and emotion regulation and the underlying neurobiology of severe mood dysregulation, particularly in comparison with other diagnoses such as bipolar disorder. Much of this research has focused on response to emotion-laden stimuli, primarily to the human face. Severe mood dysregulation and bipolar disorder share common social cognitive deficits in processing affective information from the human face, showing less accuracy in labelling expressions and less sensitivity in facial emotion recognition relative to healthy controls. There is some evidence of biased processing of threatening faces in particular (Hommer et al, 2014). Functional magnetic resonance imaging research with severe mood dysregulation patients shows differential neural activation of the posterior cingulate cortex, posterior insula, and inferior parietal lobe in relation to fearful faces (Thomas et al, 2013). Future research need to examine whether these biases are specific to DMDD/severe mood dysregulation or reflect co-morbid psychopathology such as ODD.

Compared to individuals with bipolar disorder, those with DMDD show diminished cognitive flexibility as assessed with a reversal learning task (Adleman et al, 2012), and poor motor inhibition (Deveney et al, 2012). These characteristics are shared with patients with ADHD, however, and this overlap may account for these features (Uran & Kiliç, 2015).

In summary, at this stage it can be concluded that underlying brain mechanisms related to the symptomatology of severe mood dysregulation are different between patients with severe mood dysregulation, bipolar disorder, and healthy people, which may be of importance to develop pharmacological interventions.

TREATMENT

Because DMDD is such a recent inclusion in the taxonomy, there are few clinical trials that could inform clinical practice. Therefore, most of the management recommendations are extrapolated from studies dealing with related disorders such as severe mood dysregulation, ODD, and depression (Roy et al, 2014).

Behavioral therapy

Scott and O'Connor (2012) investigated the effects of parent training and cognitive behavior therapy in children aged 4-6 years presenting with the emotion dysregulation (defined as irritable and/or hurtful) subtypes of ODD as compared to patients with ODD without such a profile. Although the children were too young to meet diagnostic criteria for either severe mood dysregulation or DMDD, the study showed that young children with emotion dysregulation were more sensitive to changed parenting and showed stronger treatment effects than children without these symptoms.

Pharmacological treatment

Given the high comorbidity of DMDD with ADHD, stimulants have been studied as a possible treatment (Posner et al, 2014). Medications that improve irritability and depressed mood may be valuable – all used "off label". Second generation antipsychotics such as risperidone have also been used. A double-blind RCT of lithium treatment did not reduce symptoms in hospitalized patients with severe mood dysregulation (Dickstein et al, 2009). Krieger and colleagues (2011) reported a significant reduction in irritability in an open-label study of risperidone. Carlson et al (2010) found similar results. This is consistent with the widely known finding that risperidone can reduce aggressive behavior and irritability in the young. However, these early findings should be seen with extreme caution considering the potentially serious side effects of antipsychotics in the young and the fact that they do not specifically refer to patients with DMDD. Preliminary studies suggest that adolescents with ODD/CD and symptoms suggestive of DMDD show a reduction of symptoms when treated with divalproex (Donovan et al, 2000), a commonly used treatment for bipolar disorder. Discussion with parents and patients as well as careful monitoring of side effects is essential when prescribing these medications.

Click on the image to access "Facts for families" about DMDD

Other interventions

Educational approaches are highly relevant. Clinicians, teachers and parents need to work closely together to address and meet these patients' special needs (e.g., consistency, classroom support, more time to complete school tests, etc.). Teachers should also be made aware of the adverse effects of medication if it is prescribed. Patients and families should receive education about the disorder, comorbid symptoms and related impairments, as well as strategies for managing them. Finally, changes in lifestyle can be addressed together with the help of allied health professionals. Such changes may include strategies for dealing with crises and identifying potential stressors and triggers. A plan to manage emergencies (e.g., suicidal behavior, extreme loss of control) needs to be put in place. Moreover, parenting programs and family therapy need to be considered as many of these children come from problematic families with poor parenting and communication skills; often parents themselves suffer from psychiatric disorders. In that case a referral should be considered. This is an ideal situation. However, in many countries these resources won't be available; clinicians may need to rely on psychoeducation, school teachers, extended family and other supports.

M was 7.5 years of age when his parents became increasingly aware and worried because of his frequent temper outbursts, which seemed to happen without a noticeable or minor trigger, such as after arguing with his older sister over which TV channel they would watch. These outbursts had increased in intensity and frequency over time, with verbal and physical aggression towards his classmates as well as objects. Between these outbursts M mostly showed a negative mood. He once mentioned to his friends and parents that he was thinking about what would happen if he was no longer alive. His peers wondered why M was always so cranky and irritable; minor provocations leading to aggressive reactions far out of proportion. The mentioned outbursts happened on average 3-4 times per week; initially, however, frequency had been lower. Outbursts led to fights at school, and soon teachers began to contact the parents to come and discuss M's behavioral problems. Before the current presentation M had been taken to a community health center because teachers had raised the possibility that M was suffering from ADHD. However, the diagnostic process was lengthy as M frequently refused to participate in an evaluation and only rarely showed up for clinical appointments.

A diagnosis of disruptive mood dysregulation disorder was made. Diagnoses of major depression and conduct disorder were ruled out based on self-, parent and teacher reports. Treatment with risperidone was initiated based upon clinical experience because of the frequent temper outbursts. In addition, M received behavioral psychotherapy with a local psychologist in order to identify potential triggers and stressors leading to temper outbursts and negative mood, and to develop strategies to cope with stressful situations that could easily impact M's mood. Further, M and his parents had several meetings with teachers and community health workers to plan strategies for prevention and constructive management of his temper outbursts (such as time-out strategies, understanding and avoiding triggers for aggression and management/coping strategies for stressful situations), frequency and intensity of M's outbursts gradually decreased; he became more cooperative and willing to participate in further treatment and assessment, which lead to the diagnosis of ADHD. Subsequently, treatment with methylphenidate was initiated leading to a further improvement of his scholastic performance and, with only a short latency, to a further improvement of his outbursts. M currently being treated with methylphenidate alone; risperidone had been discontinued after approximately six months. Treatment for ADHD symptoms needed to be continued, but his mood dysregulation problems had improved significantly.

Summary

In the absence of research evidence, treatment of DMDD is currently guided by clinical experience or based on limited evidence about the treatment of specific behaviors such as persistent aggression or temper outbursts. Management needs to be judicious to avoid doing harm rather than good (Roy et al, 2014, Tourian et al, 2015). In summary, this would entail:

- A careful evaluation of symptoms and potential causal factors such as child maltreatment or neglect
- Dealing with the factors that may be causing or maintain the symptoms. That may include CBT, improving parenting skills through parenting programs, psychoeducation, providing support to the family, or fostering if the child is unsafe
- Family therapy when family interactions are severely dysfunctional
- Education and support to teachers
- If symptoms of ADHD are significant, specific ADHD treatment can be tried
- Antipsychotics and sodium valproate may be used when there is lack of response to other interventions
- Temper outburst and aggression may benefit from methylphenidate in children with ADHD. Risperidone or valproate, with the appropriate precautions, may also be helpful

- In spite of the fact that DMDD is considered to be related to major depression, there is no evidence yet that antidepressants are useful
- One important unresolved issue is for how long medication should be prescribed, particularly because some of these drugs have significant side effects
- In most cases, medication should be combined with CBT and parent training for optimal results.

CONCLUSIONS

Irrespective of whether the diagnosis of DMDD in its current incarnation survives the test of time, children and adolescents suffering from chronic irritability are highly impaired and hospitalized frequently. Experienced clinicians are aware that many of these children come from very disturbed families in which abuse, neglect and separation from attachment figures is often the norm, sometimes ignored in taxonomic and research studies. This adds another layer of complexity, in particular because it becomes very difficult to establish which behaviors are due to a "biological" disorder and which are the results of, or a response to family dysfunction, or how one interacts with the other.

- Do you have questions?
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Key practitioner messages

- DMDD is a useful diagnosis for children with severe, non-episodic irritability. Current evidence suggests that such irritability may be related to the depression dimension
- Young people with severe, non-episodic irritability differ from those with bipolar disorder in longitudinal course, family history, and performance on some, although not all, neuropsychological features.
- The diagnosis of pediatric bipolar disorder should be reserved for children who have distinct episodes of mania. During such an episode, the child's mood and behavior must differ from the usual comportment
- There is limited empirical evidence to guide treatment decisions in these patients.

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