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Review article

Focus on Disruptive Mood Dysregulation Disorder: A review of the literature

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ABSTRACT

The inclusion of the Disruptive Mood Dysregulation Disorder (DMDD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), under the category of depressive disorders, provides a diagnosis for those children and adolescents with severe persistent irritability and temper outbursts, once misdiagnosed as Bipolar Disorders. The main and constantly present features of DMDD are chronic, non-episodic and persistent irritability, and temper tantrums disproportionate with the trigger. DMDD is characterized by high rates of comorbidity with other psychiatric disorders. Its main clinical manifestations overlap with Oppositional Defiant Disorder, Conduct Disorder, and Attention-Deficit/Hyperactivity Disorder. For this diagnostic overlap and the increasing use of pharmacological treatments in children and adolescents, the inclusion of DMDD diagnosis has been subjected to many criticisms. Since it is a new diagnostic entity, literature on DMDD prevalence, epidemiology, risk factors, and treatment guidelines, is still sparse and unclear. The aim of this review is to collect and analyze the literature on DMDD diagnostic criteria and main hallmarks, with particular attention to comorbidities and treatment options.

1. Introduction

Disruptive Mood Dysregulation Disorder (DMDD) is a new diagnostic entity annexed in the depressive disorders' domain of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition - DSM-5 (American Psychiatric Association, 2013). It is characterized by non-episodic irritability, defined as persistently negative mood, and severe temper outbursts, a condition of proneness to anger that is disproportionate to the situation, consisting of anger and rages manifested behaviorally and/or verbally. Temper outbursts last more than one minute, but less than five minutes (Potegal et al., 2003). The diagnosis of DMDD has caused disputes for the lack of valid empirical studies and the absence of standard guidelines for pharmacological treatment (Parens and Johnston, 2010; Axelson et al., 2011; Stringaris, 2011). DMDD was introduced as a new diagnostic category, due to an overdiagnosis of Bipolar Disorder (BD) in youth (Baweja et al., 2016), maybe because of the over-inclusive and broader concept of BD (Wozniak et al., 1995). However, clinical presentation of pediatric mania is quite different from adult forms: Leibenluft et al. (2013) proposed a classification of mania in children and adolescents into a "narrow" phenotype, with classical mania/hypomania symptoms, and a "broad" phenotype, without classical symptoms of mania. On the other hand, the broad phenotype is characterized by chronic, non-episodic irritability, and hyperarousal, and it is also known as Severe Mood Dysregulation Disorder (SMDD). This diagnosis was introduced in DSM-IV to forecast the development of Bipolar Spectrum Disorders in youths with irritability. SMDD and DMDD may seem the same disorder, and studies describing the main features of DMDD derive from SMDD studies (Leibenluft, 2011; Stringaris et al., 2010; Brotman et al., 2006). To diagnose DMDD, all criteria in Table 1 are required (American Psychiatric Association, 2013). These criteria coincide with the ones for SMDD diagnosis, except for the so-called hyperarousal criteria (insomnia, distractibility, agitation, racing thoughts or flight of ideas, pressured speech, and intrusiveness), that are not included in DMDD diagnosis. Moreover, onset age was reduced from 12 to 10 years in DMDD. The removal of the hyperarousal criteria for the diagnosis of DMDD led to higher rates of prevalence of children positive for DMDD rather than SMDD.

2. Methods

The aim of this paper is to collect and analyze the recent literature on DMDD diagnostic criteria and main hallmarks of this mood disorder, with particular attention to comorbidities and treatment options. Selected articles were obtained through Pubmed, Scopus Search Paper, Web of Science, and Science Direct. Each database was searched using

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Table 1
DSM-5 diagnostic criteria for disruptive mood dysregulation disorder (American Psychiatric Association, 2013).

A. Severe, recurrent temper outburst (verbally and/or behaviorally) that are grossly out of proportion in intensity or duration to the situation/provocation
B. Outbursts are inconsistent with the developmental level
C. Occur three or more times a week
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observed by others
E. Duration is 12 or more months, without a symptom-free interval of three or more consecutive months
F. Symptoms are present in at least two of three settings (at home, at school, with peers) and are severe in at least one setting
G. Age at onset, either by history or observation, is before 10 years
H. Diagnoses should not be made for the first time before age 6 years or after 18 years
I. Full symptom criteria for manic/hypomanic episode have never been met for longer than one day
J. Behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by other disorders (diagnosis cannot coexist with bipolar disorder, intermittent explosive disorder, and oppositional defiant disorder)
K. Symptoms not due to physiological effects of a substance, a medical or neurological condition

the keywords “disruptive” AND “mood” AND “dysregulation” AND “disorder” OR “temper” AND “outburst” AND “children” OR “temper” AND “outburst” AND “adolescents” OR “temper” AND “outburst” AND “youth” OR “irritability” AND “children” OR “irritability” AND “adolescents” OR “irritability” AND “youth” OR “aggression” AND “children” OR “aggression” AND “adolescents” OR “aggression” AND “youth”. To retrieve all available information on DMDD, neither limits nor inclusion/exclusion criteria were applied. Any original study, case-report, case-series, meta-analysis and systematic review of the subjects of Disruptive Mood Dysregulation Disorder in children and adolescents were qualified for inclusion in this review. References from the obtained articles were also checked. Fig. 1 summarizes the flow chart of articles selected for the review.

3. Clinical features

The core feature of DMDD is irritability: this is the first reason that leads caregivers to seek medical screenings or treatments in youth (Yeh and Weisz, 2001). Although irritability is a common symptom of many psychiatric disorders, in DMDD it is chronic and persistent, occurring in different settings (at school, at home, with peers) for most of the day, almost every day. Other main symptoms are temper outbursts which can be verbally or behaviorally expressed, and out of proportion to the triggers. It is important to underline that irritability is constantly present between temper tantrums. A typical patient affected by DMDD is described in a review of Tufan et al. (2016): a child with impatience, restlessness, and temper tantrums causing harm to him/herself and other people, and verbally and physically aggressive toward parents and family members. Other features are inattention and distractibility, especially at school, with difficulty in engaging in activities that require protracted mental efforts. As highlighted by the findings from the Great Smoky Mountains Study (Copeland et al., 2013), an epidemiological, longitudinal study of children in rural counties of North Carolina, U.S., SMDD/DMDD-affected youth exhibited significantly higher levels of psychosocial impairment than unaffected subjects. Psychosocial

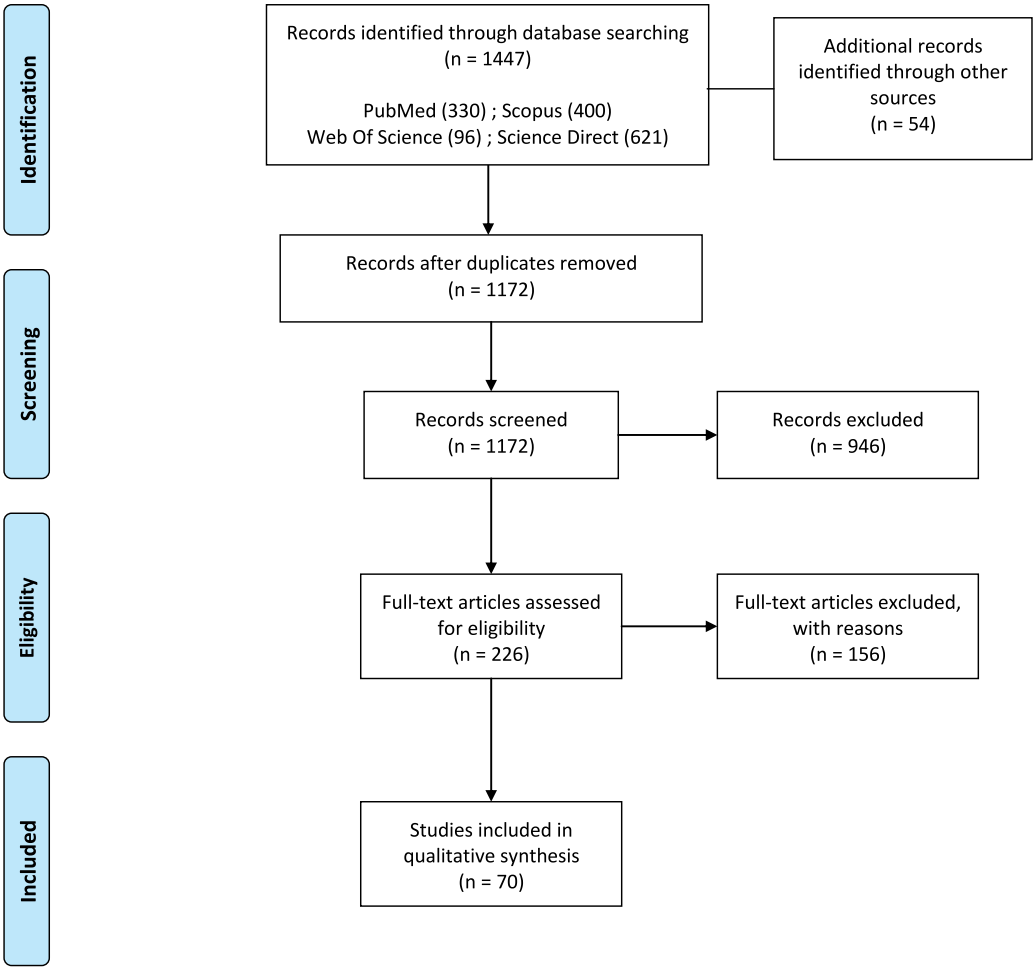

Fig. 1. Flow diagram of the literature selection process.

impairment was particularly evident in the relationships with parents (57.3%) and siblings (25.4%), and also documented by school suspensions (35.1%). Moreover, these children often came from poor families (42.9%), or single-parent families (40.0%). Several variables can predict which DMDD-positive children would have a later psychiatric diagnosis (Dougherty et al., 2017): children with higher levels of externalizing symptoms, anger or frustration, willful and harmful behaviors, functional impairment, temper outbursts and negative affect, lower levels of executive functioning or effortful control, and offspring of depressed mothers, are more likely to develop a later psychopathological condition with functional impairment during adolescence and adulthood (Klein et al., 2005; Weissmann et al., 2006, 2016; Matijasevich et al., 2015). For what concern comorbidity with other psychiatric disorders, children and adolescents diagnosed with DMDD experience higher risk for long-term issues. They are more likely to have adult depression or anxiety disorders, and risky or illegal behaviors. Nevertheless, chronic irritability in youth is not a predictor of BD; episodic irritability is a predisposing factor for a BD diagnosis in adulthood, whereas typical chronic irritability in DMDD is related to unipolar depression and anxiety in adulthood (Brotman et al., 2006; Copeland et al., 2014; Stringaris et al., 2009). Regardless of the functional outcome, youth with DMDD are more likely to have a disability in activities of daily living, learning difficulties, self-injurious behavior, and suicidal ideation when compared to youth with at least one psychiatric diagnosis different from DMDD (Althoff et al., 2016). Copeland et al. (2014) presented a functional outcome profile of youth with a history of DMDD, highlighting how being positive for the hallmark symptoms predicted general health issues, such as worse health outcomes than controls; in addition, subjects with a history of DMDD had higher rates of sexually transmitted diseases (21.9%), regular smoking (75%), illegal or risky behaviors, such as occasional sex with strangers (16.3%), police contact (30.5%), illegally breaking into buildings or property (18.9%), and physical fighting (26.8%). Furthermore, among social risk factors and outcomes, DMDD-positive subjects were more likely to come from disadvantaged families (86.3%) and divorced or single parents, and to be dismissed from work (37.7%) or having difficulties to keep a job (27.8%). Psychiatric comparison subjects, on the other hand, were at higher risk for serious illnesses (7%), but they had lower rates of sexually transmitted diseases (4.4%). It is less common to have a DMDD diagnosis without co-occurrence of other psychiatric disorders and, according to these findings, it is not easy to establish if the functional outcome is influenced by comorbidity or by the severity of cardinal symptoms.

4. Prevalence and epidemiology

Most of the studies focused on epidemiological factors in DMDD are retrospective and refer to SMDD diagnosis. The Great Smoky Mountains Study compared prevalence rates of DMDD and SMDD in preschoolers and school-age youth, showing a higher prevalence in the former, with rates ranging from 0.8% to 3.3%, although the prevalence of DMDD seems to decrease with age. It should also be underlined that the strict application of the criteria related to symptom duration and frequency has significantly restricted the total number of DMDD-positive subjects (Copeland et al., 2013).

5. Pathophysiology

Leibenluft et al. (2013) analyzed the pathophysiology of both episodic and non-episodic irritability by neuroimaging techniques, such as functional Magnetic Resonance Imaging (fMRI), Event-Related Potentials (ERP) and Magnetoencephalography (MEG). Children and adolescents with SMDD were compared with BD-affected subjects and healthy controls, matched for age. Either youth with SMDD and BD had attention deficits; nevertheless, the neural circuits responsible for these patterns seemed to be different between the two disorders (Leibenluft and Stoddard, 2013). SMDD-positive subjects revealed deficient bottom-up attention, whereas BD patients had abnormalities in top-down executive attention (Rich et al., 2007). Furthermore, youth with SMDD manifested hyperarousal elicited by frustrating stimuli (Rich et al., 2011; Roy et al., 2013). Another deficit is the dysfunction in emotional processing, which seems to be involved in the typical aggressive reactions of these subjects (Guyer et al., 2007); the peculiar disturbance in emotional processing relies in a general difficulty in identifying emotions through facial expressions, especially the negative ones, possibly leading to experience exaggerated fear in the presence of neutral faces. A functional MRI study has compared children with SMDD with healthy controls in an attention task under non-frustrating and frustrating circumstances, with the aim of examining affective, behavioral, and neural mechanisms of frustration tolerance (Deveney et al., 2013). During the frustrating condition, both groups exhibited increased frustration and difficulties in shifting spatial attention, although the deficit was significantly more pronounced in SMDD subjects. Furthermore, SMDD subjects showed decreased activation in regions involved in emotions, attention and reward mechanisms, such as the left amygdala, the striatum, the parietal cortex and the posterior cingulate. Similar results have been obtained in studies on DMDD subjects: abnormal amygdala activation, related to irritability intensity, has been observed during a facial affect recognition task (Wiggins et al., 2016). DMDD patients constantly showed excessive amygdala activation for all facial emotions, whereas BD subjects showed the same activation only for fearful facial expressions. A MEG study on patients with pediatric BD compared with healthy controls showed different neural pathways to negative affects (Rich et al., 2011): SMDD-affected youth exhibited greater activation of the medial frontal gyrus and anterior cingulate cortex, whereas BD subjects had reduced insula activation and enhanced superior frontal gyrus activation.

6. Risk factors

To the best of our knowledge, the number of studies analyzing early risk factors for DMDD is still limited (Vidal-Ribas et al., 2016). Risk and protective factors for the development of youth mental disorders are influenced by both environmental and genetic features (Kieling et al., 2011). Table 2 summarizes the main predisposing factors associated with the risk of developing disruptive behaviors. Roberson-Nay et al. (2015) noticed gender differences in the genetic load for irritability, with genetic influence being higher in female subjects, but only during childhood. Furthermore, they observed that environmental features had less influence than genetic ones for developing DMDD. Both Sparks et al. (2014) and Tufan et al. (2016) observed that the offspring of parents with psychopathology had a high risk of developing DMDD. Children born by mothers affected by peripartum depression

Table 2
Risk factors and predisposing factors for disruptive behaviors.

Family history	Stressful life events	Nutritional status
- Substance abuse - Psychiatric problems - Maternal depression during pregnancy and/or the first year after birth	- Early life trauma (emotional, physical or sexual abuse) - Recent family divorce, grief or relocation	- Iron deficiency - Vitamin B12 deficiency - Folate deficiency

(during pregnancy and the first year after childbirth) had higher rates of DMDD diagnosis with greater severity of irritability; also, paternal depression and substance use were risk factors for worse symptom patterns of irritability (Dougherty et al., 2014; Munhoz et al., 2017; Wiggins et al., 2014). An increased risk of receiving a DMDD diagnosis was observed if one or both parents were not living with the children and adolescents, or if one of them had not completed college (Althoff et al., 2016). Regarding environmental risk factors, the role of early trauma has been emphasized, with particular attention to psychological trauma and abuse (Starr et al., 1991; Wolfe and McGree, 1991). Furthermore, other factors, such as grief, divorce, and malnutrition or vitamin deficiencies (Bellisle, 2004) are supposed to be potential predisposing factors for the onset of disruptive behaviors (Matijasevich et al., 2015).

7. Comorbidity

DMDD has usually high rates of comorbidity with other psychiatric disorders, and this co-occurrence also extends into adulthood (Copeland et al., 2013, 2014). The majority of patients with a DMDD diagnosis present at least one other comorbid disorder, mainly ODD, CD and ADHD, whereas they are less likely to meet criteria for BD I or II (Freeman et al., 2016). In order to evaluate the presence of other psychiatric conditions, a careful assessment can be realized through a comparison between DMDD and the disorders included in Table 3. The most common comorbid disorder in DMDD is ODD with rates up to 96% of the cases, followed by ADHD (81%), and CD (13%). According to DSM-5, ODD criteria include a pattern of angry/irritable mood, argumentative/defiant behaviors, and revengefulness for at least 6 months, accompanied by four or more of the following features: often loses temper, often touchy or easily annoyed, often angry and resentful, often argues with adults or authority figures, often actively defies/refuses to comply with request or rules, often deliberately annoys others, often blames others for his/her mistakes or misbehavior (American Psychiatric Association, 2013). It is almost evident that such criteria facilitate a diagnostic overlap between ODD and DMDD, due to the inclusion of the two main symptoms of DMDD, angry or irritable mood and recurrent temper outburst, in the ODD criteria (Safer, 2009; Mayes et al., 2011; Stringaris, 2011; Leibenluft et al., 2012; Roy et al., 2014); however, according to DSM-5, no diagnosis of ODD can be confirmed if a patient meets criteria for both disorders. Moreover, besides ODD, cardinal symptoms of DMDD (irritability and temper outburst) are common in children with a variety of disorders, including Autism Spectrum Disorders (ASD), and ADHD (Mayes et al., 2016). More than one-third of children with ASD are affected by maladaptive emotional problems (Pan and Yeh, 2016). Although chronically irritable/angry mood and temper outbursts are distinct from the typical symptoms of ASD for having a better response to pharmacological treatment, yet they are consistently related to subsequent psychosocial impairment, harmful consequences, and emotional distress for family members and caregivers. Actually, more severe social impairment has been reported in children with both ASD and chronic irritability than in ASD subjects without chronic irritability (Gadow et al., 2008). It is not completely clear whether mood dysregulation in youth with ASD are epiphenomena or comorbid disorders, since emotional problems have similar clinical features in ASD patients and in non-autistic controls (Gadow et al., 2005). In DSM-5, a dual-diagnosis of ASD and ADHD is permitted, so that mood dysregulation can be considered a core symptom of ADHD and, moreover, mood disorders are a possible comorbid option in children and adolescents with ASD. This implies the co-existence of a DMDD diagnosis in the autistic population. Nevertheless, neuroimaging evidence has shown differences between ADHD and DMDD in those neural circuits implicated in emotional processing (Brotman et al., 2010). Children and adolescents with autism are not able to understand emotions and intentions, whereas youth affected by comorbid ASD and DMDD exhibite an excessive negative response to

Table 3
Differential diagnosis of DMDD (DSM-5).

Disorder	BD	ODD	IED	ADHD	MDD-GAD-ASD
Characteristics of irritability	Episodic irritability	Irritability commonly present, but not required for diagnosis	No persistent irritable or angry mood between outbursts	Irritability commonly present, but not required for diagnosis	Irritability occurs in relation to the context
Characteristics of outbursts	Fluctuating mood (euthymia, depression, mania)	Outbursts occur less frequently (once a week)	Outbursts occur less frequently (twice a week)	Outbursts commonly present, but not required for diagnosis	Outbursts occur in relation to the context
Eventual age limit	No age limits	No minimum or maximum onset age	At least 6 years old, or equivalent developmental level; no maximum age	Age at onset < 12 years	
Duration		Duration is 6 months	Duration is 3 months	Inattention, hyperactivity and impulsivity criteria present for at least 6 months	
Setting		No setting stipulated	No setting stipulated		The symptoms only occur in an anxiety-provoking context
Additional differentiating features	Psychosis may be present				The symptoms only occur when the routines are disturbed or change

Abbreviations: BD, Bipolar Disorder; ODD, Oppositional Defiant Disorder; IED, Intermittent Explosive Disorder; ADHD, Attention-Deficit/Hyperactivity Disorder; MDD, Major Depressive Disorder; GAD, Generalized Anxiety Disorders; ASD, Autism Spectrum Disorder.

Table 4
Published efficacy trials on pharmacological treatment of DMDD.

Authors / year of publication	Study design	Trial duration	Number of patients	Age	Pharmacological agent	Pharmacological regimen	Active comparator	Principal outcome measures	Main efficacy results
Owen et al. (2009)	Double-blind, randomized, placebo-controlled, parallel-group study	8 weeks	98	6–17 years of age	A	2–5–10–15 mg/day	Pl	Caregiver-rated aberrant behavior checklist (ABC) irritability subscale Clinical Global Impression-Improvement score (CGI-I)	A (any regimen) more effective than Pl
Shea et al. (2004)	Double-blind, randomized, placebo-controlled trial	8 weeks	79	5–12 years of age	R	1.17 mg/day	Pl	Caregiver-rated aberrant behavior checklist (ABC) Nisonger Child Behavior Rating Form (parent version) Visual Analog Scale	Greater decrease on the irritability compared with patients who were taking Pl
Jaselskis et al. (1992)	Double-blind, placebo-controlled, crossover trial	13 weeks	8	Mean age of 8.1 years	C	0.15–0.20 mg x	Pl	Conners abbreviated parent-teachers questionnaire Home situational scale Symptom checklist Caregiver-rated aberrant behavior checklist (ABC) Attention deficit disorder with hyperactivity (ADD-H) Comprehensive Teacher Rating Scale	Significant improvement in C compared with Pl
Scahill et al. (2011)	Double-blind, randomized, placebo-controlled	8 weeks	34	Mean age of 10.4 years	G	0.5–4 mg/day	Pl	Clinical Global Improvement Scale teacher-rated ADHD Rating Scale Parent-rated Hyperactivity Index Continuous Performance Test	G was associated with an improvement in the total score compared to placebo; parent-rated hyperactivity index improved with a non-significant difference between G and Pl
Campbell et al. (1995)	Double-blind, placebo-controlled, clinical trial	6 weeks	50	Mean age of 9.4 years	L	600–1800 mg/day	Pl	Global Clinical Judgments (Consensus) Scale Children's Psychiatric Rating Scale Conners Teacher Questionnaire Parent-Teacher Questionnaire Profile of mood states (POMS)	Lithium was superior to placebo
Rifkin et al. (1997)	Double-blind fashion	2 weeks	33	12–17 years of age	L	Adjusted to maintain a blood level of 0.6–1.0 mmol/liter, after administration of 600 mg of lithium carbonate	Pl	Overt Aggression Scale Behavior Rating Scale Conners Teacher Rating Scale	Lithium does not appear beneficial for this indication

(*continued on next page*)

Table 4 (*continued*)

Authors / year of publication	Study design	Trial duration	Number of patients	Age	Pharmacological agent	Pharmacological regimen	Active comparator	Principal outcome measures	Main efficacy results
								Hamilton Rating Scale for Depression	
Malone et al. (2000)	Double-blind, placebo-controlled, clinical trial	4 weeks	40	Median age 12.5	L	300–2100 mg/die	Pl	Clinical global impressions	Lithium was superior to placebo
								Global Clinical Judgements (Consensus) Scale	
								Overt Aggression Scale	
Donovan et al. (2000)	Double-blind, placebo-controlled, crossover design	12 weeks	20	10–18 years of age	D	750–1500 mg/day	Pl	Modified Overt Aggression Scale	Of the 15 subjects who completed both phases, 12 has superior response taking D
								Anger hostility subscale of the SCL-90	

Abbreviations: A, Aripiprazole; R, Risperidone; C, Clonidine; G, Guanfacine; L, Lithium; D, Divalproex; Pl, Placebo.

frustration overlapping with a scarce ability to detect emotions and intentions; the result is a more frequent and severe frustration in ASD plus DMDD subjects. Both emotional dysregulation and frustration may be well explained by dysfunctions in the meta-representation system and in its neurobiological correlates, such as orbitofrontal-amygdala and cingulate circuits (Gallese et al., 2013; Bachevalier and Loveland, 2006). Regarding the relationship between BD and DMDD, it has been hypothesized that the offspring of parents with BD would be more likely to be diagnosed with DMDD than controls (Sparks et al., 2014), although this result has not been thoroughly confirmed (Propper et al., 2017). Also, the offspring of parents with depressive disorder met the main criteria for DMDD. The association between family history of depressive disorders and DMDD has been supported by data from population-based (Wiggins et al., 2014; Whelan et al., 2015; Dougherty et al., 2013) and longitudinal studies, whereas no evidence supporting a developmental continuity with BD has been reported (Stringaris et al., 2009; Copeland et al., 2014; Krieger et al., 2013).

Finally, episodic irritability in youth is usually associated with Generalized Anxiety Disorder (GAD) in late adolescence, and with Mania in late adolescence and adulthood, whereas chronic irritability in childhood and early adolescence is associated with behavioral disorders in late adolescence and unipolar depressive disorder in adulthood (Krieger et al., 2013).

8. Treatment options

8.1. Pharmacological treatment

Since no guidelines for treatment, pharmacological therapy usually targets core symptoms of DMDD, such as severe chronic irritability and temper outburst. However, as DMDD shares several core symptoms with SMDD, most of the studies refer to the latter. The results of the main pharmacological studies are shown in Table 4. Before DSM-5, treatment with antidepressants or stimulants was considered a risk because of the possibility of turning into mania or worsening irritability. Convincing evidence of a close association among DMDD, unipolar depression, and anxiety disorders has shifted current treatment trends towards the use of psychostimulants and antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenalin reuptake inhibitors (SNRIs), for treating chronic and persistent irritability and anger in children and adolescents (Tourian et al., 2015). These classes of agents have a documented efficacy in ADHD for their positive effect on aggressive behaviors: both psychostimulants (methylphenidate), and antidepressants, such as atomoxetine, bupropion, fluoxetine, and desipramine, improve aggression (Pappadopulos et al., 2006). Other drugs with a good outcome on irritability and aggression are atypical antipsychotics, mainly risperidone and aripiprazole (Cohen et al., 2013; Owen et al., 2009; Shea et al., 2004). Methylphenidate is one of the most efficacious agents for decreasing aggression in subjects with ADHD; when clinical improvement is not achieved, risperidone add-on could be a valid therapeutic choice. The rationale for using atypical antipsychotics in SMDD or DMDD derives from the observed clinical effect in children with ASD and symptoms of irritability and temper outburst (Pappadopulos et al., 2006; Owen et al., 2009). Furthermore, other agents, such as the alpha-2 agonists clonidine (Connor et al., 2003; Jaselskis et al., 1992) and guanfacine (Scahill et al., 2011), have been shown effective in reducing aggressive symptoms in ADHD patients. Finally, lithium and anticonvulsants, respectively the mainstays in the treatment of BD and seizure disorders, have been found to moderately reduce aggression (Campbell et al., 1995; Rifkin et al., 1997; Malone et al., 2000; Donovan et al., 2000). A case report has suggested the efficacy of naltrexone, a competitive opioid antagonist, in improving aggressive outbursts and functioning in an adolescent male with DMDD (Parmar et al., 2014), based on the assumption that endogenous opiates, either directly or by modifying dopaminergic pathways, are involved in repetitive self-injurious and addictive behaviors (Stanley et al., 2010).

8.2. Non-pharmacological treatment

Psychotherapeutic treatments, such as behavioral therapy and parent training interventions, must be considered a cornerstone in DMDD treatment. Given the significant impairment in social functioning and the emotional dysregulation associates with the disorder, behavioral therapy and parent interventions should always be incorporated into the management of DMDD patients. Dialectical behavior therapy adapted for pre-adolescent children (DBT-C) has attained a response rate around 90.4% in subjects with severe emotional and behavioral disorders, as shown by a randomized clinical trial (Perepletchikova et al., 2017). It has been underlined that the addition of a parent training component may have contributed to reduce disruptive behaviors, as documented by retention rates, positive outcomes, and no reports to child services during DBT-C treatment. Moreover, parental active participation may have been more effective and significant than child's compliance and participation for symptoms relief, that can be achieved without additional psychopharmacological treatments. Finally, the rapid improvement in functioning observed during DBT-C may help to maintain children's compliance with treatment.

9. Conclusions and future perspectives

After its introduction in the DSM-5, the new DMDD diagnosis received a certain criticism, mainly due to general worries for an increased use of psychotropic medications for treating behavioral problems in children and adolescents, and to the effect of lowering the threshold for the diagnosis of a psychiatric disorder in presence of anger outbursts and temper tantrums, which may be common behavioral problems during childhood. For these reasons, an empirically based alternative to the DMDD diagnostic category has been proposed in ICD-11. According to the ICD-11, DMDD is a diagnostic specifier of ODD, targeting those ODD patients who also show chronic irritability and anger (Lochman et al., 2015). Before its introduction in the DSM-5, no peer-reviewed research was conducted for DMDD, because substantial changes in SMDD symptoms were made before revision and adaptation for inclusion in DSM-5. It is evident that further studies bringing new evidence on DMDD are necessary for a better validation of this new diagnostic entity and for its treatment. Regarding treatment, one of the major problems is the preponderant use of medications usually administered to treat adult BD. Any pharmacological choice is associated with side effects: psychostimulants require monitoring, and atypical antipsychotics are correlated with metabolic syndrome (weight gain, dyslipidemia, and insulin resistance), possibly leading to cardiovascular illnesses in adult age. Moreover, although the risk for extrapyramidal symptoms is low with second-generation antipsychotics, this should be borne in mind when treating young patients. Further randomized, controlled trials in large samples of youth meeting the full diagnostic criteria for DMDD across different developmental periods are needed for better define which classes of psychotropic drugs are safe and effective for controlling aggression and disruptive mood in children and adolescents.

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