Journal of Affective Disorders 265 (2020) 207–215

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Are youths with disruptive mood dysregulation disorder different from youths with major depressive disorder or persistent depressive disorder?

Xavier Benarous[a,b,c], Johanne Renaud[d,e], Jean Jacques Breton[f], David Cohen[c,g], Réal Labelle[f,h,i,j], Jean-Marc Guilé[a,b,e,*]

[a] Child and Adolescent Psychopathology Services, Amiens University Hospital, Amiens, France
[b] INSERM Unit U1105 Research Group for Analysis of the Multimodal Cerebral Function, University of Picardy Jules Verne (UPJV), Amiens, France
[c] Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France
[d] Manulife Centre for Breakthroughs in Teen Depression and Suicide Prevention, Douglas Mental Health University Institute, McGill University, Montreal, Canada
[e] Department of psychiatry, McGill University, Montreal, Canada
[f] Department of psychiatry, University of Montreal, Montreal, Canada
[g] CNRS UMR 7222, Institute for Intelligent Systems and Robotics, Sorbonne Universités, UPMC, Paris, France
[h] Département de psychologie, Université du Québec à Montréal, Montréal, Canada
[i] Centre de recherche, Hôpital en santé mentale Rivière-des-Prairies, CIUSSS du Nord-de-l'Île-de-Montréal, Canada
[j] Centre for Research and Intervention on Suicide, Ethical Issues and End-of-life practices, (CRISE), Montreal, Canada

ARTICLE INFO

Keywords:
Disruptive mood dysregulation disorder
Major depressive disorder
Persistent depressive disorder
Suicidal behavior
Adolescent
Retrospective chart review

ABSTRACT

Background: Although the disruptive mood dysregulation disorder (DMDD) was included in the depressive disorders (DD) section of the DSM-5, common and distinctive features between DMDD and the pre-existing DD (i.e., major depressive disorder, MDD, and persistent depressive disorder, PDD) received little scrutiny. Methods: Youths consecutively assessed as outpatients at two Canadian mood clinics over four years were included in the study (n = 163; mean age:13.4 ± 0.3; range:7–17). After controlling for inter-rater agreement, data were extracted from medical charts, using previously validated chart-review instruments.

Results: Twenty-two percent of youths were diagnosed with DMDD (compared to 36% for MDD and 25% for PDD), with substantial overlap between the three disorders. Youths with DMDD were more likely to have a comorbid non-depressive psychiatric disorder – particularly attention deficit hyperactivity disorder, odds ratio (OR = 3.9), disruptive, impulse-control and conduct disorder (OR = 3.0) or trauma- and stressor-related disorder (OR = 2.5). Youths with DMDD did not differ with regard to the level of global functioning, but reported more school and peer-relationship difficulties compared to MDD and/or PDD. The vulnerability factors associated with mood disorders (i.e., history of parental depression and adverse life events) were found at a comparable frequency across the three groups. Limitations: The retrospective design and the selection bias for mood disordered patients restricted the generalizability of the results. Conclusions: Youths with DMDD share several clinical features with youths with MDD and PDD. Further studies are required to determine the developmental trajectories and the benefits of expanding pharmacotherapy for DD to DMDD.

1. Introduction

Over the last two decades, the diagnosis and treatment of children presenting with severe and chronic irritability has become a challenge within the context of the pediatric bipolar controversy (Masi et al., 2015; Roy et al., 2014; Consoli and Cohen, 2013; Tourian et al., 2015). On the basis of studies of youths with severe mood dysregulation (SMD), a clinical presentation characterized by persisting irritability and recurrent temper outbursts, the disruptive mood dysregulation disorder (DMDD) was included as a new diagnostic entity in the depressive disorders (DD) section of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013). The DMDD is characterized by persistent irritable mood and, severe (i.e. out of proportion in intensity or duration) and frequent (i.e. three or more times per week) temper outbursts.

The discriminant validity of DMDD and its inclusion among DD

* Corresponding author at: Child and Adolescent Psychiatry Services, Amiens University Hospital, Amiens, France, CHU Amiens-Picardie, Site Sud, F-80054 Amiens, France.
E-mail address: guile.jean-marc@chu-amiens.fr (J.-M. Guilé).

https://doi.org/10.1016/j.jad.2020.01.020
Received 12 March 2019; Received in revised form 27 November 2019; Accepted 5 January 2020
Available online 08 January 2020
0165-0327/

have been, and still are, controversial issues (Roy et al., 2014; Stringaris et al., 2017). The inclusion of DMDD in the DD section of the DSM-5 was supported by longitudinal studies showing that chronic irritability in childhood led to internalizing disorders in adolescence and early adulthood, in particular anxiety and depressive disorders (Brotman et al., 2006; Stringaris et al., 2009; Stringaris et al., 2010; Leibenluft E. Severe Mood Dysregulation 2011; Vidal-Ribas et al., 2016). The relationship between childhood irritability and depression in adolescence was also supported by genetic and family studies (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Propper et al., 2017; Krieger et al., 2013; Wiggins et al., 2018; Brotman et al., 2007; Stringaris et al., 2012; Savage et al., 2015).

The delimitation of DMDD from other psychiatric disorders, and, in particular mood disorders, is an essential step towards the establishment of its diagnostic validity (Robins and Guze, 1970). To date, the literature has mainly focused on the distinction between DMDD (and the research clinical entity of SMD) and bipolar disorder (BD) (Stringaris et al., 2010). In contrast, the validity of DMDD has not been questioned against DD, i.e., major depressive disorder (MDD) and persistent depressive disorder (PDD). PDD differs from MDD with respect to the severity and duration of depressive symptoms. PDD is a chronic DD whereas MDD is regarded as mostly, but not exclusively, episodic. Cumulative findings showed that the chronic versus episodic course of mood symptoms is a key clinical feature with distinctive clinical correlates (Masi et al., 2006) and outcome in adulthood (Leibenluft et al., 2006). DMDD differs from DD, both PDD and MDD, with respect to the presence of temper outbursts and the nature of mood symptoms. Findings from the prospective population-based Great Smoky Mountains Study (Stringaris et al., 2013) showed that depressed mood was the most common cardinal mood symptom in youth meeting criteria for DD. On the contrary, irritable mood alone was rare (5.7%). Given that no study has questioned DMDD against MDD or PDD, the differences between MDD, PDD and DMDD (in terms of clinical correlates, natural course, and vulnerability factors) have yet to be characterized. The present study aimed to address these issues.

The first objective of the present study was to determine the frequency of DMDD (compared to MDD and PDD) in a clinical outpatient sample. The frequency of DMDD is expected to be similar to the values reported in outpatient samples (22–31%) (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016). The extent of overlap between DMDD, MDD and PDD would help to document the validity of the diagnosis of DMDD. Indeed, if DMDD is a distinct, valid clinical entity, its overlap with MDD and/or PDD should be moderate - or at least no larger than for the two other disorders.

The study's second objective was to compare the clinical characteristics of youths with DMDD, MDD and PDD. We hypothesized that the comorbidity rate would be higher for DMDD than for the two other disorders. This would be in line with previous studies showing a high rate of comorbidity in children and adolescents with DMDD compared to other psychiatric disorders (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016; Dougherty et al., 2014; Axelson, 2013; Stringaris and Taylor, 2015; Copeland et al., 2013). This would also be consistent with the assumption that irritability, the core symptom in DMDD, is located at the interface between internalizing disorders and externalizing disorders (Stringaris and Taylor, 2015).

The study's third objective was to compare the impairments respectively associated with DMDD, MDD and PDD. We expected that youths with DMDD would present a range of peer-relationship difficulties that went beyond aggressive behavior. Several dysfunctions in social information processing have been reported in youths with chronic irritability; this exposes them to a greater risk of experiencing repeated interpersonal difficulties (Leibenluft E. Severe Mood Dysregulation 2011; Vidal-Ribas et al., 2016; Vidal-Ribas et al., 2018). Based on preliminary findings, we would also expect school functioning to be more impaired in youths with DMDD than in youths with MDD or PDD (Dougherty et al., 2014; Copeland et al., 2013).

Lastly, the study's fourth objective was to compare the vulnerability factors profile for mood disorders in youths with DMDD, MDD and PDD. The focus was placed on vulnerability factors consistently associated with DD in children and adolescents, i.e., a first-degree family history of depression, a history of adverse life events and an impaired developmental history (Thapar et al., 2012).

2. Methods

2.1. Participants

Data were retrospectively reviewed after their extraction from the medical records of youths referred to the two mood disorder outpatient clinics in Montreal (Canada) between November 2006 and December 2010. The recruitment sites for French-speaking and English-speaking youths were respectively the Rivière des Prairies Hospital (RPH) and the Douglas Mental Health University Institute (DMHU). The main inclusion criteria were age between 7 and 17, and admission to one of the two outpatient clinics following a standardized diagnostic evaluation by a multidisciplinary team (including a child psychiatrist). A total of 163 consecutive participants were assessed (114 at RPH and 49 at DMHU) during the study period. The study population comprised 65 males (40%) and 98 females (60%), and the mean ± standard deviation (range) age was 13.4 ± 0.3 (7–17).

2.2. Setting and study design

Clinical and sociodemographic data were gathered using a chart review instrument that had previously been validated in a retrospective study of adolescent outpatients with DD (Breton et al., 2012; Guile et al., 2016; LeBoeuf et al., 2017). The instrument recorded all the clinical data noted by healthcare professionals (clinicians, social workers and nurses) in the patient's medical file. All information pertaining to a participant's identity was removed. The inter-rater agreement ($\kappa = 0.80$) had previously been measured at each site, using a sample of ten charts. Data on sociodemographic characteristics, family and personal medical histories, DSM diagnoses, symptoms, and treatment were extracted using the instrument. In the medical records, the psychiatric diagnoses had been defined according to the DSM-IV-TR criteria and categories. In the current analysis, the psychiatric diagnoses were presented with respect to the DSM-5 criteria and categories. At both recruitment sites, the routine diagnostic work-up encompassed several standardized evaluations including the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) (Kaufman et al., 1997) and the Children-Global Assessment Scale (C-GAS) (Shaffer et al., 1983). In accordance with the ethics regulatory framework enforced in the province of Québec (Canada), access to medical files was authorized by the Director of Professional Services at each of the two investigating centers.

2.3. Measurements

2.3.1. Psychiatric diagnoses

The K-SADS-PL was completed as part of each patient's routine clinical assessment at DMHU and RPH. The parents were the informants in the present study. The K-SADS-PL' internal validity (inter-rater reliability: 93–100%; test-retest reliability: 0.74–0.90) and external validity are excellent. Clinical data relative to psychiatric diagnoses were extracted using the chart review instrument. Apart from the removal of the bereavement exclusion criteria, the diagnostic criteria for MDD in DSM-5 (notably the presence of symptoms for at least two weeks) are the same as those in DSM-IV-TR. The diagnosis of PDD was introduced in the DSM-5 as a consolidation of the previously defined DSM-IV-TR category of dysthymia and the chronic subtype of MDD. All participants meeting criteria for dysthymia have been identified as PDD. None of the study participants met the criteria for chronic subtype of MDD.

With respect to the DMDD diagnosis, symptoms reported in the patient's medical file were compared with the DSM-5 criteria for DMDD. Data were abstracted using an additional chart review instrument based on the criteria for temper dysregulation disorder with dysphoria - a research entity developed by the DSM-5 Task Force prior to the publication of the final criteria for DMDD (Leibenluft E. Severe Mood Dysregulation 2011; American Psychiatric Association Taskforce DV 2010) . Each criterion was scored as *present, absent* or *unknown*. The diagnostic algorithm is provided in the Supplementary Material, and follows the international guidelines (Table S1) (American Psychiatric Association Taskforce DV 2010). In particular, DMDD was endorsed only if the patient met the criteria for duration, cross-domain impairment, and age of onset, with the exclusion criteria rule for bipolar disorder. The psychometric properties of this diagnostic instrument for DMDD have previously been explored in another sample of 12- to 15-year-old outpatients (n = 192; Cronbach's α for internal validity: 0.90; κ for test-retest reliability: 0.87) (Boudjerida et al., 2018).

2.3.2. Suicidal behavior and substance use

Suicidal behavior was documented by rating a set of four items: "*prior suicidal ideation", "a single prior suicide attempt", "multiple prior suicide attempts", and "prior self-aggressive behavior"*. The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007) was completed for the study participants at the DMHU clinic. The C-SSRS assesses various forms of suicidal behaviors (active suicidal ideation, interrupted suicide attempts, and aborted suicide attempts), and non-suicidal self-injuries.

Substance use was documented using a set of five items: *"prior use of a substance", "regular alcohol use", "regular alcohol use before the age of 12", "regular tobacco use", and "regular tobacco use before the age of 12"*. In the study sample from DMHU, the DEP-ADO questionnaire (Germain et al., 2007) was additionally used to document substance use in the previous 12 months. The screening question was "*During the last twelve months, how often have you [has X] used one of the following substances: alcohol, cannabis, cocaine, inhalant/solvent, stimulant, hallucinogen, or heroin*"; examples and trivial names were provided for each substance.

2.3.3. Functional impairment

The level of global functioning was evaluated using the Children-Global Assessment Scale (C-GAS) (Shaffer et al., 1983) on the basis of the multidisciplinary evaluation at the first medical visit. Peer-relationship problems were assessed by the clinician using an eight-item checklist used in chart reviews for the assessment of social functioning in youths with DD (Breton et al., 2012; Guile et al., 2016; LeBoeuf et al., 2017). The instrument whose reliability has been previously assessed (Breton et al., 2012), regroups the following items: physical and aggressive behaviors, stealing goods from other youths, passive and active social withdrawal, feeling of being rejected by other youths, victim of physical or verbal aggression. School impairments were assessed using the school reports annexed to the medical file with regard to the following domains: prior grade repetition, reported learning difficulties, repeated unjustified school absence.

2.3.4. Vulnerability factors

A modified version of the Family History Screen (Weissman et al., 2000) was used to retrospectively collect information on the psychiatric history of the participants' first- and second-degree relatives. This included the history of paternal and maternal depression, which is the most well-recognized risk factor for children and adolescent depression (Thapar et al., 2012). Adverse childhood experiences (ACE) were assessed using all available data, with respect to a set of ten items from the Adverse Childhood Experience Questionnaire (Anda et al., 2010) A major ACE was defined as an episode of physical and/or sexual and/or emotional abuse and/or a severe form of emotional and/or physical neglect (Anda et al., 2010). Data from administrative sources (e.g. a history of placement in foster care) were also collected following the method used in previous chart-review studies for pediatric mood disorders (Garno et al., 2005; Benarous et al., 2017a). The developmental history was explored regarding four domains: a history of complicated pregnancy, a history of delayed psychomotor development, the presence of an associated neurological disorder, and a history of head trauma.

2.4. Statistical analyses

Considering the small sample size and the non-Gaussian data distribution, non-parametric Kruskal-Wallis tests were used to compare three groups: (i) youths with DMDD (and, in some cases, a concomitant DD), (ii) youths with MDD only (i.e., without DMDD and/or PDD), and (iii) youths with PDD only (i.e., without DMDD and/or MDD). First, we aimed at increasing the homogeneity of the control groups and thus raise the study's statistical power. Second, in order to increase external validity, we wanted to form the largest possible and most representative clinical sample of youths with DMDD. In order to facilitate the interpretation of our findings with respect to the previous studies (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016), we compared the DMDD group with the rest of the sample ("non-DMDD youths") (studies detailed in Table S2). The groups were compared using Pearson's chi-squared test or Fisher's exact test for categorical variables (e.g., DSM-5 diagnoses), and Student's test or a Mann-Whitney test for continuous variables (e.g., age). Similar analyses were performed for the study's third and fourth objectives. The results were not corrected for multiple comparisons; we considered that in the context of an exploratory analysis, the type II error outweighed the type I error. All statistical analyses were performed with STATASE software (version 12). The threshold for statistical significance was set to $p < .05$. All analyses were replicated with (i) a more homogeneous DMDD group (i.e., after the exclusion of youths with associated MDD and/or PDD), and (ii) a DMDD group without associated Attention Deficit with/out Hyperactivity Disorder (ADHD) (Table S3).

3. Results

3.1. Objective 1. Frequency of DMDD and overlap with MDD and/or PDD

Thirty-six youths (22%) met the criteria for DMDD (Table 1). The frequencies of MDD and PDD were respectively 36% and 25%. The two sites did not differ significantly (p = .191) with regard to the frequency of DMDD. Thirty-six percent of the youths with DMDD were also diagnosed with a DD (MDD n = 7, PDD n = 6), but none met the diagnostic criteria for all three disorders (Fig. 1).

3.2. Objective 2. Clinical characteristics of youths with DMDD, MDD and PDD

Youths with DMDD were an average of 3.3 years younger than those with MDD and 2.5 years younger than those with PDD. The proportion of boys was significantly higher in the DMDD group than in the other two groups.

The comorbidity profiles of youths with DMDD and youths with other DD are summarized in Table 2. All the youths with DMDD had at least one other comorbid DSM-5 diagnosis. The number of comorbidities was significantly higher among youths with DMDD than among youths with MDD or PDD. Compared with youths with PDD or MDD, youths with DMDD were more likely to have concurrent trauma- and stressor-related disorders (odds ratio (OR) = 2.5, p = .004), ADHD (OR = 3.9, p < .001) or disruptive, impulse-control and conduct disorders (DICCD) (OR = 3.0, p = .006). The frequency of anxiety disorders was highest in the PDD group and lowest in the MDD group. The DMDD, MDD or PDD groups did not differ significantly with regard to the frequency of substance use (see Fig. 3), learning disorders or other

Table 1
Frequency of psychiatric disorders among recruitment sites.

	RPH (n = 114)	DMHU (n = 49)	Total (N = 163)
Internalizing disorders			
Mood disorders			
MDD	40 (35%)	19 (39%)	59 (36%)
PDD	30 (26%)	10 (20%)	40 (25%)
DMDD	22 (19%)	14 (29%)	36 (22%)
BD-I/II	12 (11%)	1 (2%)	13 (8%)
Anxiety disorders	18 (16%)	21 (43%)	39 (24%)
Trauma- and stressor-related disorders [a]	13 (11%)	14 (29%)	27 (17%)
Externalizing disorders			
ADHD	28 (25%)	16 (33%)	44 (30%)
DICCD	34 (30%)	9 (18%)	43 (26%)
Substance use disorder	7 (6%)	4 (8%)	11 (7%)
Psychotic and developmental disorder			
Schizophrenic disorder and other psychotic disorder	1 (1%)	0	1 (1%)
Learning disorder	10 (9%)	11 (22%)	21 (13%)
Other psychiatric disorders [b]	8 (7%)	7 (14%)	15 (9%)

Note. RPH = Mood Disorders Clinic at the Rivière-des-Prairies Hospital; DMHU = Program of DD Pediatric section of the Douglas Mental Health University Institute; MDD = major depressive disorder; PDD = persistent depressive disorder; DMDD = disruptive mood dysregulation disorder; ADHD = attention deficit hyperactivity disorder; BD = bipolar disorder type 1 and type 2; DICCD = disruptive, impulse-control and conduct disorders.

[a] The category "Trauma- and Stressor-Related Disorders" encompasses adjustment disorder, acute stress disorder and post-traumatic stress disorder.

[b] The category "Other psychiatric disorders" encompasses sleep disorder, tics and Tourette syndrome, obsessive compulsive disorder, eating disorder.

psychiatric disorders.

The proportion of youths with suicidal ideation was significantly lower for the youths with DMDD than for youths with MDD or PDD (Fig. 2). However, the frequencies of suicide attempts, multiple suicide attempts, and non-suicidal self-injuries were similar in the three groups. After examining the C-SSRS data for the 14 youths with DMDD from the DMHU site, we found that 8 participants had made a suicide attempt (hanging in one case, wrist-cutting in three cases, and another method in four cases). Six of the 8 suicide attempts were impulsive. Only one participant had made multiple suicide attempts.

3.3. Objective 3. Impairments associated with DMDD, MDD and/or PDD

The C-GAS score, as measured during the first medical visit, did not statistically differ between the three groups (Table 3). However, youths with DMDD reported more learning difficulties and a more frequent history of grade repetition, relative to youths with MDD or PDD. Peer relationships were significantly more impaired in youths with DMDD compared to youths with MDD or PDD. Youths with DMDD were 3–4 times more likely to display physically or verbally aggressive behavior; they were also more likely to have been victims of verbal and physical aggression.

3.4. Objective 4. Vulnerability factors associated with DMDD, MDD and/or PDD

Exposure to parental mental illness was more frequent in youths with MDD than in youths with DMDD or PDD (Table 4). However, no statistically significant difference was found between the three groups with regard to the family history of psychiatric diagnoses, including depression and substance use.

The proportion of major ACE and the frequency of foster care placement did not differ between the DMDD, MDD and PDD groups.

Youths with DMDD were significantly more likely to have a history of complicated pregnancy than youths with MDD or PDD, but the association was no longer statistically significant after youths with DMDD

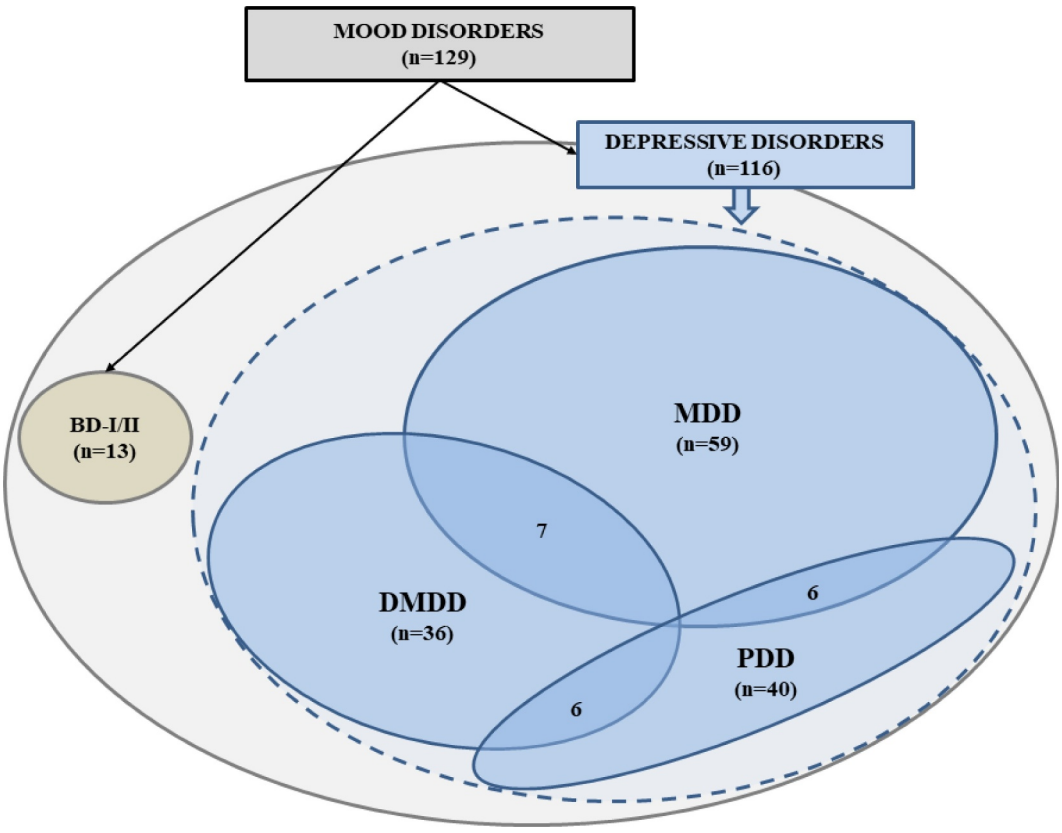

Fig. 1. Overlap between disruptive mood dysregulation disorder, major depressive disorder and persistent depressive disorder.

Table 2
Clinical characteristics of children and adolescents with DMDD, MDD, and PDD.

	DMDD (n = 36)	MDD only (n = 46)	PDD only(n = 28)	Comparisons between the three groups[d]	Non DMDD (n = 127)	Comparisons DMDD vs. non-DMDD[e]
Socio-demographic features						
Gender, male, n (%)	22 (61%)	13 (28%)	11 (39%)	***p* = .01**	43 (34%)	***p* < .01**
Age (years) (mean ± SD)	11.5 ± 3.4	14.8 ± 2.53	14.0 ± 2.93	***p* < .01**	13.9 ± 2.91	***p* < .01**
Socio economic difficulties	4 (11%)	2 (4%)	12 (43%)	***p* < .01**	24 (19%)	*p = .274*
Number of psychiatric disorders	2.5 ± 0.6	1.9 ± 0.8	2.2 ± 0.7	***p* < .01**	2.1 ± 0.8	***p* < .01**
DSM-5 associated psychiatric disorders						
Internalizing disorders						
Anxiety disorders	9 (25%)	5 (11%)	11 (39%)	***p* = .016**	30 (24%)	*p = .829*
Trauma- and stressor-related disorders [a]	10 (28%)	0	1 (4%)	***p* < .01**	17 (13%)	***p* = .040**
Externalizing disorders						
ADHD	18 (50%)	5 (11%)	4 (14%)	***p* < .01**	26 (21%)	***p* < .01**
DICCD	16 (44%)	11 (24%)	3 (11%)	***p* = .009**	27 (21%)	***p* = .005**
Substance use disorder	3 (8%)	2 (4%)	1 (4%)	*p = .651*	8 (6%)	*p = .668*
Developmental and other disorders [b]						
Learning disorder	7 (19%)	5 (11%)	3 (11%)	*p = .472*	14 (11%)	*p = .257*
Other psychiatric disorders [c]	4 (11%)	4 (9%)	3 (11%)	*p = .927*	11 (9%)	*p = .654*

Note. Statistically significant results are presented in bold. ADHD = attention deficit hyperactivity disorder; DICCD = disruptive, impulse-control and conduct disorders.

[a] The category "Trauma- and Stressor-Related Disorders" encompasses adjustment disorder, acute stress disorder and post-traumatic stress disorder.

[b] Nobody presented a schizophrenic disorder or other psychotic disorder among youths with DMDD, MDD or PDD.

[c] The category "Other psychiatric disorder" encompasses sleep disorder, tics and Tourette syndrome, obsessive compulsive disorder, eating disorder.

[d] Kruskal-Wallis test.

[e] Fisher's Exact test, except for "number of psychiatric diagnosed" where Mann-Whitney U-test was used.

and ADHD were excluded from the analysis (Table S3). No difference was observed regarding the psychomotor development and the association with a neurological disorder.

4. Discussion

4.1. Interpretation

Regarding the study's first objective, the frequency of DMDD observed (22%) was slightly lower than that reported for two other outpatient studies using retrospective diagnoses (see Table S2) (Axelson et al., 2012; Freeman et al., 2016). Twenty-six to 31% of the 706 children aged 6–12 years in the Longitudinal Assessment of Manic Symptoms study met the criteria for DMDD (Axelson et al., 2012). Among the 597 children and adolescents (ages 6–18) treated at a community mental health center in the US, 31% were diagnosed with DMDD (Freeman et al., 2016). The frequencies observed in child psychiatry facilities clearly contrast with the relatively low prevalence estimate of 1% in the general population (Stringaris et al., 2018). The disparity in the reported frequencies may result from disparities in countries' prevalence rates, sampling bias, and more likely, differences in the diagnostic procedures, our study being uniquely based on the DMDD algorithm of the DSM-5.

The degree of overlap between DMDD and DD was substantial (36%), but comparable to the overlap observed with each other group: 30% with PDD and 22% with MDD.

Regarding our second objective, youths with DMDD were younger and more likely to be male than youths with either PDD or MDD. This higher proportion of males among youths with DMDD has been consistently reported in previous studies (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016; Dougherty et al., 2014; Axelson, 2013; Stringaris and Taylor, 2015;

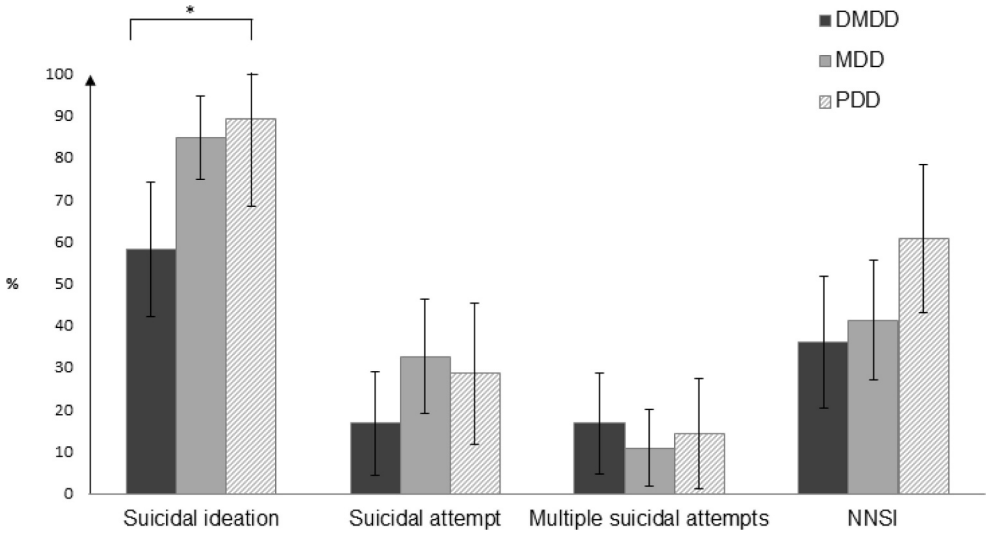

Fig. 2. Suicidal behaviors among youth with DMDD, MDD without DMDD/PDD, and PDD without DMDD/MDD.

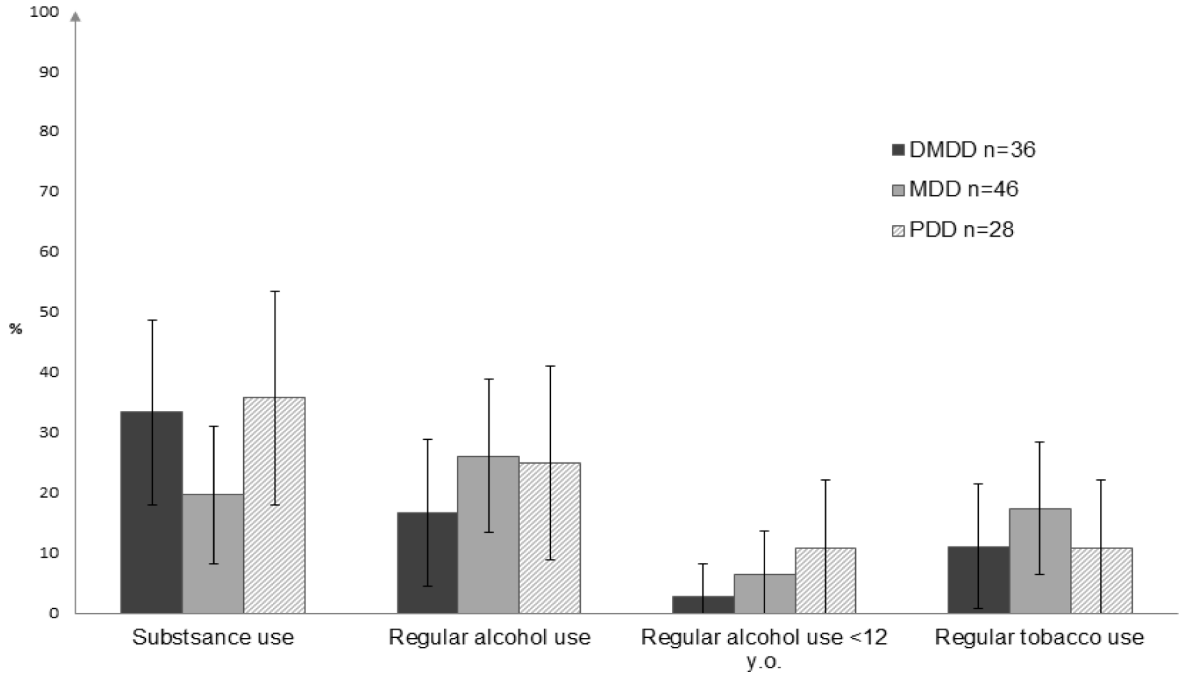

Fig. 3. Substance use among youth with DMDD, MDD without DMDD/PDD, and PDD without DMDD/MDD.

Table 3
Functional impairment associated with DMDD, MDD, and PDD.

	DMDD (n = 36)	MDD only (n = 46)	PDD only(n = 28)	Comparisons between the three groups[b]	Non DMDD (n = 127)	Comparisons DMDD vs. non-DMDD[c]
C-GAS: Mild or severe functional impairment [a]	10 (28%)	23 (50%)	9 (32%)	*p = .092*	58 (45%)	*p = .064*
School achievement						
Prior grade repetition	14 (39%)	6 (15%)	5 (18%)	***p = .030***	23 (20%)	***p = .044***
Reported learning difficulties	9 (25%)	2 (4%)	4 (14%)	***p = .025***	15 (12%)	***p = .049***
Repeated school absence	7 (19%)	9 (20%)	9 (32%)	*p = .394*	26 (21%)	*p = .892*
Peer relationship problems						
1. Physical aggressive behaviors	14 (39%)	5 (11%)	2 (7%)	***p < .01***	14 (11%)	***p < .01***
2. Verbal aggressive behaviors	17 (47%)	5 (11%)	4 (14%)	***p < .01***	19 (15%)	***p < .01***
3. Stealing goods from other youths	5 (14%)	5 (11%)	2 (7%)	*p = .698*	10 (8%)	*p = .326*
4. Passive social withdrawal	20 (56%)	26 (56%)	15 (54%)	*p = .971*	69 (54%)	*p = .956*
5. Active social avoidance	3 (8%)	2 (4%)	1 (4%)	*p = .651*	5 (4%)	*p = .376*
6. Rejected by other youths	13 (36%)	9 (20%)	8 (29%)	*p = .249*	46 (35%)	*p = .960*
7. Victim of physical aggression	5(14%)	3 (7%)	1 (4%)	*p = .205*	5 (4%)	***p = .026***
8. Victim of verbal aggression	14 (39%)	10 (22%)	5 (18%)	*p = .109*	28 (22%)	***p = .037***
Mean total score (0 to 8)	2.4 ± 1.6	1.3 ± 1.2	1.3 ± 1.2	***p < .001***	1.5 ± 1.2	***p < .01***

Note. Statistically significant results are presented in bold.
[a] Mild or severe functional impairment is defined as a C-GAS score strictly above 60.
[b] Kruskal-Wallis test.
[c] Fisher's Exact test.

Copeland et al., 2013; Copeland et al., 2014). The higher comorbidity, observed in our sample, with externalizing disorders associated with a predominantly male sex ratio (Breton et al., 1999), could have contribute to this finding. Of note, the sex ratio observed with DMDD differs from the more balanced sex ratio reported in depressed prepubertal children (Angold and Rutter, 1992). The high comorbidity rate among youths with DMDD reported in the present study is in line with all the prior studies, in which other psychiatric disorders were observed in between 60% and 92% of outpatients with DMDD (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016; Dougherty et al., 2014; Axelson, 2013; Stringaris and Taylor, 2015; Copeland et al., 2013). In our sample, ADHD and DICCD were the most frequently associated diagnoses in youths with DMDD. Most interestingly, youths with DMDD were 2.5 times more likely to have an associated trauma-and stressor-related disorder, compared to youths without DMDD. To our knowledge this is the first study reporting a positive association between DMDD and trauma-related disorders (Table S2). Albeit preliminary, this finding brings additional support to the postulated relationship between the exposure to chronic stress/repeated trauma and chronic mood dysregulation (Dvir et al., 2014).

In the present study, youths with DMDD presented with a lower frequency of suicidal ideation than the other two groups. In keeping with the relationship between suicidal behavior and the DMDD core symptom of irritability, and as previously discussed (Benarous et al., 2018), suicide attempts might result from the intermixture of covert suicidal ideation and a temporary increase in irritability caused by intercurrent triggering stressors. This model described in literature (Benarous et al., 2018; Stringaris and Vidal-Ribas, 2019; Orri et al., 2018) is further supported by our data as youths with DMDD mostly reported suicidal attempts as unplanned and impulsive.

Table 4
Vulnerability factors associated with DMDD, MDD, and PDD.

	DMDD (n = 36)	MDD only (n = 46)	PDD only(n = 28)	Comparisons between the three groups[a]	Non DMDD (n = 127)	Comparisons DMDD vs. non-DMDD[b]
Family psychiatric history						
Maternal depression	11 (31%)	21 (46%)	8 (29%)	p = .231	54 (43%)	p = .198
Paternal depression	6 (17%)	13 (28%)	4 (14%)	p = .273	24 (19%)	p = .762
Stressful life events						
History of major ACEs	14 (39%)	15 (33%)	16 (57%)	p = .111	56 (44%)	p = .703
Exposure to parental substance abuse	11 (31%)	8 (17%)	2 (7%)	p = .057	23 (18%)	p = .110
Exposure to parental mental illness	19 (53%)	33 (72%)	12 (43%)	**p = .036**	83 (64%)	p = .249
Foster care placement	5 (14%)	4 (9%)	1 (3%)	p = .367	7 (19%)	p = .326
Developmental history						
Complicated pregnancy	8 (22%)	2 (4%)	2 (7%)	**p = .027**	7 (6%)	**p < .01**
Delay in psychomotor development	2 (6%)	0	2 (7%)	p = .217	4 (3%)	p = .614
Neurological disorder associated	5 (14%)	4 (9%)	4 (14%)	p = .696	12 (10%)	p = .536

Note. Statistically significant results are presented in bold.
[a] Kruskal-Wallis test.
[b] Fisher's Exact test.

With respect to the study's third objective, unlike prior studies (Dougherty et al., 2014; Copeland et al., 2013), no significant difference was observed between the three groups relative to the measure of global functioning (C-GAS score). However, several other findings mitigated this overall absence of association. First, youths with DMDD presented more school difficulties (leaning difficulties and a more frequent history of grade repetition) and peer-relationship problems compared to youths with MDD or PDD. The poor levels of school achievement of youths with DMDD was in line with previous community studies (Dougherty et al., 2014; Copeland et al., 2013). Copeland et al. (2013) reported that the frequency of recent school suspension was higher among youths with DMDD than among psychiatric case-controls (Copeland et al., 2013). Dougherty et al. (2014) (Dougherty et al., 2014) in turn, noted that youths with DMDD were more likely than their counterparts to require remedial education. Further studies are needed to determine whether the association between DMDD and learning difficulties can be explained by the presence of perinatal risk factors and other developmental difficulties. Our data support this hypothesis because the relationship was no longer statistically significant after youths with ADHD had been excluded from the analysis (Table S3).

Second, the positive association between DMDD and aggressive behavior might be seen as somewhat inevitable, since aggressive reactions can be seen as a consequence of irritability. However, youths with DMDD were more likely to be victims of aggressive behavior by peers than youths without DMDD; this finding is in line with earlier reports on youths displaying reactive aggression (Geoffroy et al., 2018). Only longitudinal studies might be able to determine the interplay between victimization by peers, reactive aggression, and mood symptoms in chronically irritable youths. Among youths with chronic irritability, it has been noted neurocognitive impairments (e.g. emotional recognition difficulties), which were involved in the daily expression of social skills (Vidal-Ribas et al., 2018; Stoddard et al., 2015) . They would be worth studying to better understand peer-relationship difficulties in youths with DMDD, in comparison to MDD and PDD.

With respect to the last objective relative to vulnerability factors, no statistically significant difference was found between the three groups with regard to the family history of psychiatric diagnoses. This meant that the well-documented vulnerability factor for childhood depression, i.e., the history of parental depression, was observed at a similar rate among the three groups. The association between a history of complicated pregnancy and DMDD is probably partly mediated by the presence of developmental cognitive impairments, since the association was no longer significant after the exclusion of youths with DMDD and ADHD (Table S3).

On should remain cautious with regard to these preliminary findings. First, reporting no differences does not mean that the role of the vulnerability factor is comparable across the three groups. Second, information on the vulnerability factors resulted from a cross-sectional study design rather than a prospective longitudinal study. We can only conclude that on a small sample of help-seeking outpatients, no significant difference was observed with respect to the youth's profile of environmental vulnerability factors associated with mood disorders between DMDD, MDD, and PDD.

4.2. Strength and limitations

The results of this study should be interpreted in the context of its limitations. Firstly, the study suffered from retrospective bias and a small number of patients in the study groups - despite the four-year recruitment period. The study's statistical power was reduced by the substantial number of variables, and the small sample size also precluded the use of multivariate analysis. It will be important to confirm that the observed differences between the DMDD, MDD and PDD groups do not reflect sociodemographic features. Secondly, the evaluation of psychosocial risk factors (such as ACE) may be prone to recall bias. To limit the potential bias, we measured the data's validity against official records (i.e. administrative data from child protection agencies). Thirdly, the lack of a control group without psychiatric disorders makes it more difficult to interpret intergroup differences between groups. To facilitate comparisons with previous studies, we compared DMDD and non-DMDD subsets. Fourthly, the study sample comprised outpatients consulting at specialist mood disorders clinics in a large urban area. This might account for the high observed prevalence of mood disorders and the relative paucity of other conditions for which there are specific care pathways (e.g. severe developmental disorders). Our results could only be generalized to other clinics with similar patient profiles.

The study also had a number of strengths: (i) the use of a well-validated, DSM-5-based instrument for the clinical diagnosis of DMDD, (ii) our comparison of mood disorder groups addresses important issues in how DMDD can be discriminated from pre-existing DD diagnoses in clinical practice, and (iii) some environmental risk factors (such as the developmental history and ACE) have never been investigated in DMDD.

4.3. Clinical and research implications

In this study, we aimed at documenting the common and distinctive features of DMDD, MDD, and PDD. As mentioned in the introduction, there is still an ongoing debate about the best diagnostic approach for youths with chronic irritability, i.e. whether adding a new specifier for youths with oppositional defiant disorder (ODD) or subtyping DD with a new diagnostic entity as proposed with the DSM-5 (Roy et al., 2014; Stringaris et al., 2017). Therefore, following Occam's razor principle, it is mandatory to compare DMDD with preexisting DD diagnostic categories, i.e. MDD and PDD, to ensure that the new clinical entity is not a more fashionable label for youths with chronic depression, i.e. PDD. In keeping with the aforementioned debate, this study has several implications.

First, DMDD could be discriminated from MDD and PDD. Of the 36 youths with DMDD, only six met the criteria for PDD. This is in line with the assumption that youths with chronic irritability do not fit prior DD diagnostic categories, and therefore deserve a more specific DD diagnostic category. In contrast, the high comorbidity rate consistently reported for DMDD (Margulies et al., 2012; Axelson et al., 2012; Freeman et al., 2016; Tufan et al., 2016)., may dismiss the claim for specificity. However, in this study and all the prior studies, the DSM-5 non-dual diagnosis criterium for ODD was not applied, resulting in an overestimation of the comorbidity rate of DMDD with externalizing disorders. In addition, youths with DMDD presented a more mixed clinical presentation with mood and developmental disturbances components (i.e., younger age, predominantly male sex ratio, history of complicated pregnancy, persisting peer-relationship and school difficulties) compared to youths with MDD and/or PDD. This clinical presentation with an admixture of mood and developmental disturbances was only partially mediated by the association with ADHD (Table S3). Therefore, youths presenting with DMDD should be carefully assessed for neurodevelopmental disorders.

Second, from a research standpoint, the aforementioned neurocognitive characteristics could be seen as promising mediators between childhood irritability and later depression (Vidal-Ribas et al., 2018). The relation between chronic irritability in childhood and, depression in adolescence and adulthood has been well demonstrated, in particular on the basis of longitudinal studies (Brotman et al., 2006; Stringaris et al., 2009; Stringaris et al., 2010; Leibenluft E. Severe Mood Dysregulation 2011; Vidal-Ribas et al., 2016; Whelan et al., 2013). In a meta-analysis, Vidal-Ribas et al. (2016) reported a positive and independent relation between chronic irritability in childhood on the one hand and on the other hand, depression in adolescence and adulthood (OR = 1.80) (Vidal-Ribas et al., 2016). Consequently, search for common pathophysiological underpinnings is under way. Families studies unveiled an association between childhood irritability and a history of parental depression (Propper et al., 2017; Krieger et al., 2013; Wiggins et al., 2018; Brotman et al., 2007), in coherence with our findings. Moreover, two twin-studies suggested that the association between irritability and depression might be, in part, genetically mediated (Stringaris et al., 2012; Savage et al., 2015). Another study showed that irritability partly mediated the link between maternal depression and depression in adolescents (Whelan et al., 2015). Future research would help better disentangling the interplay between risk factors for depression, irritability, and depressive disorders in adolescence and adulthood, and clarifying transition pathways from one disorder to the other.

Third, our study has several evaluation and therapeutics implications. With respect to our findings, clinicians caring for youths with DMDD should better recognize clinical dimensions generally associated with internalized symptoms, in particular suicidal behaviors, the presence of adverse life events, and the presence of trauma-related symptoms. Second, some therapeutic interventions for DMDD have been justified by the association with depression (Benarous et al., 2017b). As depression and irritability might share common pathophysiological mechanisms (Stringaris et al., 2012; Savage et al., 2015; Vidal-Ribas et al., 2018), effective treatment for the former could be useful for the later. So far, only one randomized controlled trial showed that a positive effect of 8 weeks of citalopram, a selective serotonin reuptake inhibitor (SSRI), in youths with SMD + ADHD previously treated by methylphenidate (Towbin et al., 2019).

In conclusion, we identified DMDD as a distinct entity from MDD and/or PDD in this clinical sample of outpatient youths. While we found some clinical features more specifically associated with DMDD (association with the externalized disorders and trauma-related disorder, the severity of peer-relationship and school difficulties), the vulnerability factors studied were broadly comparable across disorders. Further studies are needed to confirm this findings and determine on which extend DMDD youths differ from those with other types of mood disturbances.

Funding

The study was funded by the Quebec Network on Suicide, Mood Disorders and Related Disorders RQSHA (grant: ASClin #2).

Disclosure

Dr. Benarous, Pr. Labelle, Pr. Guilé, Pr. Cohen, Dr. Renaud, and Dr. Breton report no biomedical financial interests or potential conflicts of interest.

Declaration of Competing Interest

None

Acknowledgments

The authors would like to thank Christophe Huynh Ph.D. for his help with data collection, Cosmin Lancu (psychiatry resident) for his assistance in studying the reliability of the chart review instrument's DMDD module, and Hughes Pellerin MSc for assistance with statistical analysis. Professor Guilé pursue his contribution during his time as invited researcher at the Center for Research and Intervention on Suicide, Ethical Issues and End-of-life practices (CRISE), Montreal, Canada. Therefore, the corresponding author would like to thank Pr Choukroun, Dean of Faculty of Medicine (Amiens) and Pr Mishara, Director of CRISE (Montreal).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.020.

References

American Psychiatric Association Taskforce DV, 2010. Justification for Temper Dysregulation Disorder with Dysphoria. Association AP, Washington, DC.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. American Psychiatric Association.
Anda, R.F., Butchart, A., Felitti, V.J., Brown, D.W., 2010. Building a framework for global surveillance of the public health implications of adverse childhood experiences. Am. J. Prev. Med. 39 (1), 93–98.
Angold, A., Rutter, M., 1992. Effects of age and pubertal status on depression in a large clinical sample. Dev. Psychopathol. 4 (1), 5–28.
Axelson, D., 2013. Taking disruptive mood dysregulation disorder out for a test drive. Am. J. Psychiatry 170 (2), 136–139.
Axelson, D., Findling, R.L., Fristad, M.A., et al., 2012. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the longitudinal assessment of manic symptoms study. J. Clin. Psychiatry 73 (10), 1342–1350.
Benarous, X., Consoli, A., Cohen, D., Renaud, J., Lahaye, H., Guile, J.M., 2018. Suicidal behaviors and irritability in children and adolescents: a systematic review of the nature and mechanisms of the association. Eur. Child. Adolesc. Psychiatry 28 (5), 667–683.
Benarous, X., Consoli, A., Guile, J.M., Garny de La Riviere, S., Cohen, D., Olliac, B.,

2017b. Evidence-based treatments for youths with severely dysregulated mood: a qualitative systematic review of trials for SMD and DMDD. Eur. Child. Adolesc. Psychiatry 26 (1), 5–23.
Benarous, X., Raffin, M., Bodeau, N., Dhossche, D., Cohen, D., Consoli, A., 2017a. Adverse childhood experiences among inpatient youths with severe and early-onset psychiatric disorders: prevalence and clinical correlates. Child. Psychiatry Hum. Dev. 48 (2), 248–259.
Boudjerida, A., Labelle, R., Bergeron, L., Berthiaume, C., Breton, J.J, 2018. Disruptive Mood Dysregulation Disorder Scale in Adolescence. International Association for Child & Adolescent Psychiatry and Allied Professions, Prague 2018.
Breton, J.J., Bergeron, L., Valla, J.P., et al., 1999. Quebec child mental health survey: prevalence of DSM-III-R mental health disorders. J. Child. Psychol. Psychiatry 40 (3), 375–384.
Breton, J.J., Labelle, R., Huynh, C., Berthiaume, C., St-Georges, M., Guile, J.M., 2012. Clinical characteristics of depressed youths in child psychiatry. J. Can. Acad. Child. Adolesc. Psychiatry 21 (1), 16–29.
Brotman, M.A., Kassem, L., Reising, M.M., et al., 2007. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. Am. J. Psychiatry 164 (8), 1238–1241.
Brotman, M.A., Schmajuk, M., Rich, B.A., et al., 2006. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol. Psychiatry 60 (9), 991–997.
Consoli, A., Cohen, D., 2013. Manic-like symptoms in youths: diagnosis issues and controversies. Neuropsychiatrie de l'Enfance et de l'Adolescence 61, 154–159.
Copeland, W.E., Angold, A., Costello, E.J., Egger, H., 2013. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. Am. J. Psychiatry 170 (2), 173–179.
Copeland, W.E., Shanahan, L., Egger, H., Angold, A., Costello, E.J., 2014. Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. Am. J. Psychiatry 171 (6), 668–674.
Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381 (9875), 1371–1379.
Dougherty, L.R., Smith, V.C., Bufferd, S.J., et al., 2014. DSM-5 disruptive mood dysregulation disorder: correlates and predictors in young children. Psychol. Med. 44 (11), 2339–2350.
Dvir, Y., Ford, J.D., Hill, M., Frazier, J.A., 2014. Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. Harv. Rev. Psychiatry 22 (3), 149–161.
Freeman, A.J., Youngstrom, E.A., Youngstrom, J.K., Findling, R.L., 2016. Disruptive mood dysregulation disorder in a community mental health clinic: prevalence, comorbidity and correlates. J. Child. Adolesc. Psychopharmacol. 26 (2), 123–130.
Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. Br. J. Psychiatry 186, 121–125.
Geoffroy, M.C., Boivin, M., Arseneault, L., et al., 2018. Childhood trajectories of peer victimization and prediction of mental health outcomes in midadolescence: a longitudinal population-based study. CMAJ 190 (2), E37–e43.
Germain M., Guyon L., Landry M., Tremblay J., Brunelle N., Bergeron J. *DEP-ADO grille de dépistage de consommation problématique d'alcool et de drogues chez les adolescents et les adolescentes. version 3.2, septembre 2007.* Recherche et intervention sur les substances psychoactives - Québec (RISQ); 2007, 26p.
Guile, J.M., Huynh, C., Breton, J.J., et al., 2016. Familial and clinical correlates in depressed adolescents with borderline personality disorder traits. Front. Pediatr. 4, 87.
Kaufman, J., Birmaher, B., Brent, D., et al., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child. Adolesc. Psychiatry 36 (7), 980–988.
Krieger, F.V., Polanczyk, V.G., Goodman, R., et al., 2013. Dimensions of oppositionality in a Brazilian community sample: testing the DSM-5 proposal and etiological links. J. Am. Acad. Child. Adolesc. Psychiatry 52 (4), 389–400.
LeBoeuf, A., Breton, J.J., Berthiaume, C., et al., 2017. Exploratory study of the clinical characteristics of adolescent girls with a history of physical or sexual abuse consulting in a mood disorder clinic. J. Can. Acad. Child. Adolesc. Psychiatry 26 (2), 114–118.
Leibenluft E. Severe Mood Dysregulation, 2011. Irritability, and the diagnostic boundaries of bipolar disorder in youths. Am. J. Psychiatry 168, 129–142.
Leibenluft, E., Cohen, P., Gorrindo, T., Brook, J.S., Pine, D.S., 2006. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J. Child. Adolesc. Psychopharmacol. 16 (4), 456–466.
Margulies, D.M., Weintraub, S., Basile, J., Grover, P.J., Carlson, G.A., 2012. Will disruptive mood dysregulation disorder reduce false diagnosis of bipolar disorder in children? Bipolar Disord. 14 (5), 488–496.
Masi, G., Perugi, G., Toni, C., et al., 2006. The clinical phenotypes of juvenile bipolar disorder:toward a validation of the episodic-chronic-distinction. Biol. Psychiatry 59, 603–610.
Masi, G., Pisano, S., Milone, A., Muratori, P., 2015. Child behavior checklist dysregulation profile in children with disruptive behavior disorders: a longitudinal study. J. Affect. Disord. 186, 249–253.
Orri, M., Galera, C., Turecki, G., et al., 2018. Association of childhood irritability and depressive/anxious mood profiles with adolescent suicidal ideation and attemptsassociation of childhood irritability and depressive/anxious mood profiles with adolescent suicidalityassociation of childhood irritability and depressive/anxious mood profiles with adolescent suicidality. JAMA Psychiatry 75 (5), 465–473.
Posner, K., Oquendo, M.A., Gould, M., Stanley, B., Davies, M., 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am. J. Psychiatry 164 (7), 1035–1043.
Propper, L., Cumby, J., Patterson, V.C., et al., 2017. Disruptive mood dysregulation disorder in offspring of parents with depression and bipolar disorder. Br. J. Psychiatry 210 (6), 408–412.
Robins, E., Guze, S.B., 1970. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am. J. Psychiatry 126 (7), 983–987.
Roy, A.K., Lopes, V., Klein, R.G., 2014. Disruptive mood dysregulation disorder: a new diagnostic approach to chronic irritability in youth. Am. J. Psychiatry 171 (9), 918–924.
Savage, J., Verhulst, B., Copeland, W., Althoff, R.R., Lichtenstein, P., Roberson-Nay, R., 2015. A genetically informed study of the longitudinal relation between irritability and anxious/depressed symptoms. J. Am. Acad. Child. Adolesc. Psychiatry 54 (5), 377–384.
Shaffer, D., Gould, M.S., Brasic, J., et al., 1983. A children's global assessment scale (CGAS). Arch. Gen. Psychiatry 40 (11), 1228–1231.
Stoddard, J., Hsu, D., Reynolds, R.C., et al., 2015. Aberrant amygdala intrinsic functional connectivity distinguishes youths with bipolar disorder from those with severe mood dysregulation. Psychiatry Res. 231 (2), 120–125.
Stringaris, A., Baroni, A., Haimm, C., et al., 2010. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. J. Am. Acad. Child. Adolesc. Psychiatry 49 (4), 397–405.
Stringaris, A., Cohen, P., Pine, D.S., Leibenluft, E., 2009. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am. J. Psychiatry 166 (9), 1048–1054.
Stringaris, A., Maughan, B., Copeland, W.S., Costello, E.J., Angold, A., 2013. Irritable mood as a symptom of depression in youth: prevalence, developmental, and clinical correlates in the great smoky mountains study. J. Am. Acad. Child. Adolesc. Psychiatry 52 (8), 831–840.
Stringaris, A., Taylor, E., 2015. Disruptive Mood: Irritability in Children and Adolescent. Oxford University Press, New York.
Stringaris, A., Vidal-Ribas, P., 2019. Probing the irritability-suicidality nexus. J. Am. Acad. Child. Adolesc. Psychiatry 58 (1), 18–19.
Stringaris, A., Vidal-Ribas, P., Brotman, M.A., Leibenluft, E., 2017. Practitioner review: definition, recognition, and treatment challenges of irritability in young people. J. Child. Psychol. Psychiatry.
Stringaris, A., Vidal-Ribas, P., Brotman, M.A., Leibenluft, E., 2018. Practitioner review: definition, recognition, and treatment challenges of irritability in young people. J. Child. Psychol. Psychiatry 59 (7), 721–739.
Stringaris, A., Zavos, H., Leibenluft, E., Maughan, B., Eley, T.C., 2012. Adolescent irritability: phenotypic associations and genetic links with depressed mood. Am. J. Psychiatry 169 (1), 47–54.
Thapar, A., Collishaw, S., Pine, D.S., Thapar, A.K., 2012. Depression in adolescence. Lancet 379 (9820), 1056–1067.
Tourian, L., LeBoeuf, A., Breton, J.J., et al., 2015. Treatment options for the cardinal symptoms of disruptive mood dysregulation disorder. J. Can. Acad. Child. Adolesc. Psychiatry 24 (1), 41–54.
Towbin, K., Vidal-Ribas, P., Brotman, M.A., et al., 2019. A double-blind randomized placebo-controlled trial of citalopram adjunctive to stimulant medication in youth with chronic severe irritability. J. Am. Acad. Child Adoles. Psychiatry.
Tufan, E., Topal, Z., Demir, N., et al., 2016. Sociodemographic and clinical features of disruptive mood dysregulation disorder: a chart review. J. Child. Adolesc. Psychopharmacol. 26 (2), 94–100.
Vidal-Ribas, P., Brotman, M.A., Salum, G.A., et al., 2018. Deficits in emotion recognition are associated with depressive symptoms in youth with disruptive mood dysregulation disorder. Depress. Anxiety 35 (12), 1207–1217.
Vidal-Ribas, P., Brotman, M.A., Valdivieso, I., Leibenluft, E., Stringaris, A., 2016. The status of irritability in psychiatry: a conceptual and quantitative review. J. Am. Acad. Child. Adolesc. Psychiatry 55 (7), 556–570.
Weissman, M.M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., Olfson, M., 2000. Brief screening for family psychiatric history: the family history screen. Arch. Gen. Psychiatry 57 (7), 675–682.
Whelan, Y.M., Leibenluft, E., Stringaris, A., Barker, E.D., 2015. Pathways from maternal depressive symptoms to adolescent depressive symptoms: the unique contribution of irritability symptoms. J. Child. Psychol. Psychiatry 56 (10), 1092–1100.
Whelan, Y.M., Stringaris, A., Maughan, B., Barker, E.D., 2013. Developmental continuity of oppositional defiant disorder subdimensions at ages 8, 10, and 13 years and their distinct psychiatric outcomes at age 16 years. J. Am. Acad. Child. Adolesc. Psychiatry 52 (9), 961–969.
Wiggins, J.L., Briggs-Gowan, M.J., Estabrook, R., et al., 2018. Identifying clinically significant irritability in early childhood. J. Am. Acad. Child. Adolesc. Psychiatry 57 (3), 191–199.