Evidence-based treatments for youths with severely dysregulated mood: a qualitative systematic review of trials for SMD and DMDD

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ABSTRACT

The aim of this literature review was to examine the evidence for psychotherapeutic and pharmacological treatments in subjects with severely dysregulated mood and to identify potential areas for improvements in research designs. A literature search was conducted using several databases for published (PubMed, PsycINFO) and ongoing (clinical trial registries) studies conducted in youths who met NIMH's criteria for Severe Mood Dysregulation (SMD) or the DSM-5 diagnosis of Disruptive Mood Dysregulation Disorder (DMDD). Eight completed studies were identified: three randomized trials, four open pilot studies and one case report. Seven ongoing studies were found in trial registries. The available evidence suggests potential efficacy of psychotherapies which have previously been developed for internalizing and externalizing disorders. The two main pharmacological strategies tested are, first, a monotherapy of psychostimulant or atypical antipsychotic such as risperidone, already used in the treatment of severe irritability in youths with developmental disorders; and second, the use of a serotonergic antidepressant as an add-on therapy in youths treated with psychostimulant. Ongoing studies will further clarify the effectiveness of psychotherapeutic interventions for DMDD individuals and whether they should be given alone or in conjunction with other treatments. The short duration of the trials for a chronic disorder, the low number of studies, the lack of placebo or active comparator arm, and restrictive inclusion criteria in most of the controlled trials dramatically limit the interpretation of the results. Finally, future research should be conducted across multiple sites, with standardized procedures to measure DMDD symptoms reduction, and include a run-in period to limit placebo effect.

KEYWORDS: disruptive mood dysregulation disorder; severe mood dysregulation; psychotherapy; pharmacotherapy; therapeutics; irritability

1. INTRODUCTION

1.1.General background

Children with severely dysregulated mood have become diagnostic and therapeutic challenges over the last two decades within the context of pediatric bipolar controversy [1-4]. In view of facilitating research programs researchers at the U.S. National Institute of Mental Health (NIMH) operationalized the criteria of "Severe Mood Dysregulation" (SMD), a syndrome characterized by chronic abnormal levels of anger or sadness, hyperarousal and heightened verbal or physical reactivity [5]. On the grounds of studies conducted in youths with SMD and in view of improving mental health care of youths with chronic irritability, the Disruptive Mood Dysregulation Disorder (DMDD) was introduced as a new diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) within the Depressive Disorders section [6]. Youths with DMDD present chronic irritability combined with severe and recurrent episodes of temper outburst inconsistent with their developmental level at least three times per week and occurring in different settings (e.g., in family, school). These symptoms should persist more than twelve months with no symptom-free period longer than three months and with an initial onset prior to the age of 10. Prevalence of DMDD is reported to be around 8.2% in general population [7-9] and around 26-31% in clinical settings [10,11]. There is much evidence supporting that DMDD symptoms severely affect a youth's level of social functioning [7,8] and that such negative effects could persist into adulthood [9]. Copeland et al. showed that as adults youths with DMDD present a much higher level of functional impairments (i.e., adverse health outcomes, financial problems, police contact, and low educational attainment) than those with any other psychiatric disorders (e.g., depressive

disorders, anxiety disorders, attention deficit hyperactivity disorder ADHD, disruptive disorder, or substance disorders) [9].

1.2.Phenomenology of youths with severely dysregulated mood

Mood dysregulation (i.e., severe irritability and high level of anger) is seen as a transdiagnostic symptom, with a dimensional continuum from its typical expression in normal development of children and adolescences to severely impairing forms in psychiatric disorders [12]. In this vein, the development of studies based on specific cognitive and emotional domains rather than DSM-5 categories of disorders has been encouraged, in particular research aligned with the framework of the Research Domain Criteria articulated by the NIMH. This strategy has led to significant improvements in our knowledge of the mechanisms underlying varying aspects of mood dysregulation in youths. Such progress may ultimately lead to discovering new markers of the disorder and targets for specific interventions. The study published by Stoddard et al. [13] provides a good example of how these different levels of analysis can be integrated in research based on a dimensional view of psychopathology; with the articulation between impaired neural substrates (i.e., orbitofrontal cortex and amygdala activation), a clinical or psychological marker (i.e., the result at a face-emotion labelling task), and a therapeutic (i.e., computer-based) intervention targeting interpretation bias.

A different approach has been used in the present review as we specifically focused on studies where the clinical categories of SMD or DMDD were applied to define the population of interest. The SMD (i.e., the research syndrome) and then DMDD (i.e., the DMS-5 diagnosis) criteria were originally developed in view of facilitating the identification of youths with severe, persistent and functionally impairing forms of irritability, who were likely to fulfil criteria for different disorders at different times (“diagnostically homeless”) [14]. The development of a

specific category for these youths was endorsed due to the need to facilitate access to treatment, to reduce the rate of misdiagnosis especially early-onset bipolar disorder, and finally to reduce excessive and inappropriate medication. The inclusion of the DMDD in the 5th version of the DSM has encouraged the development of evidence-based trials which would have been difficult if mood dysregulation had been operationalized as a dimension. The use of specific disorders for youths with severely dysregulated mood was encouraged to limit the confusion with early-onset bipolar disorder and to enhance a more rational use of psychotropic medications (in particular, mood stabilizers). This issue was regarded as a major public health challenge considering the trend to overmedication and polypharmacy observed in prepubertal youths [15]. Mood dysregulation can be found in youths with various forms of psychopathology for example among youths with autistic spectrum disorder and sensory integration issues or in patients with post-traumatic stress disorder who experience episodic hyperarousal [16]. If a treatment has a positive impact only in patients with a comorbid psychiatric disorder, its overall benefit in clinical trial would be under- or overestimated with regards to its prevalence in the sample studied. The use of a categorical approach can help to explore the heterogeneity of the response to treatment in DMDD youths, for example through secondary analyses of subgroups with different associated psychiatric disorders.

1.3.Validity of SMD and DMDD diagnoses

Evidence for the validity of SMD and later DMDD diagnosis was raised on the ground of studies exploring the internal and external validity of these disorders, especially data on discriminant validity [17,18], familial studies [19], psychophysiological and neuroimaging studies [20-23], as well as response to pharmacological treatment [24,14]. However, concerns have been raised regarding different aspects of the diagnostic validity: the paucity of data

regarding reliability in literature, the difficulty in delineating the normal and abnormal mood lability in children, and above all the high rate of overlap with others psychiatric disorders, especially ADHD and ODD [8,10,11]. In addition, other aspects of child psychopathology are still rarely taken into consideration in these studies regarding some aspects of a child's individual characteristics (e.g., temperamental traits and attachment style) and environmental backgrounds (e.g., parent-child interaction patterns, possibility of co-occurring maltreatment). Lastly, significant changes were made in the process of integrating the category of SMD in DSM-5 including removing the criterion of hyperarousal (e.g., insomnia, agitation, distractibility, racing thoughts/flight of ideas, pressured speech, and intrusiveness), and the criterion of low intelligence (IQ<80) from the exclusionary criteria, as well as lowering the age of onset from 12 to 10 years old [6]. Such differences are not trivial and could affect the comorbidity profiles of SMD and DMDD. For example, despite the lack of direct comparison between the two clinical entities, data suggests that DMDD most often co-occurs with depressive disorders and ODD and less with ADHD compared to SMD [10].

1.4.Therapeutic strategies

Little is known about effective treatments of SMD and DMDD. The DSM-5 Task Force suggested that "individual therapy, as well as work with the child's family and/or school [and] the use of medication to help address specific symptoms" could be useful for DMDD youths [6]. However, the use of treatments targeting symptoms without considering the overall diagnosis has been criticized as it may contribute to the high rates of polypharmacy in this population [25-27]. Given that SMD and DMDD frequently occur with comorbid psychiatric disorders [8,10,11,28-30], it has been suggested that therapeutic interventions should primarily focus on treating associated disorders. However, studies examining the benefit of

psychotherapy or pharmacotherapy on mood dysregulation in different psychiatric disorders are somewhat mixed [31,32]. Galanter et al. [32] found that the higher baseline levels of psychopathology of children with ADHD and mood dysregulation, compared to those without prominent mood dysregulation, persisted after intensive multimodal treatments for ADHD, suggesting the need for additional treatment. In a recent systematic review, Tourian et al. examined empirical evidence supporting the use of pharmacological treatments for severe anger/irritability symptoms in youths [4]. They found that pharmacotherapeutic treatment for both aggression and chronic irritability includes various options, such as antidepressants, especially selective norepinephrine reuptake inhibitors, mood stabilizers, psychostimulants, antipsychotics, and alpha-2 agonists. However, such findings are difficult to generalize, since, as the authors noted, a majority of the study was conducted in small and specific populations (e.g., youths with developmental disorders). Even if no treatment algorithm for severe persistent irritability in youths can be derived from this data, that study can be regarded as a first step for providing evidence-based treatments for children with DMDD as it informed about the potentially effective treatments. However, in view of meeting the needs of clinician and researcher, randomized controlled clinical trials (RCTs) specifically developed for youths with SMD or DMDD are required.

The high rates of comorbidity of SMD and DMDD with externalized disorders [8,10,11,28-30] raise questions about the best ways to conduct such trials. How should pharmacological and psychotherapeutic interventions for DMDD be tested within existing therapeutic strategies for externalized disorders? Which treatments should be allowed in the control group? How should the severity of mood symptoms be measured? Is the inclusion of only DMDD subjects without psychiatric comorbidity an acceptable strategy?

1.5.Aims of the present review

In this study we performed a systematic review to examine psychotherapeutic and pharmacological interventions for youths presenting SMD or DMDD. Considering the short delay since the development of DMDD's criteria, such an exhaustive review was not intended to determine the comparative efficacy and tolerability of these treatments. Our main aim was rather to describe the benefits and limitations of different research strategies currently developed for SMD and DMDD with the aim of guiding future research. In this vein, both published and ongoing studies are presented in this paper.

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2. METHODS

2.1.Review

The systematic review was conducted following the recommendations outlined in the PRISMA guide (Figure 1) [33]. Titles and abstracts were scanned for relevance. Full texts were ordered in case of uncertainty to maximize sensitivity. Reference lists of retrieved systematic reviews were checked. All full texts were checked for eligibility. Any original study (open trial, double-blind trial whether randomized control or not), case-report, case-series, meta-analysis and systematic review of pharmacological and non-pharmacological intervention was eligible for inclusion in this review. Abstracts and editorials were excluded. As DMDD was previously known in the literature under the alias of Severe Mood Dysregulation (SMD), studies conducted among youths with SMD were included in the current analysis. Study participants had to be diagnosed with SMD or DMDD, and to be

between five and 18 years old, or the mean age of the participants had to fall within the aforementioned age range.

[Insert Figure 1, about here]

2.2.Search method for identification of studies

Relevant articles for this study were obtained through Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Medline, PsychINFO, PsychINDEXplus and Dissertation Abstracts. Each database was searched from January 2001 to December 2015. In addition, we hand searched reference lists of identified articles and pertinent reviews for additional studies. References from the reviewed articles were also screened to find more articles of interest. Furthermore, clinical trials registries (http://www.clinicaltrials.gov of the US National Institutes of Health and the WHO International Clinical Trials Registry Platform, ICTRP) were searched for ongoing trials. We used the following search terms: "Disruptive mood dysregulation disorder" OR "Severe mood dysregulation" OR "Temper outburst" AND "Therapeutics" OR "Clinical protocols" OR "Treatment" OR "Pharmacotherapy" OR "Psychotherapy". Authors independently screened potential studies, after reading the full article, for inclusion in the review, and the results were collated. The systematic review yielded 86 hits, with 29 being a duplicate; 21 hits could be excluded based on the information in the title or abstract. The full texts of 36 hits were critically reviewed leading to exclusion of another 21 articles because these were only reviews or comments and no new original data were included; or the research was not conducted in DMDD/SMD youths. A list of 15 studies was generated: eight completed studies (one case report, four open pilot studies and three RCTs) and seven ongoing studies found in trial registries.

2.3.Data and analysis

Data and information extractions from each study were performed independently by the two first authors. For each study under review, year of publication and references were extracted. In order to summarize the treatment attributes in each report we collected the following information: description of medication, length of treatment, and dose received. Information on additional or adjunctive interventions was also collected. Additional information regarding the attributes of participants enrolled in the studies were extracted and were as follows: age, gender, how the diagnosis was made, treatment setting, comorbid conditions, sociodemographic data, and screening tools used. Although a meta-analytic review has been preferable, the diversity of statistical methods and measurement practices across studies did not allow for the calculation of pooled effect size. We categorized the level of evidence presented in each paper using the United States Preventive Services Task Force (USPSTF) criteria [35]. According to this schematic, level I evidence denotes having at least one well-designed RCT supporting a treatment's possible efficacy. Level II-1 requires a well-designed controlled trial without randomization, level II-2 requires at least one well-designed cohort or case–control study, and level II-3 requires a multiple time series design. We excluded level III evidence (opinions of respected authorities based on clinical experience or descriptive studies) from the present review.

3. RESULTS

3.1.Psychotherapeutic interventions for DMDD

3.1.1. Completed studies

Only three studies were eligible for the review (Table 1): an exploratory analysis from a controlled study of multiple interventions for ADHD children [36], the subsequent open uncontrolled feasibility study conducted by the same research team on youths with ADHD and SMD [37], and an open pilot uncontrolled study on DMDD youths [13].

Waxmonsky et al. (2008) conducted secondary analysis of data from the 2003-2004 ADHD Summer Treatment Program (ADHD-STP), a research program for children aged 5–12 in the form of an intensive 9-week therapeutic summer camp [38]. The initial study aimed to assess the relative efficacy and synergistic effects of differential doses of behavioural and pharmacologic interventions in ADHD youths. Among the 106 participants33 fulfilled NIMH criteria for SMD (mean age 8.0 ± 2.1 years and 8.7 ± 2.0 years for non SMD group). The behavioral intervention consisted of daily social skills training and a reward-based learning program (detailed in [39]). This treatment varied in frequency every three weeks with the order: no behavior modification, low-intensity (i.e., weekly sessions) and high-intensity (i.e., daily sessions). Clinicians rating mood symptoms were not blind to treatments status. There was no evidence of differential treatment efficacy or tolerability on ADHD symptoms between the participants with and without SMD, even though those with SMD were more likely to remain significantly impaired at home than non-SMD subjects. After nine weeks, multimodal treatment produced a 34% reduction in YMRS ratings in SMD subjects ($p < 0.001$).

In an open-label uncontrolled rater-blind study, Waxmonsky and colleagues examined the feasibility and preliminary efficacy of a psychotherapeutic program that integrated components of CBT focusing on affect regulation and parent training intervention [37]. The seven included children (mean age 8.7 ± 1.6 years) presented ADHD and the NIMH criteria

for SMD. All participants were male. All of the children took stimulant medication for ADHD and all but two participants were currently receiving counselling services. SMD symptoms were assessed using the depression and mania modules from the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). The sessions consisted of 105-minute concurrent parent and child meetings. Six of the seven families (86%) completed at least seven of the nine weeks in the program. Over the 16 week follow-up, participants showed a reduction in the level of depressive symptoms (CDRS-R, d=1.17) and externalizing symptoms (ADHD: d=0.30; ODD: d=0.26; CD: d=0.27). Authors interpreted the reduction in YMRS score (d=0.81) as an improvement in mood lability among participants.

In an open-label uncontrolled study, Stoddard and colleagues examined the preliminary efficacy of an intervention based on four session of computer-based Hostile Interpretation Therapy [13]. The 14 included children (mean age 14.1 ± 2.4 years) presented DMDD. The gender ratio was 8:6 for female. DMDD symptoms were assessed using the Affective Reactivity Index and the Clinical Global Impression- Improvement scale. Training is designed to shift interpretation of ambiguous morphs bias toward happy judgments. Ten subjects completed an implicit functional MRI face-emotion processing task. Active training is associated with a shift in balance point toward more happy judgments (use as a proxy for hostile attribution bias) (β = 2.25 morphs). Evidence suggests that active training may be associated with decreased irritability (β = -1.57 in parent-report ARI score, no significant change in self-report) and changes in activation patterns in the lateral orbitofrontal cortex.

3.1.2. Ongoing studies

Four trials were found searching the clinical trials registries that are underway.

The group from Yale University started a randomized open-label controlled study in May 2013 to examine feasibility and preliminary efficacy of Dialectical Behaviour Therapy adapted to children (DBT-C) (NCT01862549). The study targets to include 60 7–12 year old children meeting DSM-5 criteria for DMDD. Participants are randomly assigned to receive one of two treatments for 30 weeks: DBT-C or enhanced care (active control condition). Participants on the DBT-C arm received two pre-treatment sessions and 24 treatment sessions with once per week meetings, including 30 min individual child therapy, 20 min meeting with a caregiver and 40 min of skills training with both. Enhanced care consists of supportive individual psychotherapy, such as cognitive behavioural skills training and adjunctive family interventions (e.g., parenting skills training, structuring household environment, and safety planning). After the acute 32-week intervention period, 3-month follow-up assessments are conducted. The primary outcome is the attendance and drop-out rate measure, the level of satisfaction and compliance at 32 weeks; secondary end-points are reduction in DMDD symptoms and disruptive problems, psychosocial functioning and mental health service use. Estimated primary completion date of the study is July 2015.

The second ongoing study investigates the feasibility and acceptability of Interpersonal Psychotherapy for youths with SMD (IPT-SMD). A monocentric uncontrolled open-label study (NCT01591564) started in May 2012 and targeted to include five subjects who meet NIMH criteria for SMD. Youth receive weekly therapy sessions for 16 weeks and then bi-weekly sessions until week 20. Parent sessions are also included. The primary outcome is the retention rate and secondary end-points include various measures of clinical improvement. The investigators hypothesized that retention rates will be above 80% and the satisfaction score above six on a seven point scale. Although the results of this research have not yet been published, the same research team started a randomized rater-blind controlled study in October 2013 to test the effectiveness of Interpersonal Psychotherapy for Youth with

Mood and Behaviour Dysregulation (IPT-MBD) on a more important sample size and allow for a longer follow-up time (NCT01962623). IPT-MBD is nearly identical to IPT-SMS, except that bi-weekly sessions last until week 24. This study targets to include 44 youths between 13 and 17 years meeting criteria for SMD. Primary and secondary outcomes are similar to prior research. Estimated primary completion date of the study is August 2016.

A monocentric open-label uncontrolled study is underway since August 2015 to compare the efficacy of CBT and Interpretation Bias Training (IBT) on DMDD (NCT02531893). IBT is a newly developed computer-based training focusing on the socio-emotional information process impairments described in youths with severe irritability (e.g., anger attribution bias). IBT is performed during 14 sessions over 10 weeks (four sessions in four days, followed by eight weekly booster sessions after a two week delay) and CBT consists of 12-16 weekly meetings. Primary outcomes are improvement in the Clinical Global Impressions–Improvement score (CGI-I) and changes in irritability score using the Affective Reactivity Index (ARI). A four-week wash-out period is planned for those who participate in both treatments. Estimated primary completion date of the study is August 2019.

[Insert Table 1 about here]

3.2. Pharmacological treatments for DMDD

3.2.1. Completed studies

Only four completed pharmacological studies were eligible for the review (Table 1).

In the secondary analysis of data from the 2003-2004 ADHD Summer Treatment Program, Waxmonsky et al. examined the effectiveness of different doses of methylphenidate (MPH) in SMD symptoms in children aged 5–12 with ADHD [36]. All subjects in each

psychotherapeutic group were treated with increasing MPH doses (placebo, 0.15 mg/kg, 0.3 mg/kg, and 0.6 mg/kg). As mentioned above, multimodal treatment produced a 34% reduction in YMRS ratings in SMD subjects.

Dickstein et al. led a placebo-controlled randomized trial to test the efficacy of lithium in SMD [24]. At admission 7–17 year old youths with SMD were tapered off previously prescribed medication. Those who continued to meet SMD criteria after a 2-week, single-blind, placebo run-in were randomized to a 6-week double-blind trial of either lithium (n=14) or placebo (n=11). The primary outcome measure was the CGI-I score less than four at trial's end. Magnetic resonance spectroscopy (MRS) was performed in all participants to measure biological markers known to be associated with lithium activity (i.e., myoinositol, N-acetyl-aspartate and combined glutamate). Almost half of the subjects (n=20) were not randomized due to significant clinical improvement during the placebo run-in. Among randomized patients, there were no significant between-group differences in either clinical or MRS outcome measures.

Krieger et al. conducted an open-label trial to determine the effectiveness of risperidone on youths with DMDD [40]. Of the 97 subjects initially assessed for severe irritability symptoms only 21 met DMDD criteria and were finally enrolled in the study. Evaluations were performed at baseline and weeks 2, 4, 6, and 8. The primary outcome measures were the Aberrant Behaviour Checklist–Irritability Subscale (ABC-Irritability) score, the CGI-I score and the severity of comorbid conditions. Risperidone was titrated from 0.5 to 3 mg/day in the first two weeks. A significant reduction of the ABC-Irritability score was observed after risperidone use. Authors reported a clinically significant improvement in ADHD and depression symptoms, as well as in global functioning.

Parmar et al. reported the case of a 15-year old boy presenting a DMDD and ADHD successfully treated with 50 mg of naltrexone [41]. Previous treatments received were

methylphenidate, guanfacine extended release, and aripiprazole at 5 mg to 15 mg once daily. Tolerability profile was good, except for an increased sedation. The lack of evidence supporting long-term naltrexone justified the decision to stop the drug after three months. Authors described a resurgence of patient's aggressive symptoms after drug discontinuation, as well as an improvement after drug reintroduction.

3.2.2. Ongoing studies

Three pharmacological trials in SMD/DMDD youths are underway.

Leibenluft et al. started in November 2008 a trial to determine the feasibility and acceptability of MPH combined or not with citalopram, a selective serotonin re-uptake inhibitor (SSRI) antidepressant, in youths with SMD (NCT00794040). A wash-out period is followed by a 5-week dose stabilization phase of methylphenidate. Participants are then randomly and blindly assigned to receive citalopram (target dose: 20-40 mg/day) or a placebo. After eight weeks subjects were invited to participate in an open treatment phase for around seven weeks. This study targets to include 160 7-17 year old youths who meet NIMH criteria for SMD. The primary outcome measures are the ABC-Irritability score and the CGI-I score. Estimated primary completion date of the study is October 2016.

In January 2013, Mc Gough et al. started a preliminary study to evaluate the feasibility and acceptability of lisdexamfetamine, a psychostimulant, combined or not with fluoxetine, a SSRI antidepressant, in youths with SMD (NCT01714310). Participants have 4 weeks open titration with lisdexamfetamine to optimal dose, followed by double-blind randomization to fluoxetine or placebo in combination with optimized lisdexamfetamine for an additional eight weeks. The investigators target to include 50 children aged 7–17 years old meeting NIMH criteria for SMD (n=25, in each arm). The primary outcome is the Clinical Global Impression-Improvement-Severe Mood Dysregulation, a categorical clinician rating of overall

improvement from baseline, modified by the NIMH to assess specific domains pertinent to SMD symptoms; secondary end-points are improvement in anxiety and mood symptoms, emotion regulation and disruptive problems, changes on EEG profiles of cortical activity from baseline at week 12. Estimated primary completion date of the study is July 2015.

Gothelf et al. are conducting an ongoing trial since February 2014 in view of comparing the feasibility and acceptability of MPH vs. risperidone in the treatment of youths with both ADHD and DMDD (NCT02063945). Participants are randomly assigned to one of the two arms. The primary outcome measure is the reduction of aggressive behaviour (measured with the Retrospective Modified Overt Aggression Scale) after an 8-week treatment. This study targets to include 70 youths (5-18 year old) who meet DSM-5 criteria for both DMDD and ADHD. Estimated primary completion date of the study is February 2016.

[Insert Table 2, about here]

[Insert Table 3, about here]

4. DISCUSSION

4.1.Treatment efficacy and tolerability

At present there is only very limited empirical evidence for interventions in SMD or DMDD youths. Behaviour therapy or CBT associated with parental training showed a potential for symptom reduction and improvement of global functioning among youths with both ADHD and SMD [36,37]. This is in line with the efficacy of parental guidance

previously reported in youths with ADHD and behaviour problems [42]. In one study, the analyses were performed post-hoc in a subsample of the overall randomized group [36], thus calling successful randomization into question. In the second analysis, the small sizes of the sample make it difficult to prevent from generalizing to other population [37]. One pilot study shows encouraging results for the possible benefit of Interpretation Bias Therapy [13]. The rationale for the development of IBT in DMDD (also evaluated in NCT02531893) is based on the difficulties in performing specific cognitive tasks reported in this population (e.g., attentional bias to threat, poor inhibitory control) [20]. Four controlled studies are currently under way to test the effects of psychotherapeutic interventions. The benefit of DBT or IPT in DMDD (evaluated in NCT01862549, NCT01591564, NCT01962623) is hypothesised from available evidence for positive effects in youths with other internalizing disorders [43-46]. DBT, historically developed for chronically suicidal adults with borderline personality disorder, was regarded as effective to target mood dysregulation across a range of diagnoses [44]. Empirical studies support the use of DBT with adolescents diagnosed with depression [44], bipolar disorder [45] and ODD [47]. IPT is a brief psychotherapy successfully developed to target depressive symptoms in adolescents [46]. In addition to the patient's mood symptoms, focus is placed on the interpersonal context in which they occur. The greater emphasis of IPT on basic social skills and on learning to negotiate relationally could be particularly relevant to address emotional reactivity and poor tolerance to frustration in DMDD youths.

Concerning a pharmacological approach, four studies were identified [36,24,40,41]. Lithium carbonate was not found to be more effective than placebo in young inpatients with SMD [24]. However, preliminary results support a positive effect of risperidone for decreasing irritability and externalized symptoms in SMD youths [40]. A possible effect of naltrexone (one single case only) is reported in a 15-year old boy with ADHD and DMDD

[41]. Psychostimulant was found partly effective on youths with ADHD and SMD to treat SMD symptoms [36]. This finding is consistent with meta-analyses demonstrating an efficacy of psychostimulant on irritability [48] and in reactive aggression [49] in ADHD youths. However, in line with a prior study [32], Waxmonsky et al. [36] noted that psychostimulant remains only partially effective in this patient. In the ADHD-STP study, only 6% of youths with ADHD and SMD were in remission at endpoint, compared to 27% in the control group (ADHD without SMD) [36]. Such findings build a rationale for the development of "add-on" pharmacological strategy; i.e., the use of a second line of medication (different from psychostimulant) in youths with both ADHD and SMD/DMDD criteria. Currently, two controlled studies are under way to further clarify whether adding an SSRI antidepressant can decrease DMDD symptomatology (NCT00794040, NCT01714310). Following another pharmacological approach, one study tests the comparative efficacy of an atypical antipsychotic and a psychostimulant as a first line treatment in youths with ADHD and DMDD (NCT02063945). In particular, risperidone seems to be a promising molecule ([40], NCT02063945) in regards to its uses in the treatment of severe irritability in youths with other psychiatric disorders (e.g., autism spectrum disorder or intellectual disability) [4]. Of note, no study was conducted to test the possible benefit of selective norepinephrine reuptake inhibitors, mood stabilizers, or alpha-2 agonists, despite preliminary studies showing a possible benefit of these medications for youths with severe irritability [4].

4.2.Limitations

Several methodological weaknesses of the studies available for review may be partly responsible for the limited knowledge available in this field. We identified three sources that presented level II-1 evidence, one for level II-2 evidence, and three for level II-3 evidence. No

source for level I evidence study was found. In the next paragraphs we discuss the principal limitation of these studies and suggest possible improvements.

4.2.1. Eligibility criteria

Criteria for DMDD have only been defined since May 2013, i.e. the publishing of the DSM-5 [6], whereas NIMH criteria for SMD have been operationalized since 2001 [34]. Consequently, the participant eligibility was based on SMD criteria in most of the reviewed studies. Results of published studies focusing on SMD youths should not be extrapolated to youths with DMDD without caution, as the two constructs are not similar. As the "hyperarousal" criterion exists for SMD but not for DMDD, treatments that are effective in decreasing hyperarousal symptoms (e.g., benzodiazepines) may be mistakenly regarded as effective for DMDD. As the profile of comorbid psychiatric disorders of SMD and DMDD can differ slightly [10] the impact of specific treatments (e.g., psychostimulant) on DMDD could be under- or overestimated if data are extrapolated from studies conducted in SMD youths. We suggest that only the DMDD category should be used in future research, and if not, detailed analysis of treatment response for each symptom should be provided.

The rate of comorbidity between DMDD and externalizing disorders was high in all studies and especially between DMDD and ADHD (ranging from 71% to 100%) [24,41,40]. As diagnostic criteria overlap between these two disorders, studies conducted in youths with both ADHD and DMDD should examine whether the improvement in DMDD symptoms is not due to the impact of the treatment on shared symptoms. Waxmonsky et al. noted that 23% of the total severity score change occurred in items overlapping with ADHD symptoms [36]. Again, item-by-tem analysis that was not performed in other studies could be useful.

This review highlights the importance of using both a measure of general improvement, such as the CGI-I, and a specific measure for symptoms severity. There are two

reasons why the scales used to measure the main outcomes may be inappropriate. First, some of them were developed for manic symptoms (e.g., the YMRS) [36,37]; therefore, a decrease in total score may reflect a reduction in items such as loss of appetite or sleep changes which are not associated with DMDD. Second, other authors used subscores of scales that were not originally developed for irritability (e.g., the ABC—Irritability or the PANSS subscore) [24,40]. Content validity of such subscales is problematic as it may not cover all aspects of DMDD leading to biased results, while their poor reliability increases the risk of erroneous conclusion [50]. Moreover, as noted by Leibenluft, irritability, aggressive behaviors and hostility are embedded by distinct, even if somewhat related, pathophysiological process [51]; they therefore should be regarded as different therapeutic targets. At best, authors should use scales specifically developed to measure irritability and temper outburst such as the Affective Reactivity Index [52] or the Child Affective Lability Scale [53].

Exclusion criteria regarding intellectual disability, autism spectrum disorder and distinct manic episode were respected in line with NIMH and APA recommendations [5,6]. Of note, some studies included subjects with suicidal ideations (NCT01862549), whereas others did not (NCT01591564, NCT01962623). The status of medication was discussed in all except one study (NCT02531893). Authors recommend that psychotropic medication should not be used in a time period ranging from four weeks (NCT01591564) to six months [40]. At best, a period of medication withdrawal should be conducted after the period of inclusion (NCT00794040, [40]).

4.2.2. Design

A high level of placebo response was observed in the only placebo-controlled study [24]. This finding is consistent with the substantial decline in symptomatology scores experienced by the placebo group in RCT-DB of adolescents with mood disorders, such as

mania [54,55] or depressive disorder [56,57]. It has been noted that most of the placebo effect in antidepressant trials occurs during the first two weeks of treatment [58], possibly due to the therapeutic effects of meeting with health professionals [56]. Interestingly, Krieger et al. observed a slight increase in the level of symptomatology at four weeks compared to it at two weeks of treatment [40]. It could be somewhat comparable to the "honey moon" observed in SMD young patients who exhibited significant improvement in symptoms after admission that have not persisted with time [36], or the rapid improvement in non-medicated youths admitted to hospitalization for severe rage episodes [14]. On the one hand, we suggest that authors examine how DMDD-symptom scores change gradually over the trial to make sure than the decline does not occur only at the very beginning of the treatment after the inclusion. On the other hand, a run-in period before randomization may be useful to distinguish a "real" pharmacological effect from the positive impact of non-specific interventions (e.g., supportive psychotherapy, cares provided by a structured milieu, or the removal from a stressful environment) [56,57], in particular when the subject is randomized just after admission in a psychiatric ward.

4.2.3. Measures of tolerability and acceptance

Tolerability and acceptance were systematically measured with specific scales in all pharmacological studies. Considering the fact that irritability is both a symptom of DMDD and a possible side effect of many psychotropic medications, especially SSRI [59] and stimulant [60], it may be useful to determine whether a dose-effect relationships occurs between the treatment dose or duration and the severity of side effects (as shown in [40]). Paraclinical examinations were adequately performed to examine possible metabolic side effects of atypical antipsychotic agents [40], or the effect of lithium carbonate on thyroid function [24].

4.3.Clinical and research implications

In this research we reviewed the evidence for supporting the clinical benefits of psychotherapeutic and pharmacological treatments for DMDD/SMD youths. Further research would help to clarify the mechanisms involved at different levels (psychological, cognitive or relational). As discussed in the introduction, we thought that complementary approaches are also needed, in particular exploring the positive impact of such treatments on a clinical construct such as a youth's emotional dysregulation while adopting a trans-nosological view. Severe emotional dysregulation is a key characteristic of SMD/DMDD, but it is also seen as a core symptom for other DSM-5 disorders such as trauma-related disorders (e.g., complex PTSD, reactive attachment disorder), borderline personality disorder (BPD), or intermittent explosive disorders in DSM-5.

Future research should reveal whether, and to what extent, the severely dysregulated prepubertal youths presenting SMD/DMDD criteria develop other psychiatric disorders in adolescence (especially borderline personality disorder). In turn, findings from clinical trials conducted in youths with mood dysregulation-related disorders can inform future projects for SMD/DMDD therapeutic studies. For example, antipsychotics that have shown beneficial effects in the short-term on cognitive-perceptual symptoms, anger, and mood lability in those with BPD [61] have not demonstrated effectiveness for longer use. Interestingly, psychotherapies that focus on the development of secure bounds and relational difficulties (e.g., Dialectical Behavioral Therapy or Mentalizing-Based Therapy) exhibit the highest level of evidence for youths with BPD features [62]. The interplay between the development of emotional and social abilities throughout childhood, as stressed in various theoretical models (e.g., the socio-emotional developmental model, the psychodynamic view of object relations

theory, or the attachment theory), highlights the possible benefit of promoting the youths' social skills while caring for mood dysregulation. Surprisingly no study was devoted to the impact of family interventions in SMD/DMDD youths. The importance of parent-child quality of interactions on the emergence of child's emotion regulation strategies has however been supported in epidemiological and clinical studies (for a review [63]). Moreover, the bidirectional relationships between a child's degree of emotional distress and the parental level of adjustment has been regarded as a key mechanism to understand the persistence of symptoms [16].

4.4.Conclusion

The two current pharmacological strategies tested for SMD and DMDD patients are a monotherapy of psychostimulants or atypical antipsychotics and the use of SSRI as an add-on therapy in youths with comorbid ADHD and treated with psychostimulant. Psychotherapeutic treatments currently being tested are based on methods previously developed for depression (e.g., IPT, DBT) and/or youths with ADHD and behavioural problems (e.g., parental behavioural guidance). The overall level of available evidence remains dramatically poor regarding clinical needs, in particular with regards to the size of the sample studied and the heterogeneity of inclusion criteria. Moreover, the lack of follow-up above 8 weeks prevents current studies from being conclusive for the impact of treatment over a short-term duration. Future studies will further clarify the effectiveness of therapeutic interventions for DMDD individuals. Such studies should (i) be conducted in large multi-site studies, (ii) with specific and standardized procedures to measure DMDD symptom improvements, and (iii) include a run-in period to limit placebo effect.

LIST OF ABBREVIATIONS USED: Disruptive Mood Dysregulation Disorder (DMDD); Severe Mood Dysregulation (SMD); Attention Deficit with Hyperactivity Disorder (ADHD); Oppositional Defiant Disorder (ODD); Conduct Disorder (CD); Separation Anxiety Disorder (SAD); Anxiety Disorders (AD); Major Depressive Disorder (MDD); National Institute of Mental Health (NIMH); Cognitive Behavioral Therapy (CBT); Behavioral Parental Training (BPT); Disruptive Behavior Disorders Interview (DBD); Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS); Clinical Global Impressions–Improvement (CGI-I); Clinical Global Impressions–Severity (CGI-S)

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Evidence-based treatments for youths with severely dysregulated mood: a qualitative systematic review of trials for SMD and DMDD

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ABSTRACT

The aim of this literature review was to examine the evidence for psychotherapeutic and pharmacological treatments in subjects with severely dysregulated mood and to identify potential areas for improvements in research designs. A literature search was conducted using several databases for published (PubMed, PsycINFO) and ongoing (clinical trial registries) studies conducted in youths who met NIMH's criteria for Severe Mood Dysregulation (SMD) or the DSM-5 diagnosis of Disruptive Mood Dysregulation Disorder (DMDD). Eight completed studies were identified: three randomized trials, four open pilot studies and one case report. Seven ongoing studies were found in trial registries. The available evidence suggests potential efficacy of psychotherapies which have previously been developed for internalizing and externalizing disorders. The two main pharmacological strategies tested are, first, a monotherapy of psychostimulant or atypical antipsychotic such as risperidone, already used in the treatment of severe irritability in youths with developmental disorders; and second, the use of a serotonergic antidepressant as an add-on therapy in youths treated with psychostimulant. Ongoing studies will further clarify the effectiveness of psychotherapeutic interventions for DMDD individuals and whether they should be given alone or in conjunction with other treatments. The short duration of the trials for a chronic disorder, the low number of studies, the lack of placebo or active comparator arm, and restrictive inclusion criteria in most of the controlled trials dramatically limit the interpretation of the results. Finally, future research should be conducted across multiple sites, with standardized procedures to measure DMDD symptoms reduction, and include a run-in period to limit placebo effect.

KEYWORDS: disruptive mood dysregulation disorder; severe mood dysregulation; psychotherapy; pharmacotherapy; therapeutics; irritability

1. INTRODUCTION

1.1.General background

Children with severely dysregulated mood have become diagnostic and therapeutic challenges ~~in~~ over the last two decades within the context of pediatric bipolar controversy [1-4]. In view of facilitating research programs researchers at the U.S. National Institute of Mental Health (NIMH) operationalized the criteria of "Severe Mood Dysregulation" (SMD), a syndrome characterized by chronic abnormal levels of anger or sadness, hyperarousal and heightened verbal or physical reactivity [5]. On the grounds of studies conducted in youths with SMD and in view of improving mental health care of youths with chronic irritability, the Disruptive Mood Dysregulation Disorder (DMDD) was introduced as a new diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) within the Depressive Disorders section [6]. Youths with DMDD present chronic irritability combined with severe and recurrent episodes of temper outburst inconsistent with their developmental level at least three times per week and occurring in different settings (e.g., in family, school). These symptoms should persist more than twelve months with no symptom-free period longer than three months and with an initial onset prior to the age of 10. Prevalence of DMDD is reported to be around 8.2% in general population [7-9] and around 26-31% in clinical settings [10,11]. There is much evidence supporting that DMDD symptoms severely affect a youth's~~'~~ level of social functioning [7,8] and that such negative effects could persist into adulthood [9]. Copeland et al. showed that as adults youths with DMDD present a much higher level of functional impairments (i.e., adverse health outcomes, financial problems, police contact, and low educational attainment) than those with any other psychiatric disorders (e.g., depressive

disorders, anxiety disorders, attention deficit hyperactivity disorder ADHD, disruptive disorder, or substance disorders) [9].

1.2.Phenomenology of youths with severely dysregulated mood

Mood dysregulation (i.e., severe irritability and high level of anger) is seen as a transdiagnostic symptom, with a dimensional continuum from its typical expression in normal development of children and adolescences to severely impairing forms in psychiatric disorders [12]. In this vein, the development of studies based on specific cognitive and emotional domains rather than DSM-5 categories of disorders has been encouraged, in particular research aligned with the framework of the Research Domain Criteria articulated by the NIMH. This strategy has led to significant improvements in our knowledge of the mechanisms underlying varying aspects of mood dysregulation in youths. Such progress may ultimately lead to discovering new markers of the disorder and targets for specific interventions. The study published by Stoddard et al. [13] provides a good example of how these different levels of analysis can be integrated in research based on a dimensional view of psychopathology; with the articulation between impaired neural substrates (i.e., orbitofrontal cortex and amygdala activation), a clinical or psychological marker (i.e., the result at a face-emotion labelling task), and a therapeutic (i.e., computer-based) intervention targeting interpretation bias).

A different approach has been used in the present review as we specifically focused on studies where the clinical categories of SMD or DMDD were applied to define the population of interest. The SMD (i.e., the research syndrome) and then DMDD (i.e., the DMS-5 diagnosis) criteria were originally developed in view of facilitating the identification of youths with severe, persistent and functionally impairing forms of irritability, who were likely to fulfil criteria for different disorders at different times (“diagnostically homeless”) [14]. The development of a

specific category for these youths was endorsed due to the need to facilitate access to treatment, to reduce the rate of misdiagnosis especially early-onset bipolar disorder, and finally to reduce excessive and inappropriate medication. The inclusion of the DMDD in the 5th version of the DSM has encouraged the development of evidence-based trials which would have been difficult if mood dysregulation had been operationalized as a dimension. The use of specific disorders for youths with severely dysregulated mood was encouraged to limit the confusion with early-onset bipolar disorder and to enhance a more rational use of psychotropic medications (in particular, mood stabilizers). This issue was regarded as a major public health challenge considering the trend to overmedication and polypharmacy observed in prepubertal youths [15]. Mood dysregulation can be found in youths with various forms of psychopathology for example among youths with autistic spectrum disorder and sensory integration issues or in patients with post-traumatic stress disorder who experience episodic hyperarousal [16]. If a treatment has a positive impact only in patients with a comorbid psychiatric disorder, its overall benefit in clinical trial would be under- or overestimated with regards to its prevalence in the sample studied. The use of a categorical approach can help to explore the heterogeneity of the response to treatment in DMDD youths, for example through secondary analyses of subgroups with different associated psychiatric disorders. ~~A dimensional view of mood dysregulation in clinical trial is more likely to mask treatment efficacy if researchers fail to consider the heterogeneity of the sample studied and participants' psychiatric comorbidity.~~

1.3.Validity of SMD and DMDD diagnoses

Evidence for the validity of SMD and later DMDD diagnosis was raised on the ground of studies exploring the internal and external validity of these disorders, especially data on discriminant validity [17,18], familial studies [19], psychophysiological and neuroimaging

studies [20-23], as well as response to pharmacological treatment [24,14]. However, concerns have been raised regarding different aspects of the diagnostic validity: the paucity of data regarding reliability in literature, the difficulty in delineating the normal and abnormal mood lability in children, and above all the high rate of overlap with others psychiatric disorders, especially ADHD and ODD [8,10,11]. ~~Besides~~In addition, other~~s~~ aspects of child psychopathology are still rarely taken into consideration in these studies regarding some aspects of a child's individual characteristics (e.g., temperamental traits and attachment style) and environmental backgrounds (e.g., parent-child interaction patterns, possibility of co-occurring maltreatment). Lastly, significant changes were made in the process of integrating the category of SMD in DSM-5 including removing the criterion of hyperarousal (e.g., insomnia, agitation, distractibility, racing thoughts/flight of ideas, pressured speech, and intrusiveness), and the criterion of low intelligence (IQ<80) from the exclusionary criteria, ~~and~~ as well as lowering the age of onset from 12 to 10 years old [6]. Such differences are not trivial and could affect the comorbidity profiles of SMD and DMDD. For example, despite the lack of direct comparison between the two clinical entities, data suggests that DMDD most often co-occurs with depressive disorders and ODD and less with ADHD compared to SMD [10].

1.4.Therapeutic strategies

Little is known about effective treatments of SMD and DMDD. The DSM-5 Task Force suggested that "individual therapy, as well as work with the child's family and/or school [and] the use of medication to help address specific symptoms" could be useful for DMDD youths [6]. ~~Although~~However, the use of treatments targeting symptoms without considering the overall diagnosis has been criticized as it may contribute to the high rates of polypharmacy in this population [25-27]. Given that SMD and DMDD frequently occur with comorbid

psychiatric disorders [8,10,11,28-30], it has been suggested that therapeutic interventions should primarily focus on treating associated disorders. However, studies examining the benefit of psychotherapy or pharmacotherapy on mood dysregulation in different psychiatric disorders are somewhat mixed [31,32]. Galanter et al. [32] found that the higher baseline levels of psychopathology of children with ADHD and mood dysregulation, compared to those without prominent mood dysregulation, persisted after intensive multimodal treatments for ADHD, suggesting the need for additional treatment. In a recent systematic review, Tourian et al. examined empirical evidence supporting the use of pharmacological treatments for severe anger/irritability symptoms in youths [4]. They found that pharmacotherapeutic treatment for both aggression and chronic irritability includes various options, such as antidepressants, especially selective norepinephrine reuptake inhibitors, mood stabilizers, psychostimulants, antipsychotics, and alpha-2 agonists. However, such findings are difficult to generalize, since, as the authors noted, a majority of the study was conducted in small and specific populations (e.g., youths with developmental disorders). Even if no treatment algorithm for severe persistent irritability in youths can be derived from this data, that study can be regarded as a first step for providing evidence-based treatments for children with DMDD as it informed about the potentially effective treatments. However, in view of meeting the needs of clinician and researcher, randomized controlled clinical trials (RCTs) ~~that were~~ specifically developed for youths with SMD or DMDD are required.

The high rates of comorbidity of SMD and DMDD with externalized disorders [8,10,11,28-30] raise questions about the best ways to conduct such trials. How should pharmacological and psychotherapeutic interventions for DMDD be tested within existing therapeutic strategies for externalized disorders? Which treatments should be allowed in the control group? How should the severity of mood symptoms be measured? Is the inclusion of only DMDD subjects without psychiatric comorbidity an acceptable strategy?

1.5.Aims of the present review

In this study~~,~~ we performed a systematic review to examine psychotherapeutic and pharmacological interventions for youths presenting SMD or DMDD. Considering the short delay since the development of DMDD's criteria, such an exhaustive review was not intended to determine the comparative efficacy and tolerability of these treatments. Our main aim was rather to describe the benefits and limitations of different research strategies currently developed for SMD and DMDD with the aim of guiding future research. In this vein, both published and ongoing studies are presented in this paper.

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2. METHODS

2.1.Review

The systematic review was conducted following the recommendations outlined in the PRISMA guide (Figure 1) [33]. Titles and abstracts were scanned for relevance. Full texts were ordered in case of uncertainty to maximize sensitivity. Reference lists of retrieved systematic reviews were checked. All full texts were checked for eligibility. Any original study (open trial, double-blind trial whether randomized control or not), case-report, case-series, meta-analysis and systematic review of pharmacological and non-pharmacological intervention ~~were~~ was eligible for inclusion in this review. Abstracts and editorials were excluded. As DMDD was previously known in the literature under the alias of Severe Mood

Dysregulation (SMD), ~~-~~studies conducted among youths with SMD were included in the current analysis. Study participants had to be diagnosed with SMD or DMDD, and to be between five and 18 years old, or the mean age of the participants had to fall within the aforementioned age range.

[Insert Figure 1, about here]

2.2.Search method for identification of studies

Relevant articles for this study were obtained through Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Medline, PsychINFO, PsychINDEXplus and Dissertation Abstracts. Each database was searched from January 2001 to December 2015. In addition, we hand searched reference lists of identified articles and pertinent reviews for additional studies. References from the reviewed articles were also screened to find more articles of interest. Furthermore, clinical trials registries (http://www.clinicaltrials.gov of the US National Institutes of Health and the WHO International Clinical Trials Registry Platform, ICTRP) were searched for ongoing trials. We used the following search terms: "Disruptive mood dysregulation disorder" OR "Severe mood dysregulation" OR "Temper outburst" AND "Therapeutics" OR "Clinical protocols" OR "Treatment" OR "Pharmacotherapy" OR "Psychotherapy". Authors independently screened potential studies, after reading the full article, for inclusion in the review, and the results were collated. The systematic review yielded 86 hits, with 29 being a duplicate; 21 hits could be excluded based on the information in the title or abstract. The full texts of 36 hits were critically reviewed leading to exclusion of another 21 articles because these were only reviews or comments and no new original data were included; or the research ~~were~~ was not conducted in DMDD/SMD youths. A ~~total~~ list of

15 studies ~~were~~ was generated: eight completed studies (one case report, four open pilot studies and three RCTs) and seven ongoing studies found in trial registries.

2.3.Data and analysis

Data and information extractions from each study were performed independently by the two first authors. For each study under review, year of publication and references were extracted. In order to summarize the treatment attributes~~,~~ in each report we collected the following information: description of medication, length of treatment, and dose received. Information on additional or adjunctive interventions was also collected. Additional information regarding the attributes of participants enrolled in the studies were extracted and were as follows: age, gender, how the diagnosis was made, treatment setting, comorbid conditions, sociodemographic data, and screening tools used. Although a meta-analytic review has been preferable, the diversity of statistical methods and measurement practices across studies did not allow for the calculation of pooled effect size. We categorized the level of evidence presented in each paper using the United States Preventive Services Task Force (USPSTF) criteria [35]. According to this schematic, level I evidence denotes having at least one well-designed RCT supporting a treatment's possible efficacy. Level II-1 requires a well-designed controlled trial without randomization, level II-2 requires at least one well-designed cohort or case–control study, and level II-3 requires a multiple time series design. We excluded level III evidence (opinions of respected authorities based on clinical experience or descriptive studies) from the present review.

3. RESULTS

3.1.Psychotherapeutic interventions for DMDD

3.1.1. Completed studies

Only three studies were eligible for the review (Table 1): an exploratory analysis from a controlled study of multiple interventions for ADHD children [36], the subsequent open uncontrolled feasibility study conducted by the same research team on youths with ADHD and SMD [37], and an open pilot uncontrolled study on DMDD youths [13].

Waxmonsky et al. (2008) conducted secondary analysis of data from the 2003-2004 ADHD Summer Treatment Program (ADHD-STP), a research program for children aged 5–12 in the form of an intensive 9-week therapeutic summer camp [38]. ~~Initial~~ The initial study aimed to assess the relative efficacy and synergistic effects of differential doses of behavioural and pharmacologic interventions in ADHD youths. Among the 106 participants~~,~~ 33 fulfilled NIMH criteria for SMD (mean age 8.0 ± 2.1 years and 8.7 ± 2.0 years for non SMD group). The behavioral intervention consisted of daily social skills training and a reward-based learning program (detailed in [39]). This treatment varied in frequency every three weeks with the order: no behavior modification, low-intensity (i.e., weekly sessions) and high-intensity (i.e., daily sessions). Clinicians rating mood symptoms were not blind to treatments status. There was no evidence of differential treatment efficacy or tolerability on ADHD symptoms between the participants with and without SMD, even though those with SMD were more likely to remain significantly impaired at home than non-SMD subjects. After nine weeks, multimodal treatment produced a 34% reduction in YMRS ratings in SMD subjects ($p < 0.001$).

In an open-label uncontrolled rater-blind study, Waxmonsky and colleagues examined the feasibility and preliminary efficacy of a psychotherapeutic program that integrated

components of CBT focusing on affect regulation and parent training intervention [37]. The seven included children (mean age 8.7 ± 1.6 years) presented ADHD and the NIMH criteria for SMD. All participants were male. All of the children took stimulant medication for ADHD and all but two participants were currently receiving counselling services. SMD symptoms were assessed using the depression and mania modules from the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). The sessions consisted of 105-minute concurrent parent and child meetings. Six of the seven ~~(86%)~~ families (86%) completed at least seven of the nine weeks in the program. Over the 16 week follow-up, participants showed a reduction in the level of depressive symptoms (CDRS-R, d=1.17) and externalizing symptoms (ADHD: d=0.30; ODD: d=0.26; CD: d=0.27). Authors interpreted the reduction in YMRS score (d=0.81) as an improvement in mood lability among participants.

In an open-label uncontrolled study, Stoddard and colleagues examined the preliminary efficacy of an intervention based on four session of computer-based Hostile Interpretation Therapy [13]. The 14 included children (mean age 14.1 ± 2.4 years) ~~who~~ presented DMDD. The gender ratio was 8:6 for female. DMDD symptoms were assessed using the Affective Reactivity Index and the Clinical Global Impression- Improvement scale. Training is designed to shift interpretation of ambiguous morphs bias toward happy judgments. Ten subjects completed an implicit functional MRI face-emotion processing task. Active training is associated with a shift in balance point toward more happy judgments (use as a proxy for hostile attribution bias) (β = 2.25 morphs). Evidence suggests that active training may be associated with decreased irritability (β = -1.57 in parent-report ARI score, no significant change in self-report) and changes in activation patterns in the lateral orbitofrontal cortex.

3.1.2. Ongoing studies

Four trials were found searching the clinical trials registries that are underway.

The group from Yale University started a randomized open-label controlled study in May 2013 to examine feasibility and preliminary efficacy of Dialectical Behaviour Therapy adapted to children (DBT-C) (NCT01862549). The study targets to include 60 7–12 years old children meeting DSM-5 criteria for DMDD. Participants are randomly assigned to receive one of two treatments for 30 weeks: DBT-C or enhanced care (active control condition). Participants on the DBT-C arm received two pre-treatment sessions and 24 treatment sessions with once per week meetings, including 30 min individual child therapy, 20 min meeting with a caregiver and 40 min of skills training with both. Enhanced care consists of supportive individual psychotherapy, such as cognitive behavioural skills training and adjunctive family interventions (e.g., parenting skills training, structuring household environment, and safety planning). After the acute 32-week intervention period, 3-month follow-up assessments are conducted. The primary outcome is the attendance and drop-out rate measure, the level of satisfaction and compliance at 32 weeks; secondary end-points are reduction in DMDD symptoms and disruptive problems, psychosocial functioning and mental health service use. Estimated primary completion date of the study is July 2015.

The second ongoing study investigates the feasibility and acceptability of Interpersonal Psychotherapy for youths with SMD (IPT-SMD). A monocentric uncontrolled open-label study (NCT01591564) started in May 2012 and targeted to include five subjects who meet NIMH criteria for SMD. Youth receive weekly therapy sessions for 16 weeks and then bi-weekly sessions until week 20. Parent sessions are also included. The primary outcome is the retention rate and secondary end-points include various measures of clinical improvement. The investigators hypothesized that retention rates will be above 80% and the

satisfaction score above six on a seven point scale. Although the results of this research have not yet been published, the same research team started a randomized rater-blind controlled study in October 2013 to test the effectiveness of Interpersonal Psychotherapy for Youth with Mood and Behaviour Dysregulation (IPT-MBD) on a more important sample size and allow for a longer follow-up time (NCT01962623). IPT-MBD is nearly identical to IPT-SMS, except that bi-weekly sessions last until week 24. This study targets to include 44 youths between 13 and 17 years meeting criteria for SMD. Primary and secondary outcomes are similar to prior research. Estimated primary completion date of the study is August 2016.

A monocentric open-label uncontrolled study is underway since August 2015 to compare the efficacy of CBT and Interpretation Bias Training (IBT) on DMDD (NCT02531893). IBT is a newly developed computer-based training focusing on the socio-emotional information process impairments described in youths with severe irritability (e.g., anger attribution bias). IBT is performed during 14 sessions over 10 weeks (four sessions in four days, followed by eight weekly booster sessions after a two week~~s~~ delay) and CBT consists of 12-16 weekly meetings. Primary outcomes are improvement in the Clinical Global Impressions–Improvement score (CGI-I) and changes in irritability score using the Affective Reactivity Index (ARI). A four-week wash-out period is planned for those who participate in both treatments. Estimated primary completion date of the study is August 2019.

[Insert Table 1 about here]

3.2. Pharmacological treatments for DMDD

3.2.1. Completed studies

Only four completed pharmacological ~~completed~~ studies were eligible for the review (Table 1).

In the secondary analysis of data from the 2003-2004 ADHD Summer Treatment Program, Waxmonsky et al. examined the effectiveness of different doses of methylphenidate (MPH) in SMD symptoms in children aged 5–12 with ADHD [36]. All subjects in each psychotherapeutic group were treated with increasing MPH doses (placebo, 0.15 mg/kg, 0.3 mg/kg, and 0.6 mg/kg). As mentioned above, multimodal treatment produced a 34% reduction in YMRS ratings in SMD subjects.

Dickstein et al. led a placebo-controlled randomized trial to test the efficacy of lithium in SMD [24]. At admission 7–17 year old youths with SMD were tapered off previously prescribed medication. Those who continued to meet SMD criteria after a 2-week, single-blind, placebo run-in were randomized to a 6-week double-blind trial of either lithium (n=14) or placebo (n=11). The primary outcome measure was the CGI-I score less than four at trial's end. Magnetic resonance spectroscopy (MRS) was performed in all participants to measure biological markers known to be associated with lithium activity (i.e., myoinositol, N-acetyl-aspartate and combined glutamate). Almost half of the subjects (n=20) were not randomized due to significant clinical improvement during the placebo run-in. Among randomized patients, there were no significant between-group differences in either clinical or MRS outcome measures.

Krieger et al. conducted an open-label trial to determine the effectiveness of risperidone on youths with DMDD [40]. Of the 97 subjects initially assessed for severe irritability symptoms only 21 met DMDD criteria and were finally enrolled in the study. Evaluations were performed at baseline and weeks 2, 4, 6, and 8. The primary outcome measures were the Aberrant Behaviour Checklist–Irritability Subscale (ABC-Irritability) score, the CGI-I score and the severity of comorbid conditions. Risperidone was titrated from 0.5 to 3 mg/day in the first two weeks. A significant reduction of the ABC-Irritability score

was observed after risperidone use. Authors reported a clinically significant improvement in ADHD and depression symptoms, as well as in global functioning.

Parmar et al. reported the case of a 15-year old boy presenting a DMDD and ADHD successfully treated with 50 mg of naltrexone [41]. Previous treatments received were methylphenidate, guanfacine extended release, and aripiprazole at 5 mg to 15 mg once daily. Tolerability profile was good, except for an increased sedation. The lack of evidence supporting long-term naltrexone justified the decision to stop the drug after three months. Authors described a resurgence of patient's aggressive symptoms after drug discontinuation, as well as an improvement after drug reintroduction.

3.2.2. Ongoing studies

Three pharmacological trials in SMD/DMDD youths are underway.

Leibenluft et al. started in November 2008 a trial to determine the feasibility and acceptability of MPH combined or not with citalopram, a selective serotonin re-uptake inhibitor (SSRI) antidepressant, in youths with SMD (NCT00794040). A wash-out period is followed by a 5-week dose stabilization phase of methylphenidate. Participants are then randomly and blindly assigned to receive citalopram (target dose: 20-40 mg/day) or a placebo. After eight weeks subjects were invited to participate in an open treatment phase for around seven weeks. This study targets to include 160 7-17 year old youths who meet NIMH criteria for SMD. The primary outcome measures are the ABC-Irritability score and the CGI-I score. Estimated primary completion date of the study is October 2016.

In January 2013, Mc Gough et al. started a preliminary study to evaluate the feasibility and acceptability of lisdexamfetamine, a psychostimulant, combined or not with fluoxetine, a SSRI antidepressant, in youths with SMD (NCT01714310). Participants have 4 weeks open titration with lisdexamfetamine to optimal dose, followed by double-blind randomization

to fluoxetine or placebo in combination with optimized lisdexamfetamine for an additional eight weeks. The investigators target to include 50 children aged 7–17 years old meeting NIMH criteria for SMD (n=25, in each arm). The primary outcome is the Clinical Global Impression-Improvement-Severe Mood Dysregulation, a categorical clinician rating of overall improvement from baseline, modified by the NIMH to assess specific domains pertinent to SMD symptoms; secondary end-points are improvement in anxiety and mood symptoms, emotion regulation and disruptive problems, changes on EEG profiles of cortical activity from baseline at week 12. Estimated primary completion date of the study is July 2015.

Gothelf et al. are conducting an ongoing trial since February 2014 in view of comparing the feasibility and acceptability of MPH vs. risperidone in the treatment of youths with both ADHD and DMDD (NCT02063945). Participants are randomly assigned to one of the two arms. The primary outcome measure is the reduction of aggressive behaviour (measured with the Retrospective Modified Overt Aggression Scale) after an 8-week treatment. This study targets to include 70 youths (5-18 year old) who meet DSM-5 criteria for both DMDD and ADHD. Estimated primary completion date of the study is February 2016.

[Insert Table 2, about here]

[Insert Table 3, about here]

4. DISCUSSION

4.1.Treatment efficacy and tolerability

At present there is only very limited empirical evidence for interventions in SMD or DMDD youths. Behaviour therapy or CBT associated with parental training showed a potential for symptom reduction and improvement of global functioning among youths with both ADHD and SMD [36,37]. This is in line with the efficacy of parental guidance previously reported in youths with ADHD and behaviour problems [42]. In one study, the analyses were performed post-hoc in a subsample of the overall randomized group [36], thus calling successful randomization into question. In the second analysis, the small sizes of the sample make it difficult to prevent from generalizing to other population [37]. One pilot study shows encouraging results for the possible benefit of Interpretation Bias Therapy [13]. The rationale for the development of IBT in DMDD (also evaluated in NCT02531893) is based on the difficulties in performing specific cognitive tasks reported in this population (e.g., attentional bias to threat, poor inhibitory control) [20]. Four controlled studies are currently under way to test the effects of psychotherapeutic interventions. The benefit of DBT or IPT in DMDD (evaluated in NCT01862549, NCT01591564, NCT01962623) is hypothesised from available evidence for positive effects in youths with other internalizing disorders [43-46]. DBT, historically developed for chronically suicidal adults with borderline personality disorder, was regarded as effective to target mood dysregulation across a range of diagnoses [44]. Empirical studies support the use of DBT with adolescents diagnosed with depression [44], bipolar disorder [45] and ODD [47]. IPT is a brief psychotherapy successfully developed to target depressive symptoms in adolescents [46]. In addition to the patient's mood symptoms, focus is placed on the interpersonal context in which they occur. The greater emphasis of IPT on basic social skills and on learning to negotiate relationally could be particularly relevant to address emotional reactivity and poor tolerance to frustration in DMDD youths.

Concerning a pharmacological approach, four studies were identified [36,24,40,41]. Lithium carbonate was not found to be more effective than placebo in young inpatients with SMD [24]. However, preliminary results support a positive effect of risperidone for decreasing irritability and externalized symptoms in SMD youths [40]. A possible effect of naltrexone (one single case only) is reported in a 15-year old boy with ADHD and DMDD [41]. Psychostimulant was found partly effective on youths with ADHD and SMD to treat SMD symptoms [36]. This finding is consistent with meta-analyses demonstrating an efficacy of psychostimulant on irritability [48] and in reactive aggression [49] in ADHD youths. However, in line with a prior study [32], Waxmonsky et al. [36] noted that psychostimulant remains only partially effective in this patient. In the ADHD-STP study, only 6% of youths with ADHD and SMD were in remission at endpoint, compared to 27% in the control group (ADHD without SMD) [36]. Such findings build a rationale for the development of "add-on" pharmacological strategy; i.e., the use of a second line of medication (different from psychostimulant) in youths with both ADHD and SMD/DMDD criteria. Currently, two controlled studies are under way to further clarify whether adding an SSRI antidepressant can decrease DMDD symptomatology (NCT00794040, NCT01714310). Following another pharmacological approach, one study tests the comparative efficacy of an atypical antipsychotic and a psychostimulant as a first line treatment in youths with ADHD and DMDD (NCT02063945). In particular, risperidone seems to be a promising molecule ([40], NCT02063945) in regards to its uses in the treatment of severe irritability in youths with other psychiatric disorders (e.g., autism spectrum disorder or intellectual disability) [4]. Of note, no study was conducted to test the possible benefit of selective norepinephrine reuptake inhibitors, mood stabilizers, or alpha-2 agonists, despite preliminary studies showing a possible benefit of these medications for youths with severe irritability [4].

4.2.Limitations

Several methodological weaknesses of the studies available for review may be partly responsible for the limited knowledge available in this field. We identified three sources that presented level II-1 evidence, one for level II-2 evidence, and three for level II-3 evidence. No source for level I evidence study ~~were~~ was found. In the next paragraphs we discuss the principal limitation of these studies and suggest possible improvements.

4.2.1. Eligibility criteria

Criteria for DMDD have only been defined since May 2013, i.e. the publishing of the DSM-5 [6], whereas NIMH criteria for SMD have been operationalized since 2001 [34]. Consequently, the participant eligibility was based on SMD criteria in most of the reviewed studies. Results of published studies focusing on SMD youths should not be extrapolated to youths with DMDD without caution, as the two constructs are not similar. As the "hyperarousal" criterion exists for SMD but not for DMDD, treatments that are effective in decreasing hyperarousal symptoms (e.g., benzodiazepines) may be mistakenly regarded as effective for DMDD. As the profile of comorbid psychiatric disorders of SMD and DMDD can differ slightly [10] the impact of specific treatments (e.g., psychostimulant) on DMDD could be under- or overestimated if data are extrapolated from studies conducted in SMD youths. We suggest that only the DMDD category should be used in future research, and if not, detailed analysis of treatment response for each symptom should be provided.

The rate of comorbidity between DMDD and externalizing disorders ~~were~~ was high in all studies and especially between DMDD and ADHD (ranging from 71% to 100%) [24,41,40]. As diagnostic criteria overlap between these two disorders, studies conducted in youths with both ADHD and DMDD should examine whether the improvement in DMDD

symptoms is not due to the impact of the treatment on shared symptoms. Waxmonsky et al. noted that 23% of the total severity score change occurred in items overlapping with ADHD symptoms [36]. Again, item-by-tem analysis that was not performed in other studies could be useful.

This review highlights the importance of using both a measure of general improvement, such as the CGI-I, and a specific measure for symptoms severity. There are two reasons why the scales used to measure the main outcomes may be inappropriate. First, some of them were developed for manic symptoms (e.g., the YMRS) [36,37]; therefore, a decrease in total score may reflect a reduction in items such as loss of appetite or sleep changes which are not associated with DMDD. Second, other authors used subscores of scales that were not originally developed for irritability (e.g., the ABC—Irritability or the PANSS subscore) [24,40]. Content validity of such subscales is problematic as it may not cover all aspects of DMDD leading to biased results, while their poor reliability increases the risk of erroneous conclusion [50]. Moreover, as noted by Leibenluft, irritability, aggressive behaviors and hostility are embedded by distinct, even if somewhat related, pathophysiological process [51]; ~~and~~ they therefore should be regarded as different therapeutic targets. At best, authors should use scales specifically developed to measure irritability and temper outburst such as the Affective Reactivity Index [52] or the Child Affective Lability Scale [53].

Exclusion criteria regarding intellectual disability, autism spectrum disorder and distinct manic episode were respected in line with NIMH and APA recommendations [5,6]. Of note, some studies included subjects with suicidal ideations (NCT01862549), whereas others did not (NCT01591564, NCT01962623). The status of medication was discussed in all except one study (NCT02531893). Authors recommend that psychotropic medication should not be used in a time period ranging from four weeks (NCT01591564) to six months [40]. At

best, a period of medication withdrawal should be conducted after the period of inclusion (NCT00794040, [40]).

4.2.2. Design

A high level of placebo response was observed in the only placebo-controlled study [24]. This finding is consistent with the substantial decline in symptomatology scores experienced by the placebo group in RCT-DB of adolescents with mood disorders, such as mania [54,55] or depressive disorder [56,57]. It has been noted that most of the placebo effect in antidepressant trials occurs during the first two weeks of treatment [58], possibly due to the therapeutic effects of meeting with health professionals [56]. Interestingly, Krieger et al. observed a slight increase in the level of symptomatology at four weeks compared to it at two weeks of treatment [40]. It could be somewhat comparable to the "honey moon" observed in SMD young patients who exhibited significant improvement in symptoms after admission that have not persisted with time [36], or the rapid improvement in non-medicated youths admitted ~~in~~ to hospitalization for severe rage episodes [14]. On the one hand, we suggest that authors examine how DMDD-symptom scores change gradually over the trial~~,~~ to make sure than the decline does not occur only at the very beginning of the treatment after the inclusion. On the other hand, a run-in period before randomization may be useful to distinguish a "real" pharmacological effect from the positive impact of non-specific interventions (e.g., supportive psychotherapy, cares provided by a structured milieu, or the removal from a stressful environment) [56,57], in particular when the subject is randomized just after admission in a psychiatric ward.

4.2.3. Measures of tolerability and acceptance

Tolerability and acceptance were systematically measured with specific scales in all pharmacological studies. Considering the fact that irritability is both a symptom of DMDD and a possible side effect of many psychotropic medications, especially SSRI [59] and stimulant [60], it may be useful to determine whether a dose-effect relationships occurs between the treatment dose or duration and the severity of side effects (as shown in [40]). Paraclinical examinations were adequately performed to examine possible metabolic side effects of atypical antipsychotic agents [40], or the effect of lithium carbonate on thyroid function [24].

4.3.Clinical and research implications

In this research we reviewed the evidence for supporting the clinical benefits of psychotherapeutic and pharmacological treatments for DMDD/SMD youths. Further research would help to clarify the mechanisms involved at different levels (psychological, cognitive or relational). As discussed in the introduction, we thought that complementary approaches are also needed, in particular exploring the positive impact of such treatments on a clinical construct such as a youth's emotional dysregulation while adopting a trans-nosological view. Severe emotional dysregulation is a key characteristic of SMD/DMDD, but it is also seen as a core symptom for other DSM-5 disorders, such as trauma-related disorders (e.g., complex PTSD, reactive attachment disorder), borderline personality disorder (BPD), or intermittent explosive disorders in DSM-5.

Future research should reveal whether, and to what extent, the severely dysregulated prepubertal youths presenting SMD/DMDD criteria develop other psychiatric disorders in adolescence (especially borderline personality disorder). In turn, findings from clinical trials conducted in youths with mood dysregulation-related disorders can inform future projects for

SMD/DMDD therapeutic studies. For example, antipsychotics that have shown beneficial effects in the short-term on cognitive-perceptual symptoms, anger, and mood lability in those with BPD [61] have not demonstrated effectiveness for longer use. Interestingly, psychotherapies that focus on the development of secure bounds and relational difficulties (e.g., Dialectical Behavioral Therapy or Mentalizing-Based Therapy) exhibit the highest level of evidence for youths with BPD features [62]. The interplay between the development of emotional and social abilities throughout childhood, as stressed in various theoretical models (e.g., the socio-emotional developmental model, the psychodynamic view of object relations theory, or the attachment theory), highlights the possible benefit of promoting the youths' social skills while caring for mood dysregulation. Surprisingly no study was devoted to the impact of family interventions in SMD/DMDD youths. The importance of parent-child quality of interactions on the emergence of child's emotion regulation strategies has however ~~although~~ been supported in epidemiological and clinical studies (for a review [63]). Moreover, the bidirectional relationships between a child's degree of emotional distress and the parental level of adjustment has been regarded as a key mechanism to understand the persistence of symptoms [16].

4.4.Conclusion

The two current pharmacological strategies tested for SMD and DMDD patients are a monotherapy of psychostimulants or atypical antipsychotics and the use of SSRI as an add-on therapy in youths with comorbid ADHD and treated with psychostimulant. Psychotherapeutic treatments currently being tested are based on methods previously developed for depression (e.g., IPT, DBT) and/or youths with ADHD and behavioural problems (e.g., parental behavioural guidance). The overall level of available evidence remains dramatically poor

regarding clinical needs, in particular with regards to the size of the sample studied and the heterogeneity of inclusion criteria. Moreover, the lack of follow-up above 8 weeks prevents current studies from being conclusive for the impact of treatment over a short-term duration. Future studies will further clarify the effectiveness of therapeutic interventions for DMDD individuals. Such studies should (i) be conducted in large multi-site studies, (ii) with specific and standardized procedures to measure DMDD symptom improvements, and (iii) include a run-in period to limit placebo effect.

LIST OF ABBREVIATIONS USED: Disruptive Mood Dysregulation Disorder (DMDD); Severe Mood Dysregulation (SMD); Attention Deficit with Hyperactivity Disorder (ADHD); Oppositional Defiant Disorder (ODD); Conduct Disorder (CD); Separation Anxiety Disorder (SAD); Anxiety Disorders (AD); Major Depressive Disorder (MDD); National Institute of Mental Health (NIMH); Cognitive Behavioral Therapy (CBT); Behavioral Parental Training (BPT); Disruptive Behavior Disorders Interview (DBD); Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS); Clinical Global Impressions–Improvement (CGI-I); Clinical Global Impressions–Severity (CGI-S)

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Figure 1

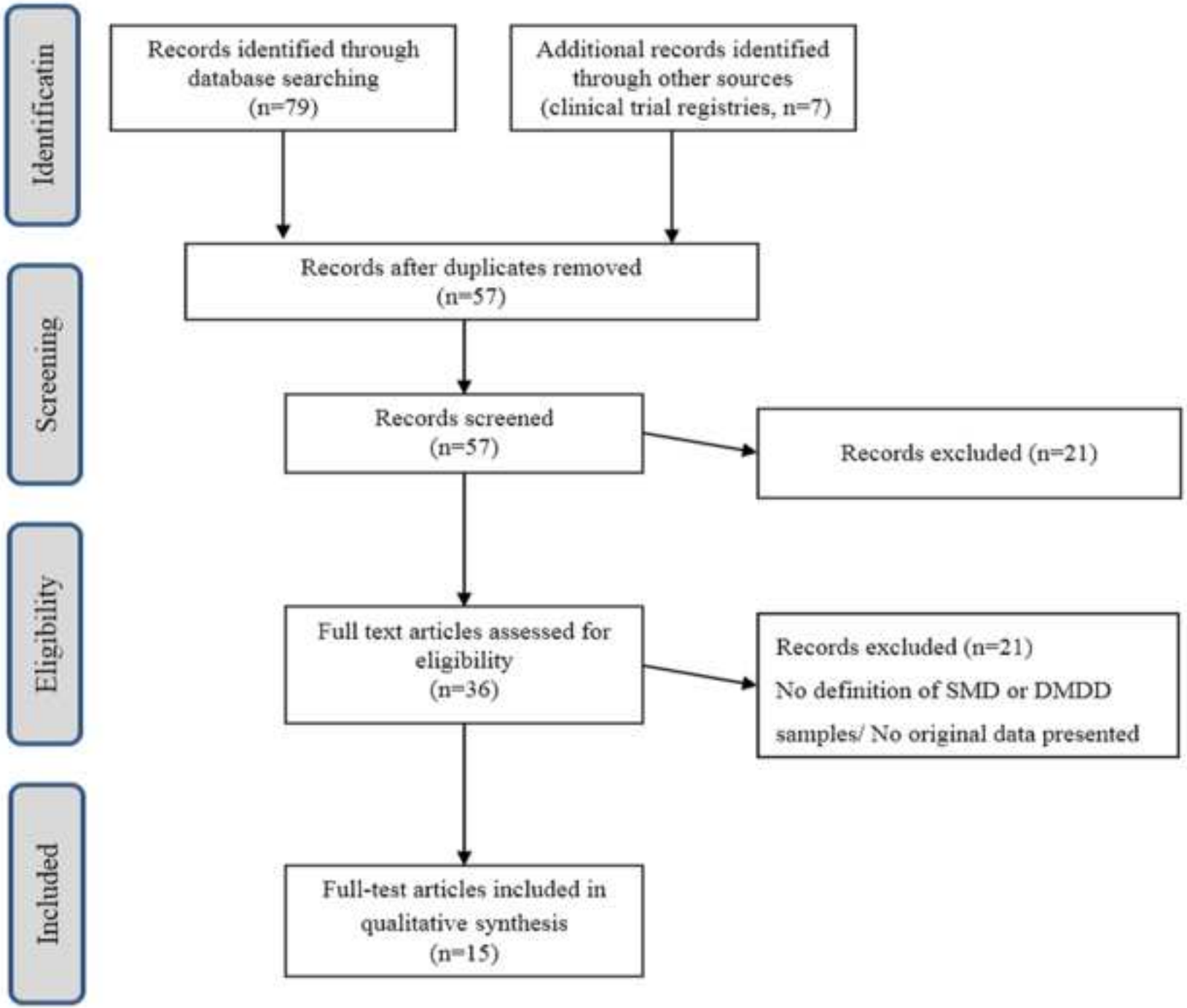

Table 1

Table 1. Trials evaluating the benefit of psychotherapeutic interventions for youths with SMD or DMDD

Authors	**Intervention Study design**	**Duration of study**	**N Recruitment**	**Age range (mean) Gender**	**Main diagnoses Inclusion criteria**	**Screening tools**	**Psychiatric comorbidities**	**Interventions and control**	**Scales for main outcomes (Mean at baseline)**
Waxmonsky et al. 2008 [36]	BMOT Secondary analysis of RCT-DB vs. TAU with cross-over	Intervention: 9 weeks	33 Recruited from schools, health-care providers and public advertisements	5-12 y.o. (8.0) Boys 82%	ADHD youths meeting criteria for SMD and manic-like sympt. treated with different doses of MPH	NIMH criteria for SMD (items from the CBCL, DISC) + Manic-like sympt YMRS (+12) CGI-S (+3)	ADHD 100% ODD 72% CD 24% Depressive sympt. (CDRS-R>28) 72%	BMOT 3 weeks each sessions: no, low intensity, high intensity	YMRS (23.7) CDRS-R (35) IRS (5.0) DBD
Waxmonsky et al. 2013 [37]	Behavioral parenting training Pilot monocentric RCT open-label vs. TAU	Intervention: 9 weeks Follow-up: 16 weeks	7 Recruited from an outpatient clinic	7 -12 y.o. (8.7) Boys 100%	ADHD (combined subtypes) youths meeting criteria for SMD treated with MPH	NIMH criteria for SMD (depression and mania items from the WASH-U-KSADS)	ADHD 100% ODD - NA CD - NA SAD 29%	CBT+ BPT behavioral parental training 105-minute concurrent parent and child meetings	YMRS (23.7) CDRS-R (35) DBD CGAS APQ
Stoddard et al. [13]	IBT-SMD Pilot monocentric non-controlled open-label	Intervention:6 days Follow-up: 2 weeks	14 NA	8-18 y.o. (14.1) Boys: 47%	Lifetime diagnosis of DMDD and clinically significant DMDD symptoms (CGI-S $\geq$ 3)	DSM-5 criteria for DMDD	ADHD 71% ODD 100% ANX 71% MDD 14%	4 sessions of the active training IBT task	Parent- and self-report ARI SCARED STAXI-2 C/A CDI “Balance point” as a cognitive marker of angry judgment bias

http://www.clinicaltrials.gov NCT01862549 USA (Cornell University)	DBT-C Pilot monocentric RCT open-label vs. TAU	Intervention: 32 weeks Follow-up: 12 weeks	60 (target sample) NA	7-12 y.o. Both genders	DMDD youths may be medicated if stabilized for at least 6 weeks	DSM-5 criteria for DMDD	NA	2 pre-treatment and 24 treatment sessions, once per week (30 min. individual child therapy, 20 min. meeting with a caregiver and 40 min. of skills training with both)	CGI-I MSQ ERC ARI MAVRIC SSRS C-SSIS
http://www.clinicaltrials.gov NCT01591564 USA (Johns Hopkins University, NIMH)	IPT-SMD Pilot monocentric non-controlled open-label	Intervention: 16 weeks No follow-up	5 (target sample) NA	13-17 y.o. Both genders	SMD youths may be medicated if stabilized for at least 4 weeks + CGAS≤ 60	NIMH criteria for SMD	NA	once per week; 16 weeks	CGI-I
http://www.clinicaltrials.gov NCT01962623 USA (Johns Hopkins University, NIMH)	IPT-MBD Pilot monocentric RCT-SB vs. TAU	Intervention: 24 weeks No follow-up	44 (target sample) NA	12-17 y.o. Both genders	SMD youths + CGAS≤ 60 CGI-S ≥ 4	NIMH criteria for SMD	NA	once per week; 24 weeks	CGI-I
http://www.clinicaltrials.gov NCT02531893 USA (NIMH)	CBT vs. IBT Pilot monocentric open-label	Intervention: 10 weeks No follow up	40 (target sample) NA	8-18 y.o. Both genders	DMDD, ADHD, ODD youths may be medicated (no delay period) + CGI-S ≥ 3	DSM-5 criteria	NA	4 sessions over 4 days and 8 weeks of weekly booster sessions	CGI-I ARI

BMOT: Behavior Modification therapy; RCT: Randomized controlled trial; DB: Double-blind; TAU: Treatment-as-usual; y.o.: year old; NA: Not Available; Sympt.: Symptoms; SB: Single-blind; MPH: Methylphenidate; CBCL: Child Behavior Checklist; DISC: Diagnostic Interview Schedule for Children; YMRS: the Young Mania Rating Scale; CDRS-R: the Children's Depression Rating Scale Revised; IRS: Impairment Rating Scale; DBD: Disruptive Behavior Disorders Rating Scale; WASH-U-KSADS: the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia; CGAS: the Children's Global Assessment Scale; APQ: the Alabama Parenting Questionnaire; MSQ: Mood Symptoms Questionnaire; ERC: Emotion Regulation Checklist; ARI: Affective Reactivity Index; MAVRIC: Measure of Aggression Violence and Rage in Children; SSRS: Social Skills Rating Scale; C-SSIS: Columbia Suicide and Self-Injury Severity Rating Scale; IBT: Interpretation Bias Training

Table 2. Trials evaluating the benefit of pharmacological treatments for youths with SMD or DMDD

Authors	**Intervention Study design**	**Duration of study**	**N Recruitment**	**Age range (mean) Gender**	**Main diagnoses Inclusion criteria**	**Screening tools**	**Psychiatric comorbidities**	**Interventions and control**	**Scales for main outcomes**	**Main results**
Waxmonsky et al. 2008 [36]	MPH Secondary analysis of RCT-DB vs. PBO with cross-over	Intervention: 9 weeks	33 Recruited from schools, health-care providers and public advertisements	5-12 y.o. (8) Boys 82%	ADHD youths meeting criteria for SMD and manic-like sympt.treated with different intensity of psychotherapy	NIMH criteria for SMD (items from CBCL, DISC) + Manic-like sympt YMRS (+12) CGI (+3)	ADHD 100% ODD 72% CD 24% Depressive sympt. (CDRS-R>28) 72%	MPH 0.15 mg/kg, 0.3mg/kg, 0.6mg/kg	YMRS (23.7) CDRS-R (35) IRS (5.0) DBD	34% decrease in YMRS score 31% in CDRS-R score Improvement in externalizing symptoms Improvement in overall impairment
Dickstein et al. 2009 [24]	Lithium PRP, RCT-DB vs. PBO	Intervention: 6 weeks	25 Recruited via advertisements, on support groups' websites and via psychiatrists	7-17 y.o. (11.5) Boys 75%	SMD youths	NIMH criteria for SMD (K-SADS-PL with an additional SMD module)	ADHD 92% ODD 88% CD - NA MDD 20% SAD 12%	Lithium carbonate between 0.8-1.2 mEq/l	PANSS factor 4 YMRS (14.6) CDRS (29.8) CGI-S (4.9) CGAS (44.7) Conners' teacher OAS CGI-I	No significant differences in CGI-I or PANSS scores.
Krieger et al. 2011 [40]	Risperidone Pilot monocentric non-controlled open-label	Intervention:8 week Follow-up 8 weeks	21 Recruited via advertisements	7-17 y.o. (10.4) Boys 43%	SMD youths	NIMH criteria for SMD (K-SADS-PL with an additional SMD module)	ADHD 71% ODD 81% CD 14% MDD 14% AD 71%	Risperidone 0.5 to 3 mg/d (mean 1.28 mg)	ABC-Irritability (25.9) SNAP-IV (1.71) YMRS (12.7) CDRS (34.3) CGI-S (4.5) CGAS (46.9) MSQ (37.4) SCARED (34.7)	56% decrease in ABC-irritability 64% decrease in YMRS 34% decrease in CDRS 34% increase of CGAS
Parmar et al. 2014 [41]	Naltrexone Case report	3 months	1 inpatient	15 y.o. Boy	DMDD youths	DSM-5 criteria for DMDD	ADHD	Naltrexone 50mg/d	No	Significant improvement in aggressive symptoms

http://www.clinicaltrials.gov NCT01714310 USA (University of California, NIMH)	LDX combined or not with Fluoxetine Monocentric open-label period followed by RCT-DB vs. PBO	Intervention:12 weeks (Open-label LDX: 4 weeks; CRT-DB Fluoxetine vs. PBO: 8 weeks) Follow-up period 4 weeks	50 (target sample) NA	7-17 y.o. Both genders	Youths with both SMD and ADHD criteria	NIMH criteria for SMD + inattentive or hyperactive/Impulsive subscales ADHD-RS>9 + ABC<12	NA	LDX low, medium, and high dose Fluoxetine	Safety/Efficacy CGI-I PARS CDRS ADHD-IV RS CSSS CALS R-MOAS ARI	NA
http://www.clinicaltrials.gov NCT00794040 USA (NIMH)	MPH combined or not with Citalopram PRP, Open-label period followed by RCT-DB vs. PBO	Intervention:4-5 months Medication withdrawal PRP: 1 week Open-label MPH: 5weeks CRT-DB Citalopram vs PBO: 8 weeks Open treatments phase: 10 weeks	160 (target sample) NA	7-17 y.o Both genders	SMD youths	SMD + ADHD + CGAS≤ 60	NA	Methylphenidate + Citalopram: 20-40 mg/d	Safety/Efficacy CGI-I ABC-Irritability	NA
http://www.clinicaltrials.gov NCT02063945 Israel (Sheba Medical Center)	Risperidone vs. Methylphenidate Open label randomized	Intervention: 8 weeks	70 (target sample) NA	5-18 y.o Both genders.	ADHD youths with comorbid disruptive disorder (ODD/CD)	ADHD + ODD or CD or DMDD	NA	Methylphenidate (Ritaline LA®: 0.6 to 1.5 mg/kg/day; Concerta®: 1 to 2 mg/kg/day) vs. Risperidone (0.5 to 2 mg/day)	Safety/Efficacy R-MOAS CGI-I CGI-S ADHD-RS CDRS YMRS CSHQ	NA

PBO: Placebo; PRP: pre-randomization run-in period; PANSS: the Positive and Negative Syndrome Scale (factor 4= sum of excitement, hostility, uncooperativeness, and poor impulse control); OAS: Overt Aggression Scale; SNAP-IV: the Swanson, Nolan, and Pelham Scale-version IV; SCARED: Screen for Child Anxiety-Related Emotional Disorders; LDX: Lisdexamfetamine; PARS: the Pediatric Anxiety Rating Scale; ADHD-RS: the ADHD-IV Rating Scale; CSSS: the Columbia Suicide Severity Scale; CALS: the Children's Affective Lability Scale; R-MOAS: the Revised Modified Overt Aggression Scale; CSHQ: the Children Sleep Habits Questionnaire

Table 3

Table 3. Trials evaluating the benefit of psychotherapeutic interventions for youths with SMD or DMDD

Authors	**USPSTF's grade**[a]	**Main results**	**Limitations**	**Strengths**
Psychotherapeutic studies				
Waxmonsky et al. 2008 [36]	Level II-1	34% decrease in YMRS score 31% in CDRS-R score Improvement in externalizing symptoms Improvement in overall impairment	- Selected sample size (already enrolled in the STP study) - Use of psychometric instruments nonstandardized (YMRS for SMD criteria) - Only one assessment instrument for the measure of SMD/DMDD symptoms - Complex cross-over design (two within-subjects factors) not clear if change attributable to medication or psychotherapy - No procedures to evaluate treatment adherence - No follow-up evaluation of treatment effects	- Size of the sample - Description of the treatments detailed - Measure of tolerability provided - Teacher-report information - LOCF analysis
Waxmonsky et al. 2013 [37]	Level II-3	Decrease in CDRS-R *d*=1.17, YMRS *d*=0.81, DBD (ADHD *d*=0.30, ODD *d*=0.26, CD *d*=0.27), C-GAS (*d*=2.17) Decrease in parenting behavior (parental involvement *d*=-0.37 and inconsistent discipline *d*=0.46)	- Small sample size - Sample bias: only boys included, only combined subtype of ADHD - Use of psychometric instruments nonstandardized (YMRS for SMD criteria) - Only one assessment instrument for the measure of SMD/DMDD symptoms - Non-comparative design - No follow-up evaluation of treatment effects	- Ethnic diversity within sample - Assessment of comorbidity and respect of exclusion criteria (ASD, ID) - Description of the treatments detailed - Low level of drop-out rate among families - Measure of treatment fidelity
Stoddard et al. [13]	Level II-3	Decrease of balance point (away from angry judgment bias) β = 2.25 morphs. CGI-I in the ''slightly improved'' range (*d*=0.59) Decrease parent-report ARI score β = -1.57 points, no significant change in self-report ARI	- Selected sample size (22% of the initial sample) - Possible sample bias, no information is provided about the recruiting method - Non-comparative design - Only four session of treatment are tested and follow-up evaluation was planned at 2 weeks - Symptom changes were modest and remained in clinical range, results on "balance point" is difficult to interpret	- Use of DMDD criteria - Use of two standardized psychometric instruments for the measure of DMDD symptoms (ARI, CGI-I) - Use of both parent and self-report information - Description of the treatments detailed - Measure of "balance-point" suggests possible mechanisms for treatment efficacy

NCT01862549 USA	-	NA	- Sample bias: only younger than 13 year olds - Assessors were not blinded - Lack of no-treatment control group	- Use of DMDD criteria - Randomization - Twelve-weeks follow-up evaluation of treatment effects - At least two assessment instrument for the measure of SMD/DMDD symptoms - Measure of compliance
NCT01591564 USA	-	NA	- Small sample size - Sample bias: only older than 13 year olds - Only one assessment instrument for the measure of SMD symptoms - Non-comparative design - No follow-up evaluation of treatment effects	- Measure of compliance
NCT01962623 USA	-	NA	- Lack of no-treatment control group - No follow-up evaluation of treatment effects - Only one assessment instrument for the measure of SMD symptoms	- Size of the sample (expected) - Randomization - Single-blind (Outcomes Assessor) - Measure of satisfaction
NCT02531893 USA	-	NA	- No follow-up evaluation of treatment effects - Assessors and participants were not blind - Findings from the arm with both forms of therapy with a 4 weeks wash-out periods would be difficult to interpret - Non randomized allocations of treatments	- Size of the sample (expected) - Diversity in terms of age, prescribed medication - Use of DMDD criteria
Pharmacological studies				
Waxmonsky et al. 2008 [36]	Level II-1	34% decrease in YMRS score 31% in CDRS-R score Improvement in externalizing symptoms Improvement in overall impairment	- Selected sample size (already enrolled in the STP study) - Use of psychometric instruments nonstandardized (YMRS for SMD criteria) - Only one assessment instrument for the primary outcome measure - Complex cross-over design (two within-subjects factors) not clear if change attributable to medication or psychotherapy - No procedures to evaluate treatment adherence - No follow-up evaluation of treatment effects	- Size of the sample - Description of the treatments detailed - Measure of tolerability provided - Teacher-report information - LOCF analysis
Dickstein et al. 2009 [24]	Level II-1	No significant differences in CGI-I or PANSS scores.	- Selected sample bias: community-based recruitment via advertisements, assessment of only a sample of those initially screened (≈23%) - Use of psychometric instruments nonstandardized (YMRS for SMD criteria) - No comparison to a well-validated treatment - No follow-up evaluation of treatment effects	- Exclusion criteria and the prevalence of psychiatric comorbidity are detailed - Two-weeks placebo run-in period - Randomization - Assessors and participants were blind - Intent-to-treat analysis with LOCF - Measure of tolerability provided

Krieger et al. 2011 [40]	Level II-2	56% decrease in ABC-irritability 64% decrease in YMRS 34% decrease in CDRS 34% increase of CGAS	- Selected sample bias: community-based recruitment via advertisements, no current use of medication, little socio-economic diversity - Use of psychometric instrument nonstandardized (YMRS for SMD criteria) - Non-comparative design	- Exclusion criteria and the prevalence of psychiatric comorbidity are detailed - Description of the treatments detailed - At least two assessment instrument for the measure of SMD symptoms - Follow-up evaluation of treatment effects - Weekly measure of tolerability
Parmar et al. 2014 [41]	Level II-3	Significant improvement in aggressive symptoms	- Case report of a single case - Non-comparative design - No use of standardized psychometric instrument - No follow-up evaluation of treatment effects	- Use of DMDD criteria
NCT01714310	-	NA	- Selected sample bias: only ADHD youths - No procedures to evaluate the effect of Fluoxetine in naive participants (without Lisdexamfetamine) - No active-drug/placebo run-in period - Multiple scales used (risk of multiple statistical testing)	- Size of the sample (expected) - Randomization - Assessors and participants were blind - Measure of tolerability provided
NCT00794040	-	NA	- No procedures to evaluate the effect of Citalopram in naive participants (without Methylphenidate) - Only one assessment instrument for SMD symptoms	- Size of the sample (expected) - Randomization - Assessors and participants were blind - Pre-randomization phases (medication withdrawal period and 1-week placebo run-in period) - Measure of tolerability provided
NCT02063945	-	NA	- Selected sample bias: only ADHD youths with disruptive disorders - Use of psychometric instruments nonstandardized (YMRS, R-MOAS) - Assessors and participants were not blind - Lack of no-treatment control group - No active-drug/placebo run-in period	- Size of the sample (expected) - Randomization - Measure of tolerability provided

Note: STP= Summer Treatment Program, NA = Not Available

[a] The level of evidence presented in each paper was categorized using the United States Preventive Services Task Force (USPSTF) criteria. Level I evidence denotes having at least one well-designed RCT supporting a treatment's possible efficacy. Level II-1 requires a well-designed controlled trial without randomization, level II-2 requires at least one well-designed cohort or case–control study, and level II-3 requires a multiple time series design. We excluded level III evidence (opinions of respected authorities based on clinical experience or descriptive studies) from our review.