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RESEARCH ARTICLE

Treatment Options for the Cardinal Symptoms of Disruptive Mood Dysregulation Disorder

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Abstract

Objective: DSM-5 has added a new developmentally appropriate child and adolescent mood disorder subtype called disruptive mood dysregulation disorder (DMDD). The core features of DMDD are temper outbursts (manifested by either verbal rages and/or physical aggression) and unrelenting irritability or anger. Currently, the literature is lacking a thorough review of the possible treatment options for the cardinal symptoms constituting DMDD. The objective of this article is to provide a thorough review of peer-reviewed studies on the subject of pharmacological treatment options for children and adolescents with the cardinal symptoms of DMDD. **Methods:** Relevant articles for this study were obtained through Pubmed, Medline, PsychINFO and PsychINDEXplus using the key words: "adolescents," "children," "paediatric," "youth," "irritability," "temper outbursts," "aggression," "rage," "disruptive behaviour," "treatment," "dysphoria," "autism," "mental retardation/intellectual disability," "impulsivity," "ADHD," "oppositional defiant disorder," and "conduct disorder." A total of 823 studies were generated; only English studies focusing on pharmacological treatment were retained. **Results:** Currently there are no established guidelines or thorough reviews summarizing the treatment of DMDD. Pharmacotherapeutic treatment options of both aggression and chronic irritability include: antidepressants/selective norepinephrine reuptake inhibitors, mood stabilizers, psychostimulants, antipsychotics, and alpha-2 agonists. **Conclusion:** Treatment options of severe, persistent irritability in youth are numerous, and a consensual treatment algorithm has not yet emerged from the literature. Further studies and clinical trials are warranted to determine efficacious and safe treatment modalities.

Key Words: *disruptive mood dysregulation, aggression, irritability, depression, bipolar disorder, mood stabilizers*

Résumé

Objectif: Le DSM-5 a ajouté un nouveau sous-type de trouble de l'humeur adapté au développement des enfants et des adolescents qui porte le nom de trouble disruptif avec dysrégulation de l'humeur (TDDH). Les principales caractéristiques du TDHE sont des accès de colère (manifestés soit par des rages verbales et/ou une agression physique) et une irritabilité ou une colère persistante. À l'heure actuelle, la littérature ne présente pas de revue approfondie des options de traitement possibles des symptômes cardinaux constituant le TDHE. L'objectif de cet article est d'offrir une revue approfondie des

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études révisées par des pairs sur le sujet des options de traitement pharmacologique pour les enfants et les adolescents présentant les symptômes cardinaux du TDHE. **Méthodes:** Les articles pertinents pour cette étude ont été obtenus dans Pubmed, Medline, PsychINFO et PsychINDEXplus à l'aide des mots clés: « adolescents », « enfants », « pédiatrie », « jeunesse », « irritabilité », « accès de colère », « agressivité », « rage », « comportement perturbateur », « traitement », « dysphorie », « autisme », « retard mental/déficience intellectuelle », « impulsivité », « TDAH », « trouble oppositionnel avec provocation », et « trouble des conduites ». Au total, 823 études ont été relevées; seulement les études en anglais portant sur le traitement pharmacologique ont été retenues. **Résultats:** À l'heure actuelle, il n'y a pas de lignes directrices établies ou de revues approfondies qui résument le traitement du TDHE. Les options de traitement pharmacologique de l'agressivité et de l'irritabilité chronique sont notamment: les antidépresseurs/inhibiteurs spécifiques du recaptage de la noradrénaline, les stabilisateurs de l'humeur, les psychostimulants, les antipsychotiques, et les agonistes alpha-2. **Conclusion:** Les options de traitement de l'irritabilité grave et persistante chez les adolescents sont nombreuses, et un algorithme de traitement consensuel n'a pas encore été dégagé de la littérature. D'autres études et essais cliniques sont nécessaires pour déterminer des modes de traitement efficaces et sûrs.

Mots clés: *trouble de dérégulation dit d'humeur explosive, agressivité, irritabilité, dépression, trouble bipolaire, stabilisateurs de l'humeur*

Introduction

Disruptive mood dysregulation disorder (DMDD) is a new diagnosis included in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA, 2013). The rational for this proposed addition stems from an increasing, and worrisome, trend over the last two decades (Blader & Carlson, 2007; Moreno et al., 2007) to diagnose children and adolescents with severe nonepisodic irritability with bipolar disorder (Biederman et al., 2004; Biederman, Klein, Pine, & Klein, 1998; Mick, Spencer, Wozniak, & Biederman, 2005).

The diagnostic criteria for DMDD are listed in Table 1. DMDD was previously known in the literature under the alias of severe mood dysregulation (SMD), a syndrome defined by Leibenluft and colleagues (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003), who used it to study the relationship between severe nonepisodic irritability and bipolar disorder. However, the hyperarousal criterion of the SMD diagnosis (with symptoms such as insomnia, agitation, distractability, racing thoughts/flight of ideas, pressured speech, and intrusiveness) have not been included in the DMDD diagnosis criteria. The age of onset criterion was 12 years of age or earlier for SMD; this was reduced to ten for DMDD.

Epidemiological data on SMD and DMDD are, for the moment, derived from post hoc analyses of data collected using instruments that do not specifically assess for SMD or DMDD diagnostic criteria. The lifetime prevalence of SMD in a community sample was 3.3% with a three to one preponderance of males versus females. The most common axis I diagnoses in children and adolescents with SMD were attention-deficit/hyperactivity disorder (ADHD) (26.9%), conduct disorder (CD) (25.9%), oppositional defiant disorder (ODD) (24.5%), anxiety disorders (14.7%), and depressive disorders (13.7%) (Brotman et al., 2006). Leibenluft and colleagues recruited and compared children and adolescents with SMD and bipolar disorder; both these disorders have comparable degrees of severity and health care utilization. According to longitudinal studies, SMD in youth predicts major depressive disorder, but not bipolar disorder, in early adulthood (Brotman et al., 2006; Stringaris et al., 2010). Moreover, youth with bipolar disorder were more likely to have parents with bipolar disorder compared to youth with SMD (Brotman et al., 2007).

The overall six-month to one-year period prevalence of DMDD ranges from two to five percent as per DSM-5 (APA, 2013). DMDD, in clinical settings, appears to be a predominantly male disorder; the exact gender distribution in the population remains unclear. Comorbidity profiles also differ from SMD: according to a study from Copeland and colleagues (Copeland, Angold, Costello, & Egger, 2013), DMDD most often co-occurs with depressive disorders and ODD. The inclusion of DMDD in DSM-5 will represent significant challenges to clinicians in light of its high prevalence and significant disease burden.

Treatment guidelines will be necessary to aid clinicians in their management of children and adolescents presenting with DMDD. Many years will pass before official guidelines are available; until then, pharmacological management of DMDD will invariably be based on treating individual symptoms that make up this disorder. Currently, there is no thorough, published review on the treatment of youth with temper outbursts (manifested by either verbal rages and/or physical aggression) and unrelenting irritability or anger. This review's objective is to address this issue by reviewing published treatment options for temper, rage, and chronic irritability – the cardinal symptoms of DMDD.

Methods

Criteria for considering studies for this review

Any original study (open trial, double-blind trial whether randomized control or not), case-report, case-series, meta-analysis, systematic review and review of peer-reviewed

Table 1. Diagnostic criteria for disruptive mood dysregulation disorder (APA, 2013)

A. Severe recurrent temper outbursts manifested verbally and/or behaviorally that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, three or more times a week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others.
E. Criteria A-D have to be present for 12 or more months. Throughout that time, the individual has not had a period lasting three or more consecutive months without all of the symptoms in Criteria A-D.
F. Criteria A and D are present in at least two or three settings and are severe in at least one of these.
G. The diagnosis should not be made for the first time before age six or after age 18 years.
H. By history or observation, the age of onset of criteria A-E is before ten years.
I. There has never been a distinct period lasting more than one day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.
J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder.
K. The symptoms are not attributable to the physiological effect of a substance or to another medical or neurological disorder.

articles on the subject of pharmacological treatment options for children and adolescents with severe persistent irritability was eligible for inclusion in this review. Study participants had to be between six and 18 years old, or the mean age of the participants had to fall within the aforementioned age range. To be eligible for inclusion, studies had to provide results on the efficacy of pharmacological treatments of temper outbursts (manifested by either verbal rages and/or physical aggression) and unrelenting irritability or anger in paediatric and adolescent populations.

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 1965 to 2013 using the key words: "adolescents," "children," "paediatric," "youth," "irritability," "temper outbursts," "aggression," "rage," "disruptive behaviour," "treatment," "autism," "mental retardation/intellectual disability," "impulsivity," "ADHD," "oppositional defiant disorder," and "conduct disorder." A total of 823 studies were generated; only English studies focusing on pharmacological treatment were retained. When meta-analyses were available for old compounds or for drugs that were assessed in several randomized controlled trials (RCTs), we used these data and added the more recent reports. In total, we found 57 open studies and 28 RCTs investigating various compounds, and three meta-analyses.

Data and analysis

Authors independently screened potential studies, after reading the full article, for inclusion in the review, and the results were collated. References from the reviewed articles were also screened to find more articles of interest. Data and information extractions from each study were performed independently by two authors (LT/JR). For each study under review, year of publication and references were extracted. In order to summarize the pharmacological 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. In line with previous reviews, additional information regarding the attributes of participants enrolled in the studies were extracted and were as follow: age, gender, how the diagnosis was made, length and severity of illness, treatment setting, comorbid conditions, sociodemographic data, and screening tools used. The main focus of this review was to determine the efficacy of pharmacological treatment of temper outbursts, verbal rages, physical aggression, irritability, and anger.

Results

The results section is divided in two parts. The first part is a detailed review of published studies related to the treatment of temper outbursts. The second part reviews treatment of irritable mood. Only meta-analyses and RCTs are presented when available for each medication class. When no such studies were available, non RCT-derived data are presented.

Tables 2 and 3 summarize the findings of the main RCTs and meta-analyses retained for this review. Side effects of medications as well as rating scales for individual symptoms are beyond the scope of this article and will not be addressed here.

Table 2. Randomized controlled trials that investigated treatment of severe mood dysregulation in children and adolescents

Author, year	Medication	Study design	N and main diagnoses	Age range (mean)	Daily dosage/ serum level	Duration of study	Scales	Main results
Dickstein, et al. 2009	Lithium	RCT-DB vs. PBO	25 SMD	7-17 y.o. (11.45)	Serum levels: 0.8 - 1.2 mmol/L.	6 weeks	- CGI - PNSS - OAS	- CTQ -YMRS -CPRS	Lithium not superior to PBO
Waxmonsky, et al. 2008	Methylphenidate	Crossover design BMT (2 intensities) vs. MPH (3 dosages) vs. PBO	33 ADHD + SMD 68 ADHD only	5-12 y.o. (8-8.7)	0.45 mg/kg 0.9 mg/kg 01.8 mg/kg	9 weeks	- Disruptive Behavior Disorder Scale -YMRS	- CGI - CDRS - Behavioural observations	Significant effect of both behavioral modification and MPH in both groups. Dose effect relation in both groups and both treatments

ADHD = Attention Deficit with Hyperactivity Disorder; BMT = Behaviour Modification Therapy; DB = double-blind; CDRS = Children's Depression Rating Scale; CGI = Clinical Global Impressions Scale; CTQ = Conners Teacher Questionnaire; CPRS = Children's Psychiatric Rating Scale; MPH = methylphenidate; N/A = information not available; OAS = Overt Aggression Scale; PBO = Placebo; PNSS = Positive and Negative Syndrome Scale; RCT = Randomized Controlled Trial; YMRS = Young Mania Rating Scale; y.o. = years old

Treatment of SMD

Before delving into the published results of treatment outcomes of individual symptoms of DMDD we present here three treatment studies of patients with a diagnosis of severe mood dysregulation as defined by Leibenluft and colleagues, a syndrome that, as stated earlier, shares many diagnostic criteria with DMDD. The first study on the treatment of SMD was published by Waxmonsky and colleagues in 2008 (Waxmonsky et al., 2008). In a randomized crossover study of children aged five to 12 years with ADHD, Waxmonsky and colleagues show that treatment with methylphenidate (0.15 mg/kg t.i.d., 0.3mg/kg t.i.d., and 0.6mg/kg t.i.d.) combined with behaviour modification therapy is associated with a decrease in symptoms associated with SMD. Dickstein and colleagues conducted the first RCT of lithium in the treatment of young patients with SMD. After a two-week period of inpatient stay and placebo run-in, nearly half of the patients showed significant improvement. The remaining 25 patients with severe SMD were randomized and showed no observable superiority for lithium over placebo (Dickstein et al., 2009).

These two RCTs are presented in Table 2. The last published study investigating the treatment of SMD was conducted by Krieger and colleagues. In an open trial of 21 SMD adolescents, this study shows that risperidone (3 mg/day) is potentially an effective treatment for SMD, as it was associated with a significant reduction of the Aberrant Behaviour Checklist–Irritability scores after two, four, six, and eight weeks of treatment. Improvements in symptoms of ADHD, depression, and global functioning were also observed (Krieger et al., 2011).

In summary, we found only three SMD treatment studies published to date. At least tentatively, it would appear that methylphenidate and risperidone, but not lithium, are effective in decreasing symptoms of SMD in patients under the age of 18. More randomized control trials are needed to ascertain the safest, most effective and tolerable medication to treat this disorder.

PART 1: Treatment options for temper outbursts

Temper outbursts as defined by the DSM-5 (APA, 2013) manifest clinically as either verbal rages and/or physical aggression. This section delves into two different conceptual categorizations of temper outbursts: 1) temper and rage, and, 2) aggression.

Treatment of temper and rage

Temper

Temper is defined as heat of mind or emotion and proneness to anger (Merriam-Webster, 2011). Temper tantrums are developmentally appropriate up to the age of three or four years. They usually last one to five minutes and can be conceptualized as an ascending and descending phase of

emotional intensity consisting mostly of anger and distress (Potegal, Kosorok, & Davidson, 2003). Anger outbursts, often called "rages" in the literature, are increasingly understood as exaggerated and developmentally inappropriate temper tantrums and are also composed of anger and distress. Anger outbursts are generally characterized by an initial short and rapid burst of anger, that declines over the duration of the outburst, and by steady levels of distress throughout the length of the outburst (Carlson, 2007; Carlson, Potegal, & Grover, 2009; Carlson, Potegal, Margulies, Gutkovich, & Basile, 2009; Potegal, Carlson, Margulies, Gutkovitch, & Wall, 2009). Anger outbursts are typically longer than tantrums. Moreover, distress behaviours are typically less prevalent in outbursts. For example, social withdrawal tends to emerge only at higher levels of distress (Potegal et al., 2009). Some authors argue that the term "rage" may be misleading since it only refers to the intense anger-laden affect, occluding the distress that is also expressed during the outburst (Potegal et al., 2009).

We were unable to find a single RCT reporting the efficacy of pharmacological treatments of temper in the paediatric population. However, Donovan and colleagues published an underpowered RCT showing that divalproex was an efficacious treatment for explosive temper and mood lability in youth with CD (Donovan et al., 2000). There are also numerous studies (open trials and case reports) reporting the successful use of divalproex, propanolol, carbamazepine, and lithium in decreasing temper outburst in adults (Mattes, 1986).

Rage

The word rage is derived from the Latin word *rabies* and is defined as either a violent and uncontrolled anger or a fit of violent wrath.

Rage outbursts are essentially acute acts of aggression that are treated with either physical restraints or standard chemical sedation composed typically of diphenydramine and/or an antipsychotic. One study showed that liquid risperidone decreased the duration of rages by nearly half in subjects aged from five to 12 years (Carlson, Potegal, Margulies, Basile, & Gutkovich, 2010). A review published by Mandoki and colleagues in 1992 reports that lithium, carbamazepine, and propranolol decrease rage in children and adolescents (Mandoki, Sumner, & Matthews-Ferrari, 1992).

Treatment of aggression

The word aggression is derived from the Latin word *aggressio* meaning attack. Aggression is defined as hostile or injurious actions or words. Aggression is believed to be the single most common reason for referral to child and adolescent mental health clinics reaching as high as 50 to 60 per cent (Sadock, 2007).

Lithium

Lithium is considered the cornerstone of the pharmacological management of bipolar disorder. Lithium is FDA approved for the treatment of acute paediatric mania and the maintenance treatment of mania in bipolar youth (12 years of age or older).

Lithium and aggression: RCTs

We located five double-blind, randomized, controlled trials of children and adolescents with conduct disorder using lithium (Campbell et al., 1995; Campbell et al., 1984; Carlson, Rapport, Pataki, & Kelly, 1992; Malone, Delaney, Luebbert, Cater, & Campbell, 2000; Rifkin et al., 1997). Four out of these five studies concluded that lithium significantly reduced aggression when compared to placebo. The remaining study failed to find any difference between lithium and placebo, but it is thought this conclusion was a result of the study's short duration (two weeks).

Anticonvulsants

Anticonvulsants are the mainstay in the treatment of seizure disorders. However, this class of medication is also indicated in the treatment of bipolar disorder in adults but not yet in children and adolescents. This class of medication includes valproicacid (divalproex), carbamazepine, and lamotrigine.

Divalproex and aggression: RCT

We found one RCT investigating the impact of divalproex on aggression in children and adolescents with CD associated with chronic explosive temper and mood lability (Donovan et al., 2000). This study, showing the superior efficacy of divalproex compared to placebo, was underpowered and is never included in any meta-analysis. Also, two other RCTs with contradictory results investigated the efficacy of valproate in aggressive behaviour associated with autism (Hellings et al., 2005; Hollander et al., 2009) (Table 3).

Carmabazepine and aggression: RCTs

We identified one RCT investigating the impact of carbamazepine on aggression (Cueva et al., 1996). This study found that carbamazepine was not superior to placebo in reducing aggression and explosiveness.

Lamotrigine and aggression: RCTs

Lamotrigine is an antiepileptic drug commonly used as adjunctive therapy for seizure disorders in paediatric and adult populations. In adults, lamotrigine has been approved for the maintenance treatment of bipolar I disorder. In adults, lamotrigine has also been shown to decrease aggression in subjects with borderline personality disorder (Leiberich, Nickel, Tritt, & Pedrosa Gil, 2008; Tritt et al., 2005). We identified one study of autistic youth treated with lamotrigine, by Belsito and colleagues, which did not demonstrate that lamotrigine was efficacious in decreasing behavioural disturbance features commonly associated with autism (Belsito, Law, Kirk, Landa, & Zimmerman, 2001).

Table 3. Randomized controlled trials or meta-analyses that investigated cardinal symptoms of disruptive mood dysregulation disorder in children and adolescents

Author, year	Study design Medication	N	Main diagnoses	Age range (mean)	Daily dosage/serum level
LITHIUM					
Campbell, et al. 1984	DB Lithium vs. PBO vs. Haloperidol	31	CD	5.2-12.9 y.o. (8.97)	Lithium: 500-2.000 mg Serum levels: 0.32-1.81 mEq/L (mean: 0.993 mEq/L) Haloperinol: 1.0-6.0 mg (mean: 2.95 mg)
Campbell, et al. 1995	RCT-DB vs. PBO	50	CD	5.1-12 y.o. (9.4)	Mean: 1.248 mg Mean serum levels : 1.12 mEq/L
Carlson, et al. 1992	DB,Cross-over to PBO	11 (7 completed the cross-over to PBO)	CD	6.7-12.8 y.o.	600-1500 mg Serum levels: 0.7-1.1 mEq/L
Malone, et al. 2000	RCT-DB vs. PBO	40	CD	9.5-17.1 y.o. (12.3-12.6)	900 – 2.100 mg Serum level : 0.8-1.55 mEq/L
Rifkin, et al. 1997	DB vs. PBO	26	CD	12-17 y.o. (15.15)	Serum levels: 06.-1.0 mEq/L
VALPROATE					
Donovan, et al. 2000	Cross over with PBO	20	ODD or CD	10-18 y.o. (13.8)	10mg/lb Serum levels: >90 µg/mL
Hellings, et al. 2005	RCT vs. PBO	30	Autism	6-20 y.o. (10.3-12.1)	20 mg/kg Serum levels 70-100 mcg/mL
Hollander, et al. 2009	RCT vs. PBO	27	Autism	5-15 y.o. (9.4)	At least 500 mg (< 40kg) or 1000 mg (>40kg) Serum level s ≥ 50 mg/mL
OTHER ANTICONVULSIVANTS					
Belsito, et al. 2001	Lamotrigine DB, parallel group study	28	Autism	3-11 y.o. (5.8)	5 mg/kg
Cueva, et al. 1996	Carbamazepine RCT vs. PBO	22	CD	5.3-11.7 y.o (8.97)	400-800mg (mean: 683 mg) Serum levels: 4.98-9.1 µg/mL

	Duration of study	Symptom target	Scales (for RCT only)	Main results
	4 weeks	Aggression	• CPRS • CGI • GCJCS • CPTQ	Lithium and haloperidol both superior to PBO Lithium and haloperidol equally effective No difference in side effects for lithium vs PBO More side effect for haloperidol vs.PBO or vs. lithium
	6 weeks	Aggression	• CPRS • CGI • CTQ • CPTQ • Child adaptation of POMS	Lithium superior to PBO
	8 weeks on lithium Serum levels: 0.7-1.1 mEq/L	Aggression	• ADD-H Comprehensive Teacher Rating Scale • Teacher's Self-Control Rating Scale • Inpatient Global Rating Scale	Improvement on lithium, but improvement sustained during PBO week
	4 weeks	Aggression	• GCJCS • CGI • OAS	Lithium superior to PBO (80% responders) More side effects on lithium
	2 weeks	Aggression	• OAS • Behavior Rating Scale • CTQ • ADD/H Adolescent Self-Report Scale	Lithium not superior to PBO 21.4% remission on lithium (non-significant vs PBO) More side effects on lithium
	6 weeks on divalproex 6 weeks on PBO	Explosive temper and mood lability	• Modified OAS • SCL-90 anger-hostility items	Valproate superior to PBO
	8 weeks	Aggression	• ABC—Community Scale • CGI • OAS	Valproate not superior to PBO
	12 weeks	Aggression	• CGI-Improvement Scale • Irritability subscale of the ABC	Valproate superior to PBO (OR=16)
	12 weeks	Behavioural disturbance/ irritability	• Autism Behavior Checklist • ABC • Vineland Adaptive Behavior scales • Pre-Linguistic ADOS • ADOS • Childhood Autism Rating Scale	No difference
	6 weeks	Aggression	- OAS - GCJCS - CPRS	Carbamazepine not superior to PBO

table continued

Table 3. continued Randomized controlled trials or meta-analyses that investigated cardinal symptoms of disruptive mood dysregulation disorder in children and adolescents

Author, year	Study design Medication	N	Main diagnoses	Age range (mean)	Daily dosage/ serum level
METHYLPHENIDATE AND OTHER STIMULANTS					
Pappadopulos, et al. 2006	Meta-analysis of 18 RCT	1057 (total) MPH: 844 AMS: 58	ADHD/ CD/ autism/ ID/ MR	(9.1)	MPH: 0.93 mg/ kg AMS: 0.5 mg/kg DEX: 0.6 mg/kg
TYPICAL ANTIPSYCHOTICS					
Anderson, et al. 1989	Haloperidol Cross over with PBO	45	Autism	2.02-7.58 y.o. (4.49)	0.25-4.0 mg/ day (mean: 0.844 mg/day)
See also Campbell, et al. 1985 in the lithium section					
ATYPICAL ANTIPSYCHOTICS					
Cohen, et al. 2013	Meta-analysis Aripiprazole 2 RCT	316 (total)	Autism	Mean age: 9-10.2 y.o.	2-15 mg
Connor, et al. 2008	RCT-DB vs. PBO Quetiapine	19	CD	12-17 y.o. (14.1)	200-600 mg (mean: 294 mg)
Findling, et al. 2014	Aripiprazole RCT vs. PBO of pt with an initial positive response to aripiprazole	85	Autism	6-17 y.o. (10.1-10.8)	2-15 mg
Pappadopulos, et al. 2006	Meta-analysis Risperidone 9 RCT	875 (total)	Several conditions manly autism/ID/CD/ODD/ADHD	Range of mean age: 7.4-13.9 y.o (9.2.).	0.04 mg/kg
SNRI AND SSRI					
Pappadopulos, et al. 2006	Meta-analysis Atomoxetine 4 RCT	857 (total)	ADHD with comorbidities (ODD/GAD/Depression)	Range of mean age: 9.9-11.2 y.o. (10.5)	1.3 mg/kg
Pappadopulos, et al. 2006	Meta-analysis Bupropion 3 RCT Fluoxetine 2 RCT Desipramine 1 RCT	274 (total)	Bupropion: N=100 - ADHD Fluoxetine: N=112 -depression or selective mutism Desipramine: N=62 - ADHD	Range of mean age: 8.5-12.2 y.o. (10.4)	Bupropion: 5.2 mg/kg Fluoxetine: 0.5 mg/kg Desipramine: 4.6 mg/kg
OTHER AGENTS					
Connor, et al. 2003	Meta-analysis Clonidine 4 RCT	66 (total)	ADHD/ autism/ ID/ tics	Range of mean age: 8.1-15.6 y.o.	n/a

ABC= Aberrant Behavior Checklist ; ADHD=Attention Deficit with Hyperactivity Disorder; ADOS= Autism Diagnostic Observation Schedule; AMS= amphetamine mixed salts; DB=double-blind; CD=Conduct Disorder; CDRS=Children's Depression Rating Scale; CGI=Clnical Global Impressions Scale; CTQ=Conners Teacher Questionnaire; CPTQ= Conners Parent Teacher Questionnaire; CPRS=Children's Psychiatric Rating Scale; DB=double-blind; DEX= dextroamphetamine; GAD= Generalized Anxiety Disorder;

	Duration of study	Symptom target	Scales (for RCT only)	Main results
	Mean length: 27.2 days (Range: 7-42 days)	Aggression		Stimulants effect size = 0.78 MPH effect size = 0.9
	4 weeks	Aggression	• CPRS • CGI • CPTQ	Haloperidol superior to PBO
	8 weeks	Irritability		Aripiprazole superior to PBO (OR of responders vs. PBO=6)
	7 weeks	Aggression	• CGI • OAS • Conduct problems subscale of the CPQ	Quetiapine superior to PBO (on clinican-assessed measures only)
	16 weeks	Irritability	• CGI-Improvement Scale • Irritability subscale of the ABC	Aripiprazole not superior to PBO NNT = 6
	Mean length: 45.7 days (range: 28-70 days)	Aggression		Risperidone effect size=0.90
	Mean length: 129.1 days (Range 49-252 days)	Aggression		Limited effect on aggression associated with ADHD effect size=0.18
	Mean length: 45.8 days (Range: 28-70 days)	Aggression		Bupropion effect size=0-0.55 Fluoxetine effect size=0-0.3 Desipramine effect size=0.85
	6-12 weeks	Aggression		Significant but moderate effect on aggression (Effect size ranging from 0.37 to 7.84)

GCJCS= Global Clinical Judgement (Consensus) Scale; ID=Intellectual Disability; MPH=methylphenidate; MR= Mental Retardation; NNT=number need to treat; N/A=information not available; OAS= Overt Aggression Scale; OR=Odd Ratio; PBO=Placebo; PNSS= Positive and Negative Syndrome Scale; POMS=Profile of Mood States; RCT=Randomized controlled trial;YMRS=Young Mania Rating Scale; y.o=years old.

Psychostimulants

Psychostimulants and aggression in ADHD: RCTs

Impulsive aggression frequently co-occurs with ADHD with or without comorbid ODD or CD. Pappadopulos and colleagues published an extensive review of the pharmacological treatment of aggression. They retained 18 RCTs of psychostimulants in the treatment of ADHD youth with (12 studies) or without (six studies) comorbid ODD, CD, and mental retardation (MR). Methylphenidate was the most frequently used pharmacological agent. Overall, the impact of psychostimulants on decreasing aggression was significant, with an effect size of 0.78 (Pappadopulos et al., 2006).

Antipsychotics

Typical antipsychotics and aggression: RCTs

Before the advent of atypical antipsychotics, typical antipsychotics were among the few choices for treating aggression in youth. There are two RCTs of haloperidol that measured aggressive behaviour. These two studies show that haloperidol is superior to placebo in decreasing aggressive behaviour in youth with conduct disorder (Campbell et al., 1984) and autism (Anderson et al., 1989). There was one RCT of thioridazine that also measured aggressive behaviour and showed that thioridazine was superior to placebo in decreasing aggressive behaviour (Aman, Marks, Turbott, Wilsher, & Merry, 1991).

Atypical antipsychotics and aggression: RCTs

Risperidone, aripripazole, quetiapine, and olanzapine are FDA approved for the treatment of schizophrenia and acute management of mania or mixed episode in type I bipolar disorder in youth. Risperidone and aripiprazole are FDA approved for the treatment of irritability (including aggression, temper tantrums, self-injurious behaviour, and quickly-changing moods) associated with autistic disorder in children and adolescents.

Pappadopulos and colleagues identified nine RCTs of aggressive children and adolescents being treated with risperidone. All nine of these studies showed greater reductions in aggression with risperidone compared to placebo in subjects with CD, ODD, ADHD, autism, and MR/ intellectual disability (ID). The overall effect size of risperidone was quite high (0.9) (Pappadopulos et al., 2006). Since Pappadopoulos's meta-analysis, we found only one minor RCT comparing risperidone and haloperidol in the treatment of aggressive behaviours associated with autism (Miral et al., 2008).

Two studies have shown that for children and adolescents with mental retardation and ADHD symptoms, risperidone, independent of the concomitant use of psychostimulants, was an effective treatment of disruptive behaviour disorders and comoribid ADHD (Aman, Binder, & Turgay, 2004; Correia Filho et al., 2005).

Connor and colleagues have shown that for adolescents with conduct disorder, quetiapine was effective in decreasing overt aggression (Connor, McLaughlin, & Jeffers-Terry, 2008); however, this study had fewer than 30 patients.

Antidepressant agents and SNRI

SSRIs and SNRIs, and aggression: RCTs

Atomoxetine is an SNRI approved in the US and Canada for the treatment of ADHD in children and adolescents. Pappadopulous and colleagues identified four RCTs of atomoxetine and have shown that its effect size on paediatric aggression is quite small (0.18) (Pappadopulos et al., 2006). Their findings indicate that atomoxetine may not be the treatment of choice in ADHD youth with marked aggression.

This same review measured the impact of antidepressants on aggressive behaviour. The combined effect size of six antidepressant trials was 0.3. Antidepressants showcased in their review included bupropion (three RCTs; effect size ranging from 0 to 0.55), fluoxetine (two RCTs; effect size ranging from 0 to 0.3) and desipramine (one RCT; effect size of 0.85). However, it is important to note that this significant effect size represented global improvement of ADHD symptoms and not only aggression.

Other agents

Alpha-2 agonist and aggression: RCTs

Clonidine has been shown to reduce symptoms of disruptive disorders in children and adolescents. Conner and colleagues published a meta-analysis of 11 double blind RCTs published between 1980 and 1999 showing that clonidine exerts a moderate effect on symptoms of ADHD and may help diminish impulsive aggression (Connor, Glatt, Lopez, Jackson, & Melloni, 2003). Jaselskis and colleagues showed that clonidine significantly decreases aggressive behaviour compared to placebo (Jaselskis, Cook, Fletcher, & Leventhal, 1992).

Guanfacine is another alpha-2 agonist also used to treat ADHD. Scahill and colleagues showed that guanfacine also decreases aggressive behaviour compared to placebo (Scahill et al., 2001).

Beta-Blockers

We were unable to locate any RCTs showing the use of beta-blockers in children or adolescents with aggression. However, there are many non-RCT studies showing that the use of beta-blockers may lead to decreased aggression (Kuperman & Stewart, 1987; Luchins & Dojka, 1989; Williams, Mehl, Yudofsky, Adams, & Roseman, 1982).

Trazodone

One open trial using trazodone in children with disruptive behaviour disorders was shown to decrease aggression (Zubieta & Alessi, 1992).

Summary

The present review suggests that methylphenidate is very efficacious in decreasing aggression in subjects with ADHD. If aggression does not respond to methylphenidate, adjunctive risperidone or divalproex have been shown to successfully decrease aggressive behaviour. Risperidone is efficacious in decreasing aggression in patients with conduct disorder, autism, and MR/ID. Lithium, anticonvulsants, SSRI, SNRI, and alpha-2 agonists have been shown to decrease aggression; however, their effect has been found to be low to mild at best, and some compounds show secondary effect profiles that prevent their use as a first option.

PART 2: Treatment options for chronic, persistent severe irritability

Irritability and anger are the core symptoms defined as persistently negative mood in criterion D of the DMDD diagnostic criteria.

Treatment of irritability

This word stems from the Latin *irritare,* which means to excite or provoke. Irritability in youth is currently viewed as a mood characterised by anger and easy annoyance and is related to later mood and anxiety disorders in adulthood (Stringaris, 2011). Irritability, unlike aggression, is not often a major outcome variable in medication treatment trials. Scales to evaluate irritability are scarce and tend to capture the most severe manifestation such as aggression. However, recently Stringaris and colleagues developed the Affective Reactivity Index, which is designed to measure irritability in youth and appears to be quite suitable for the severe mood dysregulation population (Stringaris et al., 2012).

Atypical antipsychotics

As mentioned above, risperidone and, more recently, aripiprazole are the only FDA approved medications to treat irritability associated with autism.

Cohen and colleagues identified two short-term (eight weeks) RCTs studying the effect of aripiprazole 2-15 mg in children and adolescents with autistic disorder and behavioural problems characterized by irritability, agitation, and self-injurious behaviour. These two studies showed greater reduction in irritability with aripiprazole compared to placebo in these subjects (OR = 6) (Cohen et al., 2013).

In a recent RCT, autistic patients with marked symptoms of irritability were found to have a favourable response during the initial phase of single blind treatment with a flexible dose of aripiprazole. These patients were then randomized to either continue on aripiprazole or be switched to placebo. Aripiprazole was shown to be no more effective than placebo after 16 weeks of treatment. However, a post hoc analysis showed a number needed to treat (NNT) of six to prevent one additional relapse (Findling et al., 2014).

Psychostimulants

In ADHD youth with or without SMD, methylphenidate and behavioural modification was found to be superior to placebo. In fact, results show a twofold improvement in irritability and aggression in the active treatment group compared to placebo (Waxmonsky et al., 2008). Also, they found a dose-effect relation with both treatments and in both groups of patients.

Anticonvulsants

We were unable to find any RCTs of anticonvulsants with irritability being the major outcome variable.

Summary

The diagnostic criteria of DMDD include a mood component defined as persistently irritable or angry. However, this diagnosis is not retained if the child's or adolescent's clinical presentation is better explained by a mood disorder. To date, the literature is lacking robust findings on how to best manage chronic irritability.

Recent studies have shown that chronic, but not episodic, irritability is associated with major depressive disorder and not bipolar disorder. However, these findings need to be further replicated by other groups. If they are replicated, it is likely that the approved treatment options for paediatric major depression disorder, such as citalopram and fluoxetine, will be studied in patients with DMDD (Lam et al., 2009). However, if chronic irritability is associated with bipolar disorder, the use of an antidepressant may not be judicious.

Conclusion and recommendations

The objective of this paper was to review pharmacological treatment options for temper outburst/aggression and chronic irritability, two cardinal symptoms of the new paediatric mood disorder diagnosis entitled disruptive mood dysregulation disorder (DMDD). Unfortunately, no clinical studies, so far, have focused on the treatment of this disorder and the limited number of studies on the pharmacotherapy of SMD, a phenotype close to DMDD, offer only limited evidence about the treatment of this clinical entity. For guidance in the pharmacological treatment of these difficult patients, clinicians can turn to studies that address the cardinal symptoms/features of this disorder. The aim of this review was to summarize the findings of these numerous studies in the hope that such a summary will guide and provide treatment options to clinicians who are attempting to treat patients with symptoms of DMDD.

DMDD is a new diagnosis; however, the cardinal symptoms of this disorder are not only prevalent but also debilitating for patients and their families. Because DMDD is a new diagnosis, we could not find any clinical trial reporting on the treatment of this disorder. For this reason, our review summarizes the findings of clinical studies involving the treatment of the individual symptoms constituting the

diagnosis of DMDD. Consequently, our review's primary limitation is that it is constituted from studies representing a very heterogeneous patient population.

DMDD is highly comorbid with disruptive behaviour disorders such as ADHD, ODD, and CD. It seems legitimate to recall that psychosocial and behavioural approaches are highly effective in many cases of chronic irritability and/or aggression. Behaviour modification (Waxmonsky 2008; Frazier, 2010), multisystemic family therapy (Kazdin, 2002), or inpatient stay (Dickstein, 2009) have proved to be beneficial in well-designed studies.

According to our review, the psychostimulant treatment of comorbid ADHD is efficacious in decreasing aggression even when patients exhibit SMD. In cases of partial improvement, the addition of either risperidone or divalproex appears to further decrease aggression in ADHD patients. However, if aggression remains refractory to psychostimulants, risperidone alone should be the first option. In other psychiatric contexts, children and adolescents with marked aggression may receive risperidone, as it appears to be the best documented treatment. In paediatric populations with autism and/or MR/ID, risperidone is an approved treatment for aggression, while aripiprazole is approved for irritability.

A significant issue that we believe will need to be addressed is treatment duration. How many months do we need to treat children and adolescents with aggression and irritability? After what length of time under a given course of treatment do we attempt to remove medication?

Most of the medications used in the proposed treatment modalities above carry significant side effects. In clinical practice, children and adolescents with marked aggression often require antipsychotic and/or mood stabilizers; however, the need for continued treatment should be re-evaluated frequently to continuously ensure that the balance between benefit and hindrance of pharmacotherapy tips toward improving our young patient's quality of life and functionality. Any pharmacotherapy is associated with side effects. Psychostimulants remain safe but require monitoring. Atypical antipsychotics are associated with metabolic disorders (such as weight gain, dyslipidemia, insulin resistance) and extrapyramidal symptoms. Anticonvulsants are associated with weight gain and blood dyscrasia. Long-term use of lithium is associated with thyroid and kidney impairment.

It is important to note that while there are no treatment guidelines for DMDD, paediatric youth with persistent aggression and irritability remain a challenging and vulnerable population. These youth are debilitated and dysfunctional; their most productive years in society are spent bouncing between the criminal system and psychiatry.

In the coming years, clinical trials aimed at identifying suitable and specific pharmacological treatment options for DMDD will arise. In the meantime, clinical judgment is paramount considering the heterogeneity of the available studies (diverse patient populations, psychiatric comorbidities, medication dosage, length of treatment and specific criteria used to define treatment response) investigating the pharmacological management of the specific symptoms of DMDD.

It is of capital importance that pharmacotherapy should remain only part of the treatment of paediatric patients with significant aggression and irritability. Psychotherapeutic treatment modalities should be incorporated into the often complex management of these patients.

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