Journal of Health and Rehabilitation Sciences electronic publication ahead of print, published on January 7th, 2023

Alma Mater Europaea University – ECM, Slovenska 17, Maribor, Slovenia
Journal of Health and Rehabilitation Sciences. 2023 Jan 15; 1(1):45-53
https://doi.org/10.33700/jhrs.1.1.45
eISSN: 2820-5480
Neuroscience Research

Disruptive Mood Dysregulation Disorder Associated with Autism Spectrum Disorder: Literature Review and Case Illustrations

China PARENTEAU
Robert HENDREN
Department of Psychiatry and Behavioral Sciences,
University of California, San Francisco, USA
Email: China.Parenteau@ucsf.edu

Received: 02-December-2022
Revised: 04-January-2023
Accepted: 06-January-2023
Online first: 07-January-2023

Case series

Abstract

Introduction: Irritability has become increasingly prevalent over the past few decades and is often seen in both children with autism spectrum disorder (ASD), and disruptive mood dysregulation disorder (DMDD). Despite this overlap, there has been scant research on treatment for irritability experienced by individuals with co-occurring ASD and DMDD.
Objectives: This paper aims to explore the development of DMDD and to shed light on potential treatment regimens that address irritability through case illustrations of individuals who experience co-occurring ASD and DMDD.
Methods: Three patients seen through a specialty clinic were selected based on their co-occurring diagnoses of ASD & DMDD.
Conclusions: The case illustrations showed that ASD and DMDD often also occurred in the presence of other disorders. Antipsychotics and CBT have shown the most benefits, but mood stabilizers are becoming more prominent for certain combinations of ASD and DMDD. More research is needed on treatment for irritability across co-occurring disorders.

Keywords: Disruptive mood dysregulation disorder, autism spectrum disorder, co-occurring disorders, case series, pharmacological treatment

Citation: Parentau, C., Hendren, R. Disruptive Mood Dysregulation Disorder Associated with Autism Spectrum Disorder: Literature Review and Case Illustrations. *Journal of Health and Rehabilitation Sciences*, 2023 Jan 15; 1(1):45-53. https://doi.org/10.33700/jhrs.1.1.45

Corresponding address:
China PARENTEAU
Department of Psychiatry and Behavioral Sciences,
University of California, San Francisco
675 18th Street, San Francisco CA, 94143, USA
Email: China.Parenteau@ucsf.edu

1. Introduction

Extreme irritability, sometimes referred to as Disruptive Mood Dysregulation Disorder (DMDD), is increasingly recognized as a treatment target for children with autism spectrum disorder (ASD). We review the appreciation of irritability in ASD, the development of DMDD as a recognized disorder, and potential treatments for the combination of ASD and DMDD followed by three illustrative cases. The primary reason families seek psychiatric evaluations for their children is irritability (Kelly et al., 2010; Peterson et al., 1996). Irritability is a symptom observed across numerous psychiatric disorders and is unique in that it affects both internalizing and externalizing problems (Stringaris, 2011). Irritability can be extremely impairing due to its hallmark characteristics of anger and temper outbursts (Stringaris, 2011). Historically, extreme irritability in children was seen as a precursor to adulthood manic episodes, so it was sometimes categorized as pediatric bipolar disorder (BD) (Leibenluft, 2017; Leibenluft et al., 2003; Leibenluft et al., 2006). However, in the early 2000's, the reported prevalence of pediatric BD was increasing at an alarming rate—an approximate 500% increase was observed in the United States within a decade. This led researchers to take a closer look into the diagnostic reliability of pediatric bipolar disorder (Blader & Carlson, 2007; Moreno et al., 2007). In 2010, Stringaris et al. operationalized the syndrome called "severe mood dysregulation" (SMD) to describe the nonepisodic irritability observed in many of the children who were formerly diagnosed with BD. As a part of the initial efforts to distinguish SMD and BD, Stringaris et al. (2010) conducted a 2-year longitudinal study that revealed that children with SMD were 50 times less likely to experience a manic or mixed episode than children with BD. Further longitudinal studies revealed that nonepisodic irritability in childhood was more commonly associated with ADHD in adolescence, and anxiety and depression in adulthood, rather than BD in adulthood (Brotman et al., 2006; Copeland et al., 2014; Liebenluft et al., 2006; Stringaris et al., 2009; Vidal-Ribas et al., 2016). Additionally, children with BD were more likely to have parents who also had a diagnosis of BD, compared to parents of children with SMD (Brotman et al., 2007). Moreover, neurological differences between individuals with SMD and BD also exist (i.e., hypoactivation in the amygdala for individuals with SMD compared to BD) (Brotman et al., 2010; Deveney et al., 2013; Leibenluft & Stoddard, 2013; Rich et al., 2007). These factors combined provide evidence that SMD and BD are likely separate constructs. The research surrounding SMD led to the inception of DMDD in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V; American Psychiatric Association, 2013). While symptoms must be present by 12 years old in SMD, DMDD requires that symptoms are present before 10 years old. Another key difference is that a diagnosis of DMDD does not require the hyperarousal criterion (distractibility, insomnia, racing thoughts/flight of ideas, and agitation) that is associated with SMD and BD.

1.1 What is DMDD?

Currently, the DMDD diagnosis is given to children and adolescents between the ages of 6 and 18 who meet the following criteria: 1) Severe temper outbursts (verbally or behaviorally) that occur at least three times a week, with reactions disproportionate to the situation or inappropriate based on developmental level 2) sad, irritable, or angry mood almost every day, 3) symptoms beginning before the age of 10 and present for at least a year, and 4) symptoms impede on child's functioning in more than one context (i.e. school, home, amongst peers; American Psychiatric Association, 2013).

1.2 How does DMDD overlap with ASD?

In a subsample of 766 children between the ages of 6-16 (580 autistic participants, 186 neurotypical participants), DMDD symptoms were prevalent in 45% of the participants with autism spectrum disorder (ASD), whereas DMDD symptoms were only present in 3% of the neurotypical population (Mayes et al., 2015). While irritability and temper outbursts are core symptoms of DMDD, and they are also common symptoms for autistic youth (Dickstein et al., 2021). The main difference being that irritability and outbursts present differently in standalone ASD as they are typically tied to specific

contexts and triggers (Bruno et al., 2019). Additionally, the DSM-V states that DMDD symptoms generally lessen with age (APA, 2013). This is also supported by studies in neurotypical populations that examine symptoms related to DMDD overtime (i.e., tantrums and negative mood decrease with age in young children; Copeland et al., 2013; Osterman & Bjorkqvist, 2010). However, age has not been significantly related to temper outburst and irritability in autistic youth (Lecavalier, 2006; Mayes et al., 2017). This suggests that DMDD symptoms might manifest differently in children with ASD, and thus treatment approaches should also be tailored to the symptoms. Despite the high prevalence of DMDD symptoms in children with ASD, there has been little evidence-based research into effective treatments for these co-occurring diagnoses.

1.3 Treatment Options to Address Irritability

1.3.1 Pharmacological Treatment

The guidelines to treat DMDD are currently in progress, thus treatment outcomes have primarily been focused on targeting core symptoms of chronic irritability and temper outbursts in SMD populations (Breaux et al., 2022; Bruno et al., 2019; Tourian et al., 2015). Below, common pharmacological treatments for symptoms related to BP, SMD, and DMDD are explored.

1.3.2 Psychostimulants and Antidepressants (Specifically, Selective Serotonin Reuptake Inhibitors and Serotonin-Noradrenalin Reuptake Inhibitors)

Prior to the establishment of DMDD, psychostimulants and antidepressants were seldomly prescribed for irritability because it was believed that they may worsen mania and hyperarousal (Bruno et al., 2019). However, with the longitudinal associations between DMDD, and adulthood depression and anxiety, psychostimulants and antidepressants became a potential treatment option. As attention deficit hyperactivity disorder (ADHD) and DMDD frequently co-occur, the effects of psychostimulants on aggression have been consequently explored. In 2006, Pappadopulos et al., identified 18 randomized control trials that delivered psychostimulants to a total of 1057 participants with various diagnoses (ADHD, autism, "mental retardation", and disruptive behavior disorder). Methylphenidate was most commonly administered, with an average dose of .93 mg/kg/day. Analyses of the aggregated results across the studies revealed significant decreases in aggression in children through the use of psychostimulants. Additionally, a recent study on youth with SMD found that combination of citalopram and methylphenidate elicited a higher proportion of responses based on improvements of irritability after 8 weeks, compared to those solely receiving a placebo and methylphenidate (Towbin et al., 2020). Furthermore, a retrospective review of six children with DMDD showed significant decreases in irritability with the use of atomoxetine (Benarous et al., 2020).

1.3.3 Alpha-2 Agonists

The majority of the studies on alpha-2 agonist had a focus on individuals with ADHD. For example, clonidine and guanfacine showed improvements in aggressive symptoms (Connor et al., 2003; Connor et al., 2010; Hazell & Stuart, 2003; Jaselskis et al., 1992; Palumbo et al., 2008; Scahill et al., 2001; Wilens et al., 2012). However, a study on 12 children diagnosed with DMDD revealed reductions in the frequency of rage episodes upon administration of guanfacine and accompanying behavioral supports (Jain, 2017).

1.3.4 Lithium

Lithium has long been utilized and approved by the FDA to treat mania associated with pediatric BD (Findling et al., 2015; Findling et al., 2019; Patino et al., 2015; Pisano et al., 2019). However, in children with SMD, the first randomized double-blind, placebo-controlled trial revealed no significant differences in irritability and aggression between participants receiving lithium versus a placebo (Dickstein et al., 2009). In a review of treatments on DMDD, Hendrickson et al., (2020) further punctuates the claim that the data does not currently support benefits of lithium for youth with DMDD. While lithium has demonstrated benefits for treating acute mania in bipolar disorder, studies of its effectiveness for chronic irritability experienced by youth

with DMDD has not been demonstrated in clinical trials; although there are anecdotal and case series reports suggesting that lithium may be beneficial for some children with DMDD, supporting the need for further study (Mattes, 1986).

1.3.5 Atypical Antipsychotics

Atypical antipsychotics are commonly used to treat irritability and temper outbursts in children with autism (Fallah et al., 2019; Politte & McDougle, 2014), with risperidone and aripiprazole showing the most promising outcomes (Cohen et al, 2013; Owen et al., 2009; Shea et al., 2004). In fact, Fung et al., (2016) reviewed forty-six randomized controlled trials on treatments for irritability in autism and found risperidone and aripiprazole to exhibit the largest effect sizes. There has also been inspection of the use of atypical antipsychotics for direct treatment of SMD. Krieger et al., (2011) examined 21 participants with SMD and found that irritability significantly decreased with the intake of risperidone. Given the success of risperidone and aripiprazole for managing irritability in ASD and SMD, randomized control trials should be conducted directly on DMDD and ASD to further understand its efficacy in this population.

1.3.6 Non-pharmacological Treatment

While there are currently no non-pharmacological treatments that address the co-occurrence of DMDD and ASD, psychosocial treatments do exist for youth with BD. Commonly implemented psychosocial therapy for BD includes multi-family psychoeducation groups (MFPG; Fristad et al., 2002; Young & Fristad, 2007), Family-Focused Therapy (FFT; Miklowitz et al., 2000; Miklowitz et al., 2004), Interpersonal and Social Rhythm Therapy (Hlastala et al., 2010), Dialectical Behavioral Therapy (DBT; Goldstein et al., 2015), and Child- and Family-Focused Cognitive-Behavioral Therapy (Pavuluri et al., 2004; West et al., 2009). These therapies explore a range of outcome variables from parental skills and knowledge surrounding BD, to child outcomes such as mood, aggression, and irritability. It is often recommended that the psychosocial treatments are paired with pharmacological treatments for maximum efficacy (Fristad et al., 2003; McClellan et al., 2007). In the future, during the development and/or adaptation of psychosocial treatment for children with co-occurring DMDD and ASD, it will be important to consider the additional communication and attentional challenges that have the potential to arise.

2. Case Examples

2.1 Case 1

EP, female, was born to a 23-year-old mother who had an unclear medical history and was adopted at 3 years of age in South America. In the US., observed difficulties occurred at school, where EP was often disruptive and displayed signs of mood instability. If peers or teachers interfered with a desired task, EP became aggressive and violent. Due to these concerns, EP was frequently asked to leave her specialized school. At six years old she was diagnosed with ASD and attention deficit hyperactivity disorder (ADHD - combined). Throughout her education, she attended five different non-public school placements for children with NDD. To treat her challenging behaviors and unstable mood, psychiatrists prescribed risperidone, aripiprazole, quetiapine, ziprasidone, clonidine, and guanfacine over the years. They all showed modest benefits and expected side effects including weight gain and anticholinergic effects. Her irritable, aggressive, and impulsive behavior continued.

At the age of fourteen, she developed symptoms of further anxiety, obsessive compulsive disorder (OCD), and intrusive thoughts. To treat her OCD symptoms, she was trialed on sertraline, escitalopram, and fluoxetine and also, cognitive behavior therapy. While the medications helped with her OCD symptoms, they also increased her irritability. EP was later prescribed olanzapine and lamotrigine, but no clear benefits emerged. Asenapine (10 mg) appeared to have the most benefit of all the antipsychotics when taken concurrently with lithium (1500mg). While her mood dysregulation is still episodically present, asenapine and lith-

ium have created the most stability when the dosage levels are maintained. Currently she is in a residential program with the following diagnoses: ASD, DMDD and OCD and has been doing well there for 3 years on the same medications.

2.2 Case 2

LN, male, was adopted at 5 ½ months. His adoptive parents reported that his biological mother was likely abusing substances during the pregnancy. At the age of 3, LN was not interacting with others in a social manner, and he was diagnosed with ID and ADHD. Around this time LN also became anxious and moderately depressed when introduced to new situations. He also developed new phobias and fears. LN was first seen at the UCSF Center for ASD and NDD's at the age of 11 and was given the additional diagnoses of Psychosis NOS, ADHD, PDDNOS, and Borderline ID. Treatment included risperidone, clonidine, dexmethylphenidate and sertraline.

Dexmethylphenidate and sertraline were removed from his regime as the former increased his anxiety and the latter increased his activation and hypomania. This led to a hospitalization, where his medicines were adjusted to aripiprazole and valproic acid, which showed modest benefits. For the past four years, he has been on Abilify (20mg/da), bupropion (450mg/da), quetiapine (200mg bid), and lithium (1500mg/da). Currently, he lives in a residential home and is diagnosed with ASD and DMDD and is stable on the same medications.

2.3 Case 3

CL, male, was diagnosed with ASD at age 2 ½. His aggression became increasingly concerning between the ages of 6 and 7 years old. At that time, he was also undereating. He was prescribed risperidone which helped address both concerns. His first consultation with the UCSF Center for ASD and NDD's occurred at 15 years old, because his aggression with family members and students at school was becoming harmful. Over the next several years he was trialed on aripiprazole, quetiapine, clonidine, lisdexamfetamine, methylphenidate, and sertraline, mirtazapine, and as needed lorazepam.

At 20 years old, CL experienced increasing aggression to the extent that he began to hurt and threaten his family members again. To address the aggression, he was prescribed lithium titrated up to 600mg BID along with mirtazapine for sleep, and 1.75mg of risperidone and his aggression markedly decreased and his mood was stable.

After six months, his father requested a decrease in dosage of lithium (.5mg), however his aggression worsened. After returning to 600mg BID, his aggression and mood has been stable for the past 4 years while living in a residential facility. He also takes gabapentin, aripiprazole and low dose quetiapine for sleep.

3. Conclusion

Currently, there are no studies that explore treatment for a person with cooccurring ASD, bipolar disorder, DMDD or psychosis despite its the relatively high prevalence but there are increasing studies of the irritability common to each (Breaux et al, 2022). This could potentially be because misdiagnosis often occurs with some of the symptoms being indistinguishable from one disorder to the next. Potentially due to the indistinctness and common genetic origins, antipsychotics are used to treat both disorders when comorbid with ASD. It is also suggested to pair treatment with CBT to assist with the anxiety and emotions that may accompany the disorders.

The common theme is the symptom of irritability rather than one or more diagnostic groups. Antipsychotics and CBT are reported the most effective, but mood stabilizers may have a strong role for certain combinations of ASD and DMDD.

Conflict of Interests

Dr. Robert Hendren received research grants from Curemark, Otsuka, GW, Ltd, and Axial Biotherapeutics and is on the advisory boards for BioMarin, Axial Biotherapeutics and Janssen. China Parenteau has no conflicts of interest to declare.

4. References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Benarous, X., Ferrafiat, V., Zammit, J., Consoli, A., Gérardin, P., Guilé, J., & Cohen, D. (2020). Effective use of atomoxetine to treat six inpatient youths with disruptive mood dysregulation disorder without attention deficit disorder. CNS Spec-trums, 25(4), 455-457. doi:10.1017/S1092852919001020

Blader, J. C., & Carlson, G. A. (2007). Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. Biological Psychiatry, 62(2), 107-114.

Breaux, R., Baweja, R., Eadeh, H. M., Shroff, D. M., Cash, A. R., Swanson, C. S., Knehans, A., & Waxmonsky, J. G. (2022). Systematic review and meta-analysis: Pharmacological and non-pharmacological interventions for persistent non-episodic irritability. Journal of the American Acad-emy of Child & Adolescent Psychiatry.

Brotman, M. A., Kassem, L., Reising, M. M., Guy-er, A. E., Dickstein, D. P., Rich, B. A., Towbin, K. E., Pine, D. S., McMahon, F. J., & Leibenluft, E. (2007). Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. American Journal of Psychiatry, 164(8), 1238-1241.

Brotman, M. A., Schmajuk, M., Rich, B. A., Dick-stein, D. P., Guyer, A. E., Costello, E. J., Egger, H. L., Angold, A., Pine, D. S., & Leibenluft, E. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in chil-dren. Biological Psychiatry, 60(9), 991-997.

Brotman, M. A., Rich, B. A., Guyer, A. E., Luns-ford, J. R., Horsey, S. E., Reising, M. M., Thomas, L. A., Fromm, S. J., Towbin, K., Pine, D. S., & Leibenluft, E. (2010). Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. American Journal of Psychia-try, 167(1), 61-69.

Bruno, A., Celebre, L., Torre, G., Pandolfo, G., Mento, C., Cedro, C., Zoccali., R. A., & Muscatello, M. R. A. (2019). Focus on disruptive mood dysreg-ulation disorder: A review of the litera-ture. Psychiatry Research, 279, 323-330.

Cohen, D., Raffin, M., Canitano, R., Bodeau, N., Bonnot, O., Périsse, D., Consoli, A., & Laurent, C. (2013). Risperidone or aripiprazole in children and adolescents with autism and/or intellectual disability: A Bayesian meta-analysis of efficacy and secondary effects. Research in Autism Spectrum Disorders, 7(1), 167-175.

Connor, D. F., Boone, R. T., Steingard, R. J., Lopez, I. D., & Melloni Jr, R. H. (2003). Psychopharmacology and aggression: II. A meta-analysis of nonstimulant medication effects on overt aggression-related behaviors in youth with SED. Journal of Emotional and Behavioral Disorders, 11(3), 157-168.

Connor, D. F., Findling, R. L., Kollins, S. H., Sallee, F., López, F. A., Lyne, A., & Tremblay, G. (2010). Effects of guanfacine extended release on oppositional symptoms in children aged 6–12 years with attention-deficit hyperactivity disorder and oppositional symptoms. CNS Drugs, 24(9), 755-768.

Copeland, W. E., Shanahan, L., Egger, H., Angold, A., & Costello, E. J. (2014). Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. American Journal of Psy-chiatry, 171(6), 668-674.

Copeland, W. E., Angold, A., Costello, E. J., & Eg-ger, H. (2013). Prevalence, comorbidity, and corre-lates of DSM-5 proposed disruptive mood dysregu-lation disorder. American Journal of Psychia-try, 170(2), 173-179.

Deveney, C. M., Connolly, M. E., Haring, C. T., Bones, B. L., Reynolds, R. C., Kim, P., Pine, D. S., & Leibenluft, E. (2013). Neural mechanisms of frustration in chronically irritable children. American Journal of Psychiatry, 170(10), 1186-1194.

Dickstein, D. P., Towbin, K. E., Van Der Veen, J. W., Rich, B. A., Brotman, M. A., Knopf, L., Onelio, L., Pine, D. S., & Leibenluft, E. (2009). Random-ized double-blind placebo-controlled trial of lithi-um in youths with severe mood dysregula-tion. Journal of Child and Adolescent Psychophar-macology, 19(1), 61-73.

Dickstein, D. P., Barthelemy, C. M., Jenkins, G. A., DeYoung, L. L., Gilbert, A. C., Radoeva, P., Kim, K. L., & MacPherson, H. A. (2021). This is your brain on irritability: A clinician's guide to understanding how we know what we know now, and

what we need to know in the future, about irritability in children and adolescents. Child and Adolescent Psychiatric Clinics, 30(3), 649-666.

Fallah, M. S., Shaikh, M. R., Neupane, B., Rusiecki, D., Bennett, T. A., & Beyene, J. (2019). Atypical antipsychotics for irritability in pediatric autism: a systematic review and network meta-analysis. Journal of Child and Adolescent Psycho-pharmacology, 29(3), 168-180.

Findling, R. L., Robb, A., McNamara, N. K., Pavuluri, M. N., Kafantaris, V., Scheffer, R., Fra-zier, J. A., Rynn, M., DelBello, M., Kowatch, R. A., Rowles, B. M., Lingler, J., Martz, K., Anand, R., Clemons, T. E., & Taylor-Zapata, P. (2015). Lithi-um in the acute treatment of bipolar I disorder: A double-blind, placebo-controlled study. Pediatrics, 136(5), 885-894.

Findling, R. L., McNamara, N. K., Pavuluri, M., Frazier, J. A., Rynn, M., Scheffer, R., Kafantaris, V., Robb, A., Delbello, M., Kowatch, R. A., Rowles, B. M., Lingler, J., Zhao, J., Clemons, T., Martz, K., Anand, R., & Taylor-Zapata, P. (2019). Lithium for the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled dis-continuation study. Journal of the American Acad-emy of Child & Adolescent Psychiatry, 58(2), 287-296.

Fristad, M. A., Gavazzi, S. M., & Mackinaw-Koons, B. (2003). Family psychoeducation: An adjunctive intervention for children with bipolar disorder. Biological Psychiatry, 53(11), 1000-1008.

Fristad, M. A., Goldberg-Arnold, J. S., & Gavazzi, S. M. (2002). Multifamily psychoeducation groups (MFPG) for families of children with bipolar dis-order. Bipolar Disorders, 4(4), 254-262.

Fung, L. K., Mahajan, R., Nozzolillo, A., Bernal, P., Krasner, A., Jo, B., Coury, D., Whitaker, A., Veenstra-Vanderweele, J., & Hardan, A. Y. (2016). Pharmacologic treatment of severe irritability and problem behaviors in autism: A systematic review and meta-analysis. Pediatrics, 137 (Supplement 2), S124-S135.

Goldstein, T. R., Axelson, D. A., Birmaher, B., & Brent, D. A. (2007). Dialectical behavior therapy for adolescents with bipolar disorder: A 1-year open trial. Journal of the American Academy of Child & Adolescent Psychiatry, 46(7), 820-830.

Hazell, P. L., & Stuart, J. E. (2003). A randomized controlled trial of clonidine added to psychostimu-lant medication for hyperactive and aggressive children. Journal of the American Academy of Child & Adolescent Psychiatry, 42(8), 886-894.

Hendrickson, B., Girma, M., & Miller, L. (2020). Review of the clinical approach to the treatment of disruptive mood dysregulation disor-der. International Review of Psychiatry, 32(3), 202-211.

Hlastala, S. A., Kotler, J. S., McClellan, J. M., & McCauley, E. A. (2010). Interpersonal and social rhythm therapy for adolescents with bipolar disorder: treatment development and results from an open trial. Depression and Anxiety, 27(5), 457-464.

Jain, U. (2017). The use of guanfacine (Intuniv XR) in the treatment of disruptive mood dysregulation disorder – Clinical experience from telepsychia-try. European Psychiatry, 41(S1), S442-S442. doi:10.1016/j.eurpsy.2017.01.449

Jaselskis, C. A., Cook, E. H., Fletcher, K. E., & Leventhal, B. L. (1992). Clonidine treatment of hy-peractive and impulsive children with autistic dis-order. Journal of Clinical Psychopharmacolo-gy, 12(5), 322-327.

Kelly, C., Molcho, M., Doyle, P., & Gabhainn, S. N. (2010). Psychosomatic symptoms among schoolchildren. International Journal of Adolescent Medicine and Health, 22(2), 229-236.

Krieger, F. V., Pheula, G. F., Coelho, R., Zeni, T., Tramontina, S., Zeni, C. P., & Rohde, L. A. (2011). An open-label trial of risperidone in children and adolescents with severe mood dysregula-tion. Journal of Child and Adolescent Psychophar-macology, 21(3), 237-243.

Leibenluft, E. (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. American Journal of Psychia-try, 168(2), 129-142.

Leibenluft, E., Charney, D. S., Towbin, K. E., Bhangoo, R. K., & Pine, D. S. (2003). Defining clinical phenotypes of juvenile mania. American Journal of Psychiatry, 160(3), 430-437.

Leibenluft, E., Cohen, P., Gorrindo, T., Brook, J. S., & Pine, D. S. (2006). Chronic versus episodic irri-tability in youth: A community-based, longitudinal study of clinical and diagnostic associa-tions. Journal of

Child & Adolescent Psychophar-macology, 16(4), 456-466.

Leibenluft, E., & Stoddard, J. (2013). The devel-opmental psychopathology of irritabil-ity. Development and psychopathology, 25, 1473-1487.

Lecavalier, L. (2006). Behavioral and emotional problems in young people with pervasive devel-opmental disorders: Relative prevalence, effects of subject characteristics, and empirical classifica-tion. Journal of Autism and Developmental Disor-ders, 36, 1101–1114. doi:10.1007/s10803-006-0147-5

Mattes, J. A. (1986). Psychopharmacology of tem-per outbursts: A review. The Journal of Nervous and Mental Disease, 174(8), 464-470.

Mayes, S. D., Waxmonsky, J., Calhoun, S. L., Ko-kotovich, C., Mathiowetz, C., & Baweja, R. (2015). Disruptive mood dysregulation disorder (DMDD) symptoms in children with autism, ADHD, and neurotypical development and impact of co-occurring ODD, depression, and anxiety. Research in Autism Spectrum Disorders, 18, 64-72.

Mayes, S. D., Kokotovich, C., Mathiowetz, C., Baweja, R., Calhoun, S. L., & Waxmonsky, J. (2017). Disruptive mood dysregulation disorder symptoms by age in autism, ADHD, and general population samples. Journal of Mental Health Re-search in Intellectual Disabilities, 10(4), 345-359.

McClellan, J., Kowatch, R., & Findling, R. L. (2007). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 46(1), 107-125.

Miklowitz, D. J., Simoneau, T. L., George, E. L., Richards, J. A., Kalbag, A., Sachs-Ericsson, N., & Suddath, R. (2000). Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry, 48(6), 582-592.

Miklowitz, D. J., Axelson, D. A., Birmaher, B., George, E. L., Taylor, D. O., Schneck, C. D., Ber-esford, C. A., Dickinson, M. L., Craighead, E. W., & Brent, D. A. (2008). Family-focused treatment for adolescents with bipolar disorder: Results of a 2-year randomized trial. Archives of General Psy-chiatry, 65(9), 1053-1061.

Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A. B., & Olfson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Archives of General Psy-chiatry, 64(9), 1032-1039.

Osterman, K., & Bjorkqvist, K. (2010). A cross-sectional study of onset, cessation, frequency, and duration of children's temper tantrums in a non-clinical sample. Psychological Reports, 106, 448–454. doi:10.2466/pr0.106.2.448-454

Owen, R., Sikich, L., Marcus, R. N., Corey-Lisle, P., Manos, G., McQuade, R. D., Carson, W. H., & Findling, R. L. (2009). Aripiprazole in the treat-ment of irritability in children and adolescents with autistic disorder. Pediatrics, 124(6), 1533-1540.

Palumbo, D. R., Sallee, F. R., Pelham Jr, W. E., Bukstein, O. G., Daviss, W. B., McDermott, M. P., & CAT Study Team. (2008). Clonidine for atten-tion-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. Journal of the American Academy of Child & Adolescent Psychiatry, 47(2), 180-188.

Pappadopulos, E., Woolston, S., Chait, A., Perkins, M., Connor, D. F., & Jensen, P. S. (2006). Pharma-cotherapy of aggression in children and adoles-cents: Efficacy and effect size. Journal of the Cana-dian Academy of Child and Adolescent Psychiatry.

Patino, L. R., Bruns, K. M., Witt, N. M., McCune, N. R., & DelBello, M. P. (2015). Management of bipolar disorder in children and adoles-cents. Focus, 13(1), 25-36.

Pavuluri, M. N., Graczyk, P. A., Henry, D. B., Car-bray, J. A., Heidenreich, J., & Miklowitz, D. J. (2004). Child-and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: Development and preliminary results. Journal of the American Academy of Child & Adolescent Psychiatry, 43(5), 528-537.

Peterson, B. S., Zhang, H., Santa Lucia, R., King, R. A., & Lewis, M. (1996). Risk factors for presenting problems in child psychiatric emergencies. Journal of the American Academy of Child & Adolescent Psychiatry, 35(9), 1162-1173.

Pisano, S., Pozzi, M., Catone, G., Scrinzi, G., Clem-enti, E., Coppola, G., Milone, A., Bravaccio, C., Santosh, P., & Masi, G. (2019). Putative Mecha-nisms of Action and Clinical Use of Lithium in Children and

Adolescents: A Critical Re-view. Current Neuropharmacology, 17(4), 318–341. https://doi.org/10.2174/1570159X16666171219142120

Politte, L. C., & McDougle, C. J. (2014). Atypical antipsychotics in the treatment of children and ado-lescents with pervasive developmental disor-ders. Psychopharmacology, 231(6), 1023-1036.

Rich, B. A., Schmajuk, M., Perez-Edgar, K. E., Fox, N. A., Pine, D. S., & Leibenluft, E. (2007). Differ-ent psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. American Journal of Psychiatry, 164(2), 309-317.

Scahill, L., Chappell, P. B., Kim, Y. S., Schultz, R. T., Katsovich, L., Shepherd, E., Arnsten, A., Cohen, D. J., & Leckman, J. F. (2001). A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hy-peractivity disorder. American Journal of Psychia-try, 158(7), 1067-1074.

Shea, S., Turgay, A., Carroll, A., Schulz, M., Orlik, H., Smith, I., & Dunbar, F. (2004). Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive develop-mental disorders. Pediatrics, 114(5), e634-e641.

Stringaris, A. (2011). Irritability in children and adolescents: A challenge for DSM-5. European Child & Adolescent Psychiatry, 20(2), 61-66.

Stringaris, A., Baroni, A., Haimm, C., Brotman, M., Lowe, C. H., Myers, F., Rustgi, E., Wheeler, W., Kayser, R., Towbin, K., & Leibenluft, E. (2010). Pediatric bipolar disorder versus severe mood dysregulation: Risk for manic episodes on follow-up. Journal of the American Academy of Child & Adolescent Psychiatry, 49(4), 397-405.

Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. American Journal of Psychiatry, 166(9), 1048-1054.

Tourian, L., LeBoeuf, A., Breton, J. J., Cohen, D., Gignac, M., Labelle, R., Guile, J. M., & Renaud, J. (2015). Treatment options for the cardinal symptoms of disruptive mood dysregulation disor-der. Journal of the Canadian Academy of Child and Adolescent Psychia-try, 24(1), 41.

Towbin, K., Vidal-Ribas, P., Brotman, M. A., Pick-les, A., Miller, K. V., Kaiser, A., Vitale, A. D., En-gel, C., Overman, G. P., Davis, M., Lee, B., McNeil, C., Wheeler, W., Yokum, C. H., Haring, C. T., Rou-le, A., Wambach, C. G., Sharif-Askary, B., Pine, D. S., Leibenluft, E., & Stringaris, A. (2020). A dou-ble-blind randomized placebo-controlled trial of citalopram adjunctive to stimulant medication in youth with chronic severe irritability. Journal of the American Academy of Child and Adolescent Psy-chiatry, 59(3), 350–361. https://doi.org/10.1016/j.jaac.2019.05.015

Vidal-Ribas, P., Brotman, M. A., Valdivieso, I., Leibenluft, E., & Stringaris, A. (2016). The status of irritability in psychiatry: A conceptual and quan-titative review. Journal of the American Academy of Child & Adolescent Psychiatry, 55(7), 556-570.

West, A. E., Jacobs, R. H., Westerholm, R., Lee, A., Carbray, J., Heidenreich, J., & Pavuluri, M. N. (2009). Child and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: Pilot study of group treatment format. Journal of the Canadian Academy of Child and Adolescent Psychiatry, 18(3), 239.

Wilens, T. E., Bukstein, O., Brams, M., Cutler, A. J., Childress, A., Rugino, T., Lyne, A., Grannis, K., & Youcha, S. (2012). A controlled trial of extend-ed-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 51(1), 74-85.

Young, M. E., & Fristad, M. A. (2007). Evidence based treatments for bipolar disorder in children and adolescents. Journal of Contemporary Psycho-therapy, 37(3), 157-164.