JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 28, Number 5, 2018

Pp. 298–305
DOI: 10.1089/cap.2017.0124

Original Articles

Improvements in Irritability with Open-Label Methylphenidate Treatment in Youth with Comorbid Attention Deficit/Hyperactivity Disorder and Disruptive Mood Dysregulation Disorder

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Abstract

Objective: The purpose of this open-label study was to examine the effects of long-acting methylphenidate (MPH) treatment on irritability and related emotional symptoms associated with disruptive mood dysregulation disorder (DMDD) in youth with comorbid attention-deficit/hyperactivity disorder (ADHD).

Methods: The sample included 22 medication-free male and female subjects (ages 9–15) who met criteria for both DMDD and ADHD. Participants underwent a 4-week trial of long-acting MPH treatment (Concerta®), with weekly dosing increases until a therapeutic dose was reached. Repeated measures *t*-tests were used to compare pre- and posttreatment ratings of primary and secondary measures. The primary outcome was self-report irritability. Secondary outcomes included parent and child ratings of emotional frequency, emotional lability, and negative affect (NA). Multiple regression was used to examine the impact baseline hyperactivity, age, gender, race, socioeconomic status, or comorbid diagnosis had on treatment outcomes.

Results: Significant improvements (medium to large effect sizes) in child-rated irritability as well as parent and child ratings of emotional lability, NA, and anger were found. As anticipated, ADHD symptoms also improved. While a majority of the sample saw improvement in child-rated irritability (71%), symptoms worsened a small proportion (19%), and an even smaller portion experienced no change (10%). No demographics, psychiatric comorbidities, or severity of ADHD symptoms influenced treatment outcomes.

Conclusions: Study findings suggest that MPH treatment significantly improved mood and emotional symptoms associated with DMDD comorbid with ADHD. These findings, coupled with good tolerability in this open-label pilot study supports further research into the use of MPH as a first-line treatment for DMDD. Future work examining MPH treatment of youth with DMDD with and without comorbid ADHD is needed.

Keywords: methylphenidate, disruptive mood dysregulation disorder, attention-deficit/hyperactivity disorder, irritable mood, emotional symptoms

Introduction

Irritability, defined as a stable trait, personality dimension, or chronic mood state is characterized by a proclivity for anger and reactivity to slight provocations (Buss and Durkee 1957; Caprara et al. 1985; Berkowitz 1993; Ekkekakis 2013; Leibenluft and Stoddard 2013). Irritability is a defining severe and nonepisodic symptom in disruptive mood dysregulation disorder (DMDD) (Wiggins et al. 2016). Irritability is also seen in oppositional defiant disorder (ODD), anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) (Copeland et al. 2013). Although there had been the suggestion that severe, chronic irritability is a pediatric presentation of bipolar disorder, longitudinal studies indicate that such a clinical presentation is associated with increased risk for anxiety and unipolar depression, but not bipolar disorder (Biederman et al. 2004; Papolos et al. 2009). The syndrome of severe mood dysregulation (SMD) was a research diagnosis, and precursor to DMDD, which characterized youth with chronic irritability (Leibenluft et al. 2003). Treatment for youth with severe, chronic irritability, including those with DMDD, presents a challenge for clinicians, given the relative paucity of research studies. In practice, clinicians often prescribe multiple cross-class medications, including antipsychotics and mood stabilizers, for this population, but such

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treatment can cause significant side effects (Morden and Goodman 2012; Hilt et al. 2014). Lack of evidence about effective pharmacotherapies for the emotion regulation deficits of DMDD may contribute to polypharmacy (Baweja et al. 2016).

To date, six publications have directly addressed pharmacotherapies to treat youth with DMDD or SMD. In a randomized controlled trial (RCT), Waxmonsky et al. (2008) found a 34% reduction in Youth Mania Rating Scale (YMRS) scores when examining the effectiveness of different doses of methylphenidate (MPH) on SMD symptoms in children with ADHD between the ages of 5 and 12. In a double-blind RCT, lithium did not have beneficial effects in children (ages 7–17) with SMD (Dickstein et al. 2009). In an open-label nonrandomized study, Krieger et al. (2011) found that risperidone significantly reduced irritability in youth diagnosed with ADHD and SMD. A single case reported successful use of naltrexone in a 15-year-old boy with DMDD, noting increased sedation as the only tolerability issue (Parmar et al. 2014). Baweja et al. (2016) published an open-label study that reported that stimulant medications (no specific stimulants identified in the study) decreased depressive and ODD symptoms in youth with SMD symptoms, who were retrospectively diagnosed. In another sample, both parent-rated behavioral outbursts (i.e., ODD symptoms) and symptoms of depression were successfully treated with stimulant monotherapy and family based intervention in youth diagnosed with ADHD and mood symptoms associated with DMDD (Blader et al. 2016).

Youth with disruptive behavior disorders share clinical features with DMDD, and pharmacotherapy trials including such youth can also inform prescribers of youth with DMDD. That literature is much more extensive. For example, antipsychotics have been increasingly used for aggression in children with ADHD (Birnbaum et al. 2013). However, in a large RCT, the Treatment of Severe Childhood Aggression (TOSCA) study, comparisons between a group receiving stimulant medication ($n=84$) and a group receiving stimulant augmented with risperidone ($n=84$) showed no difference in global clinical presentation at baseline (Aman et al. 2014) or at 52-week follow-up (Gadow et al. 2016), but did differ at 12 weeks (Aman et al. 2014). Additionally, antipsychotics' capacity to change metabolism and cause marked weight gain make them a controversial first choice for treatment (Andrade et al. 2011; Maayan and Correll 2011; Seida et al. 2012). Similarly, lithium increases the risk for hypothyroidism (Churn-Shiouh et al. 2010) and no clinically significant improvement was found when using lithium to treat disruptive mood disorders in several recent studies (Dickstein et al. 2009; de la Cruz et al. 2015; Tourian et al. 2015).

On the other hand, stimulant medications, specifically long-acting MPH, have demonstrated both tolerability and effectiveness in the treatment of aggression and other disruptive behaviors in youth diagnosed with ADHD (Pappadopulos et al. 2006; Sinzig et al. 2007; Waxmonsky et al. 2008; Baweja et al. 2016; Blader et al. 2016), with fewer concerns about tolerability. MPH was used in the present study due to its efficacy in improving ''irritability'' and ''mood changes'' in comparison to placebo in youth with ADHD (Fitzpatrick et al. 1992; Ahmann et al. 1993; Firestone et al. 1998), including the long-acting Concerta® formulation (Swanson et al. 2004); whereas amphetamine-derived psychostimulants have been reported to induce or worsen irritability (Greenberg et al. 1972; Pliszka et al. 2000; Lee et al. 2011). Additionally, Concerta was chosen because of ease in once daily dosing with adequate coverage throughout the school day. Thus, the potential for MPH to address irritability in DMDD warrants further exploration.

Although relevant to the present study, recent research exploring stimulant medications' effects on DMDD symptoms, described above, are limited by their use of mania, depression, or ODD symptoms as the primary outcomes. While these constructs are related to irritability, they are not the primary symptoms of DMDD. For example, mania is a defining episodic symptom that distinguishes unipolar depression from bipolar disorder; but is phenotypically and temporally distinct from chronic irritability observed in DMDD (Mitchell et al. 2016). Similarly, episodic irritability is common in adolescent depressive episodes; however, assessments of depression focus little attention on chronic irritability and focus on many other symptoms (e.g., suicidality, guilt, appetite), which are not typically seen in DMDD (Stringaris et al. 2013). Finally, ODD includes criteria of ''often losing temper'' and ''being easily annoyed by others,'' thus nonirritable children can meet criteria for ODD because of oppositional behavior (Leibenluft 2011). Additionally, the use of a behavioral intervention in conjunction with pharmacotherapy confounds the effects of the medication. Thus, the present study builds upon the existing literature by specifically assessing chronic irritability (versus mania or ODD symptoms), without the confound of a behavioral intervention. Including secondary mood and emotional measures, provides more detailed qualitative (e.g., severity of mood) and quantitative (e.g., frequency of mood) assessments of irritability from the perspective of parents and children, than prior studies. As such, the present study yields a comprehensive assessment of irritability and its various features.

The purpose of the present investigation was to examine the effects of MPH treatment on irritability as well as other emotional symptoms associated with DMDD in youth with comorbid ADHD. To date, we are unaware of DMDD pharmacotherapy studies using irritability as the primary outcome and other relevant emotional symptoms as secondary outcomes. We hypothesized that MPH treatment of youth diagnosed with both ADHD and DMDD would (1) significantly improve irritability in most youth, (2) may worsen irritability in a smaller subset of youth, given the association with irritability in some ADHD stimulant trials and (3) cause side effects similar to those reported in routine ADHD stimulant trials. Although previous research supports the notion that MPH may be an effective treatment for irritability, a subset of youth with ADHD have been observed to experience increased irritability with stimulant treatment, although primarily amphetamine formulations (Pliszka et al. 2000; Biederman et al. 2007). Additionally, we hypothesized that, as in prior studies (Baweja et al. 2016; Blader et al. 2016), neither severity of pretreatment psychiatric symptoms or demographic variables will predict treatment outcomes. This initial exploration uses an open-label design and was conducted as part of a neuroimaging investigation.

Methods

Study population and procedure

Participants included 22 male and female subjects 9–15 (Table 1) years of age. Participants met criteria for DSM-IV (American Psychiatric Association 2000) ADHD (any subtype, although 91% of participants met criteria for combined type) as well as DMDD. Participants were recruited through clinical services at the Riley Child and Adolescent Psychiatry Clinic and through web and community postings. All participants were free of psychotropic medications for at least 2 weeks before the initial appointment. Twenty-nine participants were initially enrolled, but 7 were excluded for either not meeting inclusion criteria ($n=3$) or for withdrawing before the administration of medication ($n=4$). No participants withdrew after starting the medication.

Table 1. Sample Descriptive Statistics ($N=22$)

Participant information	*Mean ± SD or n (%)*	*Min–Max (range)*
Age	12 ± 1.63	9–15 (6)
Gender		
Male	15 (69)	
Female	7 (31)	
Race		
Caucasian	7 (32)	
African American	12 (55)	
Biracial	3 (13)	
Socioeconomic status	2.36 ± 1.29	1–5 (4)
<$20,000	6 (27)	
$20,000 < $40,000	9 (41)	
$40,000 < $60,000	2 (9)	
$60,000 < $80,000	3 (14)	
>$80,000	2 (9)	
IQ	106.41 ± 14.28	79–132 (53)
Diagnosis		
ADHD and DMDD	22 (100)	
Inattentive subtype	2 (9)	
Hyperactive subtype	0 (0)	
Combined subtype	20 (91)	
GAD[a]	2 (9)	
CD[a]	4 (18)	
ODD[b]	15 (68)	
No comorbid condition[a]	3 (14)	

[a]Comorbid with ADHD and DMDD.
[b]Not diagnosable if DMDD criteria are met, but given for descriptive purposes.
ADHD, attention deficit/hyperactivity disorder; CD, conduct disorder; DMDD, disruptive mood dysregulation disorder; GAD, generalized anxiety disorder; ODD, oppositional defiant disorder; SD, standard deviation.

Diagnoses of autism spectrum disorder, current major depressive disorder, psychotic symptoms, bipolar disorder, or posttraumatic stress disorder were exclusionary. Participants with current or past substance use disorders were excluded. History of head trauma, IQ below 79, or neurological disorders were also excluded. Individuals with prior significant side effects from MPH were excluded. Medical conditions, including glaucoma, tics, any acute medical illness, or a history of any cardiac disorder or gastrointestinal narrowing were also excluded. All potential benefits and risks were discussed before consent to participate in the study and participants were closely monitored. Informed consent was obtained from the parent and assent from the child when they presented for the initial appointment using IRB-approved materials. This IRB-approved study paid participants for their involvement and covered the costs of 4 weeks of Concerta treatment.

Treatment

All participants were prescribed long-acting MPH (Concerta; OROS delivery system) taken by mouth each morning for 4 weeks. Medication was purchased directly from a wholesale pharmacy and was packaged and processed by the hospital pharmacy. Families received a script for a 1-week supply of the medication each week following their study visit that was filled by the hospital pharmacy. The maximum dose of Concerta used in this study was 72 mg/day in adolescents and 54 mg/day in children (up to 1.5 mg/kg/day). Medication was titrated at weekly visits according to Concerta clinical trial conventions of an increase in 18 mg every 7 days, if needed and if the prior dose was tolerated. Concerta has been approved by the FDA for the treatment of ADHD in the target age range and is commercially available.

Child and adolescent participants were seen once weekly to monitor their vital signs, rate the influence on symptoms, and monitor systematically for side effects. At the end of the trial, participants were either referred for continued treatment with the provider of their choice (prescription for 2 weeks of Concerta was written) or discontinued from the medication (no taper required).

Measures

One of two doctoral-level clinicians (one principal investigator and one independent) completed the K-SADS-PL (Kaufman et al. 1997) semistructured interview separately with each parent and child dyad to determine present or lifetime psychiatric diagnoses. A consensus diagnostic procedure was used with a team of clinicians to avoid any interviewer bias. The K-SADS-PL was also used to collect demographic information, including socioeconomic status (SES). For study inclusion, DMDD criteria were assessed by querying the parent and child about outbursts, irritable mood, time course, and comorbid symptoms from criteria posted on the DSM-5 website (www.dsm5.org), as the DSM-5 manual (nor the revised K-SADS) had not yet been released. K-SADS was used only to determine comorbidities which would lead to inclusion or exclusion from the study. K-SADS items were not used as variables in the analyses. The Wechsler Abbreviated Scale of Intelligence was used to estimate full-scale IQ at baseline. Additionally, medication side effects were charted each week using a custom-made form with the following sections: indication of medication start and stop date; a description of any adverse event; the seriousness of the event (1 death–4 hospitalization, 5 congenital anomaly); severity (1 mild–3 severe); and outcome of the event (1 recovered–3 not recovered/ongoing, 4 recovered with sequela).

Primary outcome

Self-report measure of irritability. The Irritability Scale (Youth Version) is a child self-report measure of intensity and persistence of irritability, where participants rate how true items are for them. This scale has not been widely used in treatment studies; it has mostly been used in laboratory settings. The original questionnaire (Caprara et al. 1985) consists of 30 items which are rated on a six-point scale (1 = complete true for me to 6 = complete false for me) has demonstrated excellent test–retest reliability (Caprara 1983). From the original scale, 12 items (including two control items) were validated and found to have an acceptable to strong internal consistency ($\alpha = 0.70$–0.87) in Italian youth between the mean age of 12 to the mean age of 20 (Caprara et al. 2007), which were similar in the present sample ($\alpha = 0.73$). The two control items were removed from the validated child-report items leaving 10 items used in the analysis as the primary means to determine changes in irritability across treatment.

Secondary outcomes

Secondary measures assessing aspects of irritability and ADHD were also utilized. The measures relevant to irritability assess symptoms captured by the two main diagnostic criteria for DMDD: (1) *Frequent and severe temper outbursts (i.e., DSM-5 Criterion A)*: These are assessed with scales that quantify an inability to regulate emotion, particularly negative affect (NA) (e.g., inability

to control anger (Shields and Cicchetti 1997)) and (2) *Mood state occurring in between outbursts (DSM-5 Criterion C and D)*: These instruments measure the frequency at which particular emotions are experienced and persistence of mood states.

Parent-report measure of ability to regulate emotions. The Emotion Regulation Checklist (ERC) is a 24-item parent-report measure ($\alpha = 0.89$; Shields and Cicchetti 1997), which assesses parents' perceptions of their child's emotional expression, empathy, and emotional self-awareness (e.g., ''My child can modulate excitement in emotionally arousing situations''). Items are rated on a 4-point Likert scale ranging from 1 (never) to 4 (always). The ERC measures emotional dysregulation through its emotion regulation (i.e., emotion expression that is excessive in relation to context; Shaw et al. 2014) and lability (i.e., poorly controlled shifts in emotion; Shaw et al. 2014) subscales. Convergent validity and internal consistency (lability $\alpha = 0.96$, regulation $\alpha = 0.83$) were previously determined in youth between the ages of 6 and 12 (Shields and Cicchetti 1997). In the present sample, reliability coefficients were strong for lability ($\alpha = 0.79$) and just below acceptable for emotional regulation ($\alpha = 0.66$).

Self-report measure of emotional frequency. The Differential Emotions Scale-IV (DES-IV) is an established 36-item child report questionnaire (Izard et al. 1993). It was administered to examine the frequency with which children experienced positive (interest, enjoyment, and surprise) and negative (sadness, anger, disgust, contempt, fear, guilt, shame, and shyness) emotions over the past week. Items are divided into 11 discrete emotion scales and 1 inner-directed hostility scale. Each item rates the presence or absence of the target emotion on a 5-point scale ranging from rarely or never to very often. The DES-IV approximates a fifth-grade reading level (but has been administered to children as young as 5), and was read to children who could not read it independently. Higher scores indicated more emotional experience in each category. Previous psychometric properties for each subscale ranged from adequate to strong (α = interest 0.75, joy 0.83, surprise, 0.65, sadness 0.85, anger 0.85, disgust 0.56, contempt 0.82, fear 0.83, guilt 0.73, shame 0.60, shyness 0.62, and self-hostility 0.75; Izard et al. 1993), which are similar in the current sample (all $\alpha \geq 0.62$).

Self-report measures of mood intensity. The Positive and Negative Affectivity Scale for Children (PANAS-C) is a 30-item child report scale that measures the intensity that children have experienced affective dimensions of mood in the past few weeks (Laurent et al. 1999; Ekkekakis 2013). Items are rated on a 5-point Likert scale ranging from 1 (very slightly or not at all) to 5 (extremely). The PANAS-C is comprised of two affective dimensions of mood: NA and Positive Affect (PA). The NA subscale assesses the intensity of negatively valenced emotions (e.g., miserable, disgusted) and the PA subscale examines the intensity of positively valenced emotions (e.g., cheerful, proud). This measure was previously validated in youth 7–14 years of age and was reported to have strong internal consistency for both NA ($\alpha = 0.87$) and PA ($\alpha = 0.92$) (Hughes and Kendall 2009). Internal consistency for the present sample were also strong for both NA ($\alpha = 0.91$) and PA ($\alpha = 0.86$).

ADHD measure. Additionally, attentional issues play a significant role in mediating clinically significant irritability in youth (Leibenluft and Stoddard 2013). The ADHDRS-IV-Parent Inventory (DuPaul et al. 1998) is an 18-item scale with one item for each of the 18 symptoms in the DSM-IV diagnosis of ADHD. Each item is scored on a 0 to 3 scale (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). The rating scale assesses symptom severity over the past week. The scale is administered and scored based on an interview with the parent and the patient, although not necessarily together. The total score is computed as the sum of the scores for each of the 18 items. The inattention subscale is the sum of the scores for the odd-numbered items, and the hyperactivity–impulsivity subscale is the sum of the scores for the even-numbered items. Internal consistency with the present sample is strong for hyperactivity–impulsivity ($\alpha = 0.82$), inattention ($\alpha = 0.76$), and total score ($\alpha = 0.80$).

Data analyses

All analyses were conducted using SPSS 24.0 (IBM Corp, 2013). Assumptions of distribution normality and no significant outliers were tested and met. Repeated measures *t*-tests were conducted to examine the mean difference between pre and posttreatment scores on each of the rating scales (Table 2). These *t*-tests were used to test the hypothesis that treatment with MPH would improve mood-related symptoms associated with DMDD in youth with a comorbid diagnosis of ADHD. Because of the exploratory nature of this study, we did not adjust for multiple comparisons to avoid missing possibly important findings (Rothman 1990; Feise 2002). Baseline measurements were compared with posttreatment measures after four full weeks of treatment, with dosing escalation performed each week, as tolerated (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/cap). Reported significance levels are two-tailed tests with a $p < 0.05$ alpha for significance. Cohen's *d* was calculated to determine effect size for each *t*-test (Cohen 1987). Cases with missing data were excluded from the analysis.

To test for potential confounding factors on treatment effects, a regression was used to examine if the observed changes in irritability could be predicted by pretreatment factors. Because biological variation may produce different stimulant medication treatment outcomes (Chelaru et al. 2012), sex, race, and age were included in the regression. SES was added to the regression model because environmental factors may play a role in stimulant treatment outcomes (Rieppi et al. 2002). Because baseline mood symptoms could have an effect on treatment response (Arnold et al. 2003), pretreatment hyperactivity, emotional lability, and regulation were included in the regression model.

To prepare for regression equation fitting, we conducted Person and Spearman correlations (Supplementary Table S1) to examine the binary relationships among these variables with both pre- and posttreatment irritability. Due to differences in distribution categories, Spearman correlation was used for SES and Pearson correlation was used for all other variables. For race, dummy variables (i.e., 0/1 variables) were coded for each category (Table 1) and included in the regression. Assumptions of observation independence, linearity, outliers, homoscedasticity, and multicollinearity were tested. Data met assumptions for regression. After these preparatory steps, regression was run using pretreatment factors (sex, race, age, SES, hyperactivity, and pretreatment irritability) as independent variables and posttreatment irritability as the dependent variable.

Results

Descriptive statistics

The majority (69%, $n = 15$) of youth in the sample were male. The racial composition was 55% ($n = 12$) African American, 32% ($n = 7$)

Table 2. *t*-Test Results for Attention-Deficit/Hyperactivity Disorder and Emotional Measures ($N=22$)

Variable	Pretest M	Pretest *SD*	Posttest M	Posttest *SD*	95% CI for mean difference	d	t	*df*
Primary								
Irritability scale	44.95	6.47	40.97	8.29	−7.14 to −0.82,	0.57++	−2.62*	20
Secondary								
ERC								
Lability	41.64	6.06	34.68	6.81	−30.39 to −23.79	0.85+++	−4.00**	21
Regulation[a]	23.09	4.15	24.45	2.53	−0.72 to −3.44	0.29+	1.36	21
DES–IV								
Anger	9.95	2.57	8.70	2.83	−2.83 to −0.07	0.55++	−2.20*	19
Surprise	10.00	2.23	8.30	2.52	−3.33 to −0.17	0.49++	−2.31*	19
Shame	10.23	2.84	8.95	2.67	−2.86 to −0.24	0.56++	−2.46*	19
Interest	10.36	3.14	9.55	2.82	−3.22 to 0.82	0.27+	−1.24	19
Joy	10.45	2.70	9.75	2.88	−2.18 to 1.28	0.12	−0.54	19
Sadness	9.05	2.61	12.0	7.80	−3.09 to 0.29	0.39+	−1.73	19
Disgust	8.32	2.77	15.0	7.75	−1.90 to 0.90	0.18	−0.75	19
Contempt	7.50	2.87	11.0	6.80	−2.01 to 0.91	0.18	−0.79	19
Hostility	7.27	2.75	14.0	6.70	−2.29 to 0.89	0.21+	−0.92	19
Fear	1.18	3.16	13.0	6.85	−2.63 to 1.23	0.17	−0.76	19
Shyness	8.36	3.11	12.0	7.50	−2.85 to 0.65	0.30+	−1.32	19
Guilt	9.0	2.51	12.0	8.50	−1.70 to 0.51	0.25+	−1.13	19
PANAS-C								
Negative affect	37.55	9.90	32.36	12.27	−8.18 to −0.14	0.50++	−2.17*	18
Positive affect[a]	44.18	9.26	42.11	8.61	−7.11 to 2.48	0.23+	−1.01	18
ADHD								
Hyperactivity	17.09	6.04	10.36	7.35	−10.09 to −3.36	0.89+++	−4.16**	21
Inattention	22.77	4.18	12.0	5.94	−14.12 to −7.43	1.43+++	−6.71**	21
Raw score	39.86	8.21	22.36	12.63	−23.67 to −11.33	1.26+++	−5.91**	21

[a]Reverse scored.
*$p<0.05$, **$p<0.001$ two-tailed significance.
Effect size: +, small (0.20); ++, medium (0.50); +++ large (0.80).
ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; *d*, Cohen's *d*; DES-IV, Differential Emotions Scale-IV; df, degrees of freedom; ERC, Emotion Regulation Checklist; *M*, mean; PANAS-C, Positive and Negative Affectivity Scale for Children; SD, standard deviation; *t*, t-statistic.

Caucasian, and 13% ($n=3$) biracial. Approximately 68% ($n=15$) of youth came from homes with income less than $40,000 a year, and IQ ranged between 79 and 132 (106.41 ± 14.28). All participants met criteria for both ADHD and DMDD with 9% ($n=2$) also meeting criteria for generalized anxiety disorder and 18% ($n=4$) also meeting criteria for conduct. Full descriptive statistics are reported in Table 1. The rounded average MPH dose at week 4 was 61 mg (SD = 10.9) or 1.1 mg/kg (Supplementary Fig. S1).

Primary outcome

Child-rated irritability significantly improved with a moderate effect size after treatment with MPH (Table 2). Seventy one percent of the sample ($n=15$) saw improvements in symptoms of irritability, 18% ($n=4$) had a worsening of symptoms and 10% ($n=2$) had no change. Multiple regression indicated that, of baseline hyperactivity severity, pretreatment irritability, age, gender, race, SES, and comorbid diagnosis, none predicted change in posttreatment irritability (Supplementary Table 1).

Secondary outcomes

Measures of parent-rated emotion regulation (regulation subscales) also improved with a large effect size after treatment with MPH (Table 2 and Supplementary Fig. S2). Although 23% ($n=5$) of participants had a deterioration in symptoms of parent-rated lability and 9% ($n=2$) had no change, 68% ($n=15$) had an improvement in emotional outburst ratings on the ERC across the study period. Self-report measures of emotion and mood intensity and frequency of negative affective states using PANAS-C and DES-IV also showed significant improvement (medium and large effect sizes) (Table 2).

As anticipated, measures of ADHD symptoms improved significantly with MPH treatment (Table 2). MPH was well tolerated, as only 18% ($n=4$) of participants self-reported and clinician assessed side effects. These included overstimulation (feeling jittery and high strung) and somatic complaints (intermittent headaches and decreased appetite); all were judged to be minor by the study physician. Average weight loss for this sample was less than 1 pound after the 4-week trial.

Discussion

In the present pilot study, we report that open-label, long-acting MPH treatment of DMDD comorbid with ADHD resulted in moderate (child-reported irritability and mood) and large (parent ratings of emotion regulation) improvements in overall emotional functioning in a small sample of youth. We also found that most participants had improvements in self-rated irritability (71%), whereas fewer had worsening irritability (18%) or no change (10%). Furthermore, the medication was generally well tolerated.

Results of the present study, showing improvement in the core symptoms of DMDD, are consistent with previous research on stimulant treatment improving parent-rated mania with SMD-diagnosed youth (Waxmonsky et al. 2016) and depressed mood associated with DMDD (Baweja et al. 2016; Blader et al. 2016). The present study is the first to measure irritability explicitly along with related emotional and mood constructs in youth with DMDD treated with MPH.

Induction of anhedonia or a reduction in the frequency or intensity of positively valenced emotions could be anticipated with stimulant use (Blader et al. 2016). However, in the present study, we report this was not the case in chronically irritable youth. Specifically, negatively valenced emotions were endorsed as being less intense and less frequent, whereas the intensity and frequency of experiencing positively valenced emotions were unaffected. These findings are consistent with a recent meta-analysis, which reported that MPH is more likely to reduce irritability, in comparison to placebo, than amphetamine-based medications, in pediatric ADHD (Stuckelman et al. 2017). While most participants endorsed improvements in emotional lability, a minority of participants experienced worsening in emotion regulation (24%), and even fewer saw no change (9%). As with any medication, MPH responsiveness is subject to individual variability (Griffiths et al. 2017). However, consistent with findings from Blader et al. (2016), psychiatric symptoms did not predict posttreatment irritability using pretreatment hyperactivity (ADHDRS-IV-Parent Inventory), nor emotional lability/regulation (ERC). Similarly, consistent with Baweja et al. (2016), demographic factors also did not predict treatment outcomes for irritability using sex, race, SES, or age. We hypothesize that a unique biological component that is independent of demographic factors (Dickstein and Leibenluft 2012) may drive these effects. In sum, these findings suggest improvements in irritability through enhanced emotional regulation as well as less time spent experiencing negatively valenced emotions.

This is a preliminary study with clear limitations. It is an uncontrolled trial with a small sample size and no control group. The results may have been affected by an expectancy effect associated with the open-label design. Also, the use of self-report measures has the potential for response bias (Steene-Johannessen et al. 2015). Not controlling for multiple comparisons has potential to increase type I error, but also would likely miss important findings in this exploratory study. Future studies should incorporate larger sample sizes and include controls. Despite the limitations, the significant findings of the present study suggest the need for more controlled research.

In sum, this is the first study which explicitly examined parent- and child-rated changes in chronic irritability and related affective states and emotion regulation capacities before and after therapeutically dosed MPH treatment. Anecdotally, clinicians may worry about worsening mood and emotional symptoms in highly irritable youth, but we actually found improvements in these domains, in the majority of participants.

Conclusions

MPH was associated with improvement in child self-ratings of irritability (Irritability scale) and frequency and severity of negative emotions and affect (DES-IV, PANAS-C), as well as parent-reported severity of emotion dysregulation (ERC). Although a small portion of participants experienced a worsening in irritability and emotional dysregulation, the majority of participants saw improvements and medication was well tolerated. We were unable to predict, using demographic and clinical characteristics, who would experience worsening in symptoms. Despite the current study's limitations, the results warrant further exploration. The moderate–large effect sizes and good tolerability suggest that MPH is worthy of further study with a larger sample size, using a controlled design. The benefits of a single agent that can target emotional as well comorbid cognitive symptoms is clear, particularly given the risks associated with antipsychotics, mood stabilizers, and polypharmacy in youth. Overall, the study findings provide preliminary support for the use of MPH to treat mood symptoms associated with DMDD in youth with comorbid ADHD.

Clinical Significance

Our study is the first prospective study to assess the effects of MPH on irritable mood and emotional symptoms of DMDD comorbid with ADHD. Preliminarily, MPH was effective in improving irritability and related symptoms in most participants with very few side effects or worsening psychiatric symptoms. Further investigation using larger sample sizes and control groups is needed to inform clinical practice for this population.

Disclosures

No competing financial interests exist.

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