NEW RESEARCH AGGRESSIVE BEHAVIOR

Check for updates

Stimulant Medication Shortens the Duration of Impairing Emotional Outbursts

Lauren M. Spring, MD, Joseph E. Schwartz, PhD, Gabrielle A. Carlson, MD

Objective: Emotional dysregulation, often presenting as severe emotional outbursts, is being increasingly recognized as a source of considerable impairment for individuals with attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to conduct a secondary analysis of data examining the impact of standing stimulant medication on the duration of emotional outbursts.

Method: The as needed (PRN)–medicated outbursts of psychiatrically hospitalized children, 5 to 12 years of age, were tracked by psychiatric nurses using the Behavioral Activity Rating Scale from the time of PRN administration until the child became calm. The impact of extended-release (ER), immediate-release (IR) stimulant and dose, type and reason for outburst/PRN (aggression, agitation, distress), standing concomitant psychotropic medications and time of day, and days since admission were examined.

Results: Forty-seven children had a total of 405 outbursts, 96 of which occurred when no stimulant was prescribed and 309 with stimulant medication. Controlling for time of day and standing neuroleptic dose, outbursts that occurred on an ER stimulant medication were statistically significantly shorter than those that occurred on no stimulant by about 20 minutes (52.7 vs 72.4 minutes), or 30 minutes for aggressive outbursts. Results were unchanged when further controlling for stimulant type and dose, α-agonist, days since admission, PRN medication type, or reason for PRN/outburst. Immediate-release stimulants and short-acting stimulants did not shorten outburst duration.

Conclusion: In children with ADHD with severe outbursts, ER stimulants were associated with shorter outburst duration than IR stimulants.

Plain language summary: This study examined psychiatrically hospitalized children with attention-deficit/hyperactivity disorder who had emotional outbursts requiring as-needed medication. Children who took extended-release stimulant medication (stimulants that are designed to last throughout the day) had shorter outbursts (by about 20 minutes) than children on no stimulant medication or short-acting stimulant medication.

Key words: temper outburst; agitation; pro re nata; neuroleptic; stimulant

JAACAP Open 2025;3(1):114-125.

Developmentally and situationally inappropriate, frequent, and severe emotional outbursts, conceptualized as a form of irritability,[1,2] are a common problem in child and adolescent psychiatry[3,4] and are often the reason for referral to child and adolescent psychiatric emergency services,[5] outpatient departments,[6,7] and inpatient units.[8] Diagnostically, attention-deficit/hyperactivity disorder (ADHD) is common in youth who experience these emotional outbursts.[9–11] Conversely, outbursts are common in youth with ADHD.[12,13] In fact, although hyperactivity and impulsivity are considered the essential features of ADHD, emotional symptoms, including outbursts, have long been recognized as an especially impairing part of the symptomatology of ADHD. In 2019, Faraone *et al.*[10] reviewed the evidence for symptoms of emotional dysregulation in ADHD, reporting that as many as 40% to 50% of youth with ADHD experience significantly impairing anger, low frustration tolerance, rages, and irritability.

Irritability/emotional outbursts/dysregulation may also be considered a form of "impulsive" or "maladaptive aggression."[14] Jensen *et al.* defined this as "aggression that occurs outside an expectable social context. The intensity, frequency, duration, or severity of the aggressive response is disproportionate to its causes and may occur in the absence of expectable antecedent social cues."[15] In the Multimodal Treatment Study of Children With ADHD (MTA), 267 of 579 children (46%) were identified as having significant problems with aggression, and 44% of those remained so even after their ADHD had been vigorously treated.[15] These rates, not surprisingly, are very similar to the dysregulation rates reported by Faraone *et al.*[10]

There is a plethora of evidence supporting the use of stimulant treatment for aggressive symptoms in children with ADHD.[16] A meta-analysis by Connor *et al.*[17] found an overall mean effect size (ES) of Cohen d = 0.84 of stimulants on reducing occurrences of overt aggression. After reviewing 45 randomized controlled trialss, Pappadopulos

et al.[18] found that of all psychotropic medications, methylphenidate (MPH) had the largest effect on comorbid aggression in pediatric ADHD (mean ES d = 0.90, combined N = 844). Large network meta-analyses of pharmacological and non-pharmacological treatments of ADHD in children and adolescents concluded that of the medications prescribed for ADHD, methylphenidate, and amphetamine (AMP) have the greatest efficacy, although they do not specifically address aggression.[19,20]

There are both a recent review of irritability/dysregulation in ADHD[21] and a recently completed a meta-analysis of interventions for persistent, non-episodic irritability in children with psychiatric disorders.[22] The latter report an ES (Hedges g) for ADHD medications of 0.50. A secondary analysis of the MTA, using a measure of oppositional symptoms from the Swanson, Nolan and Pelam rating scale to rate irritability, reported an effect size for stimulants alone of d = 0.63.[23] Galanter *et al.*[24,25] also analyzed the MTA data but confined their study to comparing children with what is now called the Child Behavior Checklist (CBCL) Dysregulation Profile.[26] In that group of moody and aggressive children with ADHD, the ES for treatment (all stimulant treatments) was d = 1.04. However, this study makes the point that although symptoms improve, children with the dysregulation profile are more symptomatic at the start and at the end of the study than non-dysregulated children with ADHD.[24,25]

The continuing symptomatology of children with ADHD and aggression/irritability/mood dysregulation is a problem specifically identified by a number of authors[15,27,28] and has provided the impetus for several controlled studies including the Treatment of Severe Childhood Aggression (TOSCA) study[29] and the Stepped Treatment for ADHD and Aggression (SPICY) trial.[30] These studies address the question of what to do when stimulants alone are insufficient to reduce aggressive behavior in children with ADHD.

In the Treatment of Severe Childhood Aggression (TOSCA) trial, aggressive children with ADHD were selected on the basis of their assaultive behavior. They were dosed with the osmotic release oral system formulation of methylphenidate (OROS-MPH) in an open-label trial, ultimately taking about 45 mg per day and then randomized to continued stimulant and parent training alone vs continued stimulant, parent training plus risperidone. Only 8 of 168 children were well enough on stimulant alone at the point of randomization to discontinue the study. For the whole sample, the stimulant-alone ES from baseline to the start of the randomized trial was d = 0.62. Not often highlighted, however, was the ES of d = 0.29 on a reactive behavior scale, probably focusing on irritable outburst behavior. In another study, the ES for the Peer Conflict Scale and oppositional defiant disorder (ODD) irritability scale from the Child and Adolescent Symptom Inventory were a discouraging d = 0.29 and d = 0.19, respectively.[31] All suggest only minor reductions in significant aggression. Moreover, there was no indication of whether the assaultive behavior, which was an inclusion criterion for the study, changed appreciably.

The Stepped Treatment for ADHD and Aggression trial[30] also addressed aggression in children with ADHD, using ADHD and aggression measures somewhat similar to those in TOSCA, but spent longer stabilizing the children on stimulant medication and parent training (over 9 weeks) before randomizing them to risperidone, valproate, or placebo if they remained unacceptably aggressive. For the open treatment phase, children ultimately were taking a variety of mostly extended-release (ER) stimulants with mean daily doses of 42 to 44 mg per day. They did well enough with this regimen and parent training that 96 of the original 175 children did not enter the randomized, adjunctive medication phase of the study. The aggression measure raw scores were not given, but *T* scores for standardized measures on stimulants alone dropped from $T = 75.8$ to $T = 61.5$ for CBCL aggression and from $T = 82.0$ to $T = 55.4$ for the Conners emotional lability factor. Again, however, what specifically improved or did not improve of the aggressive behaviors was not spelled out.

In conclusion, although stimulant medications have consistently been shown to have a positive impact on emotional symptoms and aggression in ADHD, multiple different terms and rating scales have been used throughout the literature, making it difficult to know what exactly is improving.[32] Specifically, are emotional outbursts the focus of treatment? Are they occurring less frequently? Are they less severe when they occur? Is there a change in how long the outbursts lasts?

Two concepts that appear especially relevant to ADHD are emotional impulsivity (how reactive the child is) and deficient emotion regulation, including both the inability to prevent emotions from rising to problematic levels as well as slower than normal return to their emotional baseline.[10]

The present study will address the last issue, that is, how long it takes the severe emotions generated in an outburst to return to baseline. Using data collected on psychiatrically hospitalized children admitted mainly for aggression, the initial purpose of the study was to determine the effectiveness of mostly oral "as needed" (PRN) medication in shortening the duration of children's severe emotional outbursts. The original study[33] reported that despite adequate doses of PRN risperidone, diphenhydramine, olanzapine, lorazepam, or chlorpromazine as well as adequate doses of standing neuroleptic medication, no significant differences were found between PRNs in shortening

the duration of the outburst. Almost half (43.9%) of outbursts ended in 30 minutes or less, whereas 21.3% continued for longer than 2 hours, and outburst duration varied widely within a single child. Because most of the children with outbursts had either ADHD only or ADHD and another externalizing disorder, and because of the known improvement in aggression seen in some children with ADHD who were taking stimulant medication, we now report the results of a secondary analysis examining the impact of standing stimulant treatment on the duration of emotional outbursts.

METHOD

Sample

The original study included children 5 to 12 years of age who were admitted to Stony Brook University Hospital's 10-bed Children's Inpatient Unit between September 1, 2017, and April 23, 2018. The analysis sample for this study consists of the 66 of 70 children who were diagnosed with ADHD after evaluation by the inpatient attending psychiatrist and the interdisciplinary team consisting of a resident or fellow, psychologist, full-time special education teachers, and nurses. Four children who were subsequently discharged within a few days of admission or whose parents would not allow medication treatment were excluded. Assessments included a medical and psychiatric history and mental status. Psychoeducational testing, including the Wechsler Intelligence Scale for Children IV edition (WISC-IV) and the listening comprehension, reading and mathematics scores from the Kaufman Test of Educational Achievement[34] (KTEA), were available for the 49 children who were hospitalized during the academic calendar. Demographic characteristics and clinical measures (eg, history of abuse, domestic violence, or other severe stressors), the reason for admission (aggression, suicidal behavior, psychosis, other), and the number of psychiatric hospitalizations and emergency room visits were recorded.

Outburst Ascertainment

Described in detail elsewhere,[33] the number and duration of severe emotional outbursts were systematically gathered with the use of the nurse-completed Behavioral Activity Rating Scale (BARS)[35–37] whenever a PRN medication was administered. It should be noted that more than 1 PRN might be used for an outburst, but the outburst was the unit of analysis. The BARS uses a 7-point scale ranging from 7 (violent, requires restraint) to 1 (difficult to arouse), with 4 (normal level of activity) considered to be the end of the outburst. Ratings were recorded at the time that the PRN was given, at 15-minute intervals for the next 60 minutes, when the child became calm, and/or at 120 minutes. Time to a BARS score of $\leq$4 is called "Time to Calm," or TTC1. Although the outburst usually started before the PRN was given, we are defining outburst duration as the time from the first PRN administration until a BARS score of $\leq$4.

All unit staff were trained in verbal and non-verbal de-escalation techniques for addressing outbursts, aggression, and other challenging behaviors. Oral PRN medication was offered when the situation continued to intensify despite attempts at de-escalation. Although individual staff may have had a higher or lower threshold for administering PRN medications, staff were not always assigned the same patients, and there is no evidence that particular staff took care of either children prescribed a particular PRN or children with a particular diagnosis. So, any treatment biases were not likely distributed in a systematic way across the sample.

One treatment provider made medication decisions for all patients for the duration of this study. Medication decisions, both standing and PRN, were made clinically on an individual patient basis. PRN medications included low and high doses, respectively, of diphenhydramine (25 mg and 50 mg) and risperidone (0.5 mg and 1 mg). Medication decisions were based on both safety and experience; olanzapine (5 mg only), lorazepam (0.5 mg and 1 mg), and chlorpromazine (25 mg and 50 mg) were tried when first PRN medications failed.[33]

Patients' individual histories were considered when making stimulant medication decisions. For example, short-acting formulations were chosen when individuals had a history of insomnia with previous exposure to long-acting formulations. Twice-daily (around 7:30 and 11:30 am) short-acting medications were prescribed when appetite reduction and weight loss were important considerations, so that the child could eat a larger meal at the end of the day. In general, when there was no contraindication or no prior history of stimulant use, patients were moved from short- to long-acting stimulant formulations once tolerability and effectiveness were established. Use of short-acting stimulants preceded long-acting or ER stimulants, which is why we controlled for at what point during hospitalization a medication was administered.

To control for variables that might affect the duration of outbursts, the following specific information was ascertained about the outbursts: time of day of PRN, number of days from admission to the outburst, and the type of outburst (reason for PRN). Reasons for PRN administration/type of outbursts were classified as aggression (property destructive and/or physically assaultive behavior), agitation only (hostile/angry and/or verbally threatening behavior), or distress (crying uncontrollably or severely anxious).

Medication Treatment

ADHD medication treatment was analyzed by the absence or presence of stimulant treatment, including methylphenidate and dexmethylphenidate immediate release (IR) preparations (MPH-IR), MPH extended-release (MPH-ER), including OROS-MPH, dexmethylphenidate ER, and other ER preparations), and dextroamphetamine IR (AMP-IR), including mixed amphetamine salts (MAS) and ER preparations (eg, MAS-XR and lisdexamphetaphamine). Stimulant medication doses were converted to MPH equivalents; total daily dose on the day of the outburst divided by body weight (mg/kg/d) was calculated. For example, total daily dose of OROS-MPH 27 mg plus 10 mg at 2:30 pm was 37 mg; total daily dose of MAS-IR 10 mg b.i.d was equivalent of 40 mg MPH; total daily dose of MAS-XR 10 mg was 20 mg MPH-equivalents.[38]

Impact on TTC1 was examined in 2 ways: by formulation (IR vs ER), and by duration of action of the medication (short-acting was twice a day, IR stimulant; long-acting was either IR 3 times a day or ER stimulant). Although there is a clear overlap, the distinction is whether the duration of action or steadiness of medication release has a specific impact.

Besides the presence and type of stimulant medication (MPH or AMP), other possible medication influences on TTC1 included other ADHD medications (α-agonists; rarely atomoxetine), the type of PRN received (neuroleptic, diphenhydramine, and/or benzodiazepine), and dose of standing neuroleptic medication converted to risperidone equivalents.[39]

The following questions were examined:

1) Among a cohort of hospitalized children with ADHD, were there demographic or clinical differences between those who had outbursts and those who did not?
2) Among those children with ADHD who had outbursts, were there demographic or clinical differences or differences in the type of outburst between those children who were treated with stimulant medication during their hospitalization and those who were not?
3) Among those with outbursts, was TTC1 associated with
   a) whether the outburst occurred while the child was taking an IR vs an ER stimulant (or no stimulant) on the day of the outburst?
   b) whether the outburst occurred while the child was taking a short-acting vs long-acting stimulant (or no stimulant) on the day of the outburst?
4) Follow-up analyses controlled for the possible influences on the results for 3a and 3b of
   a) total weight-adjusted daily dose of stimulant (mg/kg)
   b) the type of stimulant (MPH vs AMP)
   c) standing α-agonist
   d) when the outburst occurred (days since admission)
   e) type(s) of PRN medication administered
   f) type of outburst prompting the nurse to administer the PRN

Statistical Analysis

Children with ADHD who experienced 1 or more outbursts were compared to those with no outbursts on demographic and clinical characteristics using *t* tests for continuous measures, Fisher exact test for dichotomous measures, and χ^2 tests for categorical measures with 3 or more categories. The same approach was used to compare children who never received stimulant medication to those who did.

For the primary analyses of the association between type of (standing) stimulant received (IR vs ER or short-acting vs long-acting) and duration of outbursts (TTC1), multilevel linear mixed models (MLMM) were estimated in which the intercept was treated as a random effect and heterogeneity of variances were accounted for. On *a priori* grounds, standing dose of neuroleptic, quantified in risperidone dose equivalents,[39] was included as a covariate in all models. Given that a preliminary analysis revealed that when time of day was subdivided into 3-hour blocks, TTC1 was significantly shorter in the evening (15.2 minutes shorter for outbursts between 6:00 pm and 8:59 pm, and 37.4 minutes shorter for outbursts starting at 9:00 pm or later), all MLMM models also included indicator variables for these 2 time periods as covariates. MLMM results are generally reported as the covariate-adjusted mean TTC1 (least squares mean) for a specific category of standing stimulant or the absence of any stimulant on the day of the outburst. Pairwise differences in unadjusted means that are statistically significant at an unadjusted p value of $<.05$ are identified.

Heuristically, the MLMM analyses provide estimates of TTC1 that represent the time to calm of the average outburst for the average child: that is, the average of children's time to calm averages. This implicitly adjusts for differences in the number of outbursts per child; several had only 1 outburst, whereas 1 child had a total of 52 outbursts (>12% of all the outbursts). Were the analysis not to treat the intercept as a random factor, the results would be disproportionately influenced by those few children who had many outbursts. This said, we conducted sensitivity analyses in which all outbursts were weighted equally (ie, the intercept is not treated as a child-level random effect).

Similarly, a few outbursts were exceptionally long. To account for this, we also performed a sensitivity analysis in which the outcome, Time to Calm, was winsorized (that is

all values above the 95th percentile [180 minutes]) were recoded to 180 minutes, and all values below the 5th percentile [15 minutes]) were recoded to 15 minutes). Although the numerical results changed slightly, the findings were substantively unchanged.

All analyses were performed using SAS, version 9.4.

RESULTS

Of the 66 children with ADHD analyzed, 47 (71.2%) were male, 32 (48.5%) were non-White (25 Black and 7 Hispanic), and 28 (42.4%) lived with both parents. The average age (SD) was 9.9 (1.8) years. Mean length of stay was 15.9 (9.5) days (median, 15 days; range, 5-46 days).

A total of 19 children (28.8%) had no PRN during their admission. The remaining 47 children experienced a total of 405 outbursts with at least 1 PRN. The BARS was successfully completed for 305 (75.3%) of these outbursts. Missing TTC1 data could usually be estimated from the nurses' notes, resulting in this primary outcome measure being available for 397 (98.0%) outbursts. The difference in mean TTC1 derived from nurses' notes vs from BARS was not significant ($p = .57$).

Of the 19 children who never had an outburst requiring a PRN, all were treated with stimulants during most of their inpatient stay. Among the 47 children with outbursts requiring a PRN, the mean number of outbursts was 8.6 (10.2); the median was 5 (interquartile range, 2-12). Seven children (14.9%) were never on a stimulant medication during an outburst; 30 (63.8%) were on a standing stimulant at the time of every outburst; and the remaining 10 (21.3%) were on a stimulant at the time of at least half of their outbursts. Of the 47 children, 15 (31.9%) had 1 or 2 outbursts; the remainder (n = 32, 68.1%) had 3 or more.

There were no significant differences between children with ADHD who had no outbursts and those who did by age, sex, race/ethnicity, or living with both biological parents (Table 1). Children did not differ on prevalence of autism, mood disorder, anxiety disorder, and trauma (physical or sexual abuse, domestic violence, or severe stressors), Full Scale IQ, or KTEA reading, mathematics, or listening comprehension scores. This was the first hospitalization for most children in both groups, and the number of prior emergency room visits did not differ between groups. However, as shown in Table 1, children with ADHD with outbursts had a longer average length of stay (19.0 vs 11.8 days), were more often admitted for aggression (78.7% vs 47.4%), and were more often diagnosed with oppositional defiant disorder (85.1% vs 47.4%).

Table S1, available online, compares the 40 children with outbursts who were prescribed stimulants with the 7 children who never had an outburst while on a stimulant. There were no differences except that stimulant-prescribed children were significantly younger than those who were never given a stimulant.

Stimulant Medication Treatment

Table 2 summarizes the different classes of stimulants taken, and the mean adjusted doses per child. MPH-ER in (126 outbursts) and MPH-IR (in 89 outbursts) were the most commonly used medications, followed by AMP-ER (in 75 outbursts) and MAS-IR (in 19 outbursts). It should be recalled that a child can be in more than 1 category: that is, some outbursts might be while the child is on no stimulant, and others might be while the child is on a stimulant.

As shown in Table 3, after controlling for standing neuroleptic dose and time of day, outbursts that occurred while the child was taking an ER stimulant medication were statistically significantly shorter than those that occurred on no stimulant by about 20 minutes (52.7 vs 72.4 minutes). The approximately 20-minute difference remained even after controlling for stimulant dose (22.0 minutes.), type of stimulant (MPH or MAS, 21.6 minutes), additional α-agonist (concomitant α-agonists in 195 of 405 outbursts, 22 minutes), PRN type (neuroleptic, diphenhydramine, and/or benzodiazepine, 22.6 minutes), and days since admission (22.4 minutes). Outbursts that occurred while the child was on an IR stimulant lasted 17.1 minutes longer than when the child was on an ER stimulant (69.8 minutes) and were almost as long as when no stimulant was used.

One important clinical confound was whether the outburst was rated by nurses as aggressive, agitated, or distressed. Aggressive outbursts without stimulants had the longest duration (86.9 minutes), followed by irritable outbursts (36.1 minutes) and distress outbursts (27.3 minutes) (Table 4). Furthermore, aggressive outbursts were 29.9 minutes shorter on ER stimulant medications (TTC1 of 57 minutes) than on no stimulant (TTC1 of 86.9 minutes). For outbursts attributed to irritability or distress (ie, not aggression), TTC1 was shorter in children not taking stimulants (compared to outbursts attributed to aggression), and stimulants had no effect on TTC1.

Table 3 further illustrates that when comparing short vs long-acting stimulants, the differences were smaller and not statistically significant; outbursts when on a short-acting stimulant were similar in length to when there was no stimulant (72.0 vs 72.4 minutes), whereas outbursts that occurred while the child was taking a long-acting stimulant lasted an average of 59.2 minutes. When the IR stimulants

TABLE 1 Demographic and Clinical Differences in Children With Attention-Deficit/Hyperactivity Disorder (ADHD) With and Without Outbursts

	ADHD		ADHD			
	No outbursts		Outbursts		Statistic	*p*
No. of children	19		47			
Demographics	n	%	n	%		
Sex, male	12	63.2	35	74.5		.38
Black	5	26.3	20	42.6		.27
Non-White	7	36.8	25	53.2		.28
Lives with 2 parents	11	57.9	17	36.2		.17
	Mean	**SD**	**Mean**	**SD**	***t***	
Age, mean/SD	10.3	1.6	9.8	1.9	−1.05	.30
Full Scale IQ	91.2	11.4	91.2	18.4	0.01	.99
KTEA reading	87.0	19.8	82.4	18.2	−0.82	.41
KTEA mathematics	84.3	10.4	84.6	18.1	0.06	.95
KTEA listening comprehension	93.3	17.6	83.5	16.5	−1.86	.07
Length of stay	11.8	6.2	19.0	9.8	3.59	.0007
No. of emergency room visits	0.7	1.1	0.8	1.3	0.46	.67
Clinical	**n**	**%**	**n**	**%**		
First hospitalization	16	84.2	33	70.2		.35
Admitted with aggression/ outbursts	9	47.4	37	78.7		.02
Any trauma	10	52.6	29	61.7		.58
Diagnosis						
Any ODD/CD	9	47.4	40	85.1		.004
Any ASD	3	15.8	10	21.3		.74
Any mood disorder	10	52.6	15	31.9		.16
Any anxiety disorder	5	26.3	6	12.8		.27
Any mood/anxiety disorder	13	68.4	19	40.4		.06
Treatment						
Any stimulant	19	100	40	85.1		.08
Any α-agonist	5	26.3	21	44.7		.27
Any antidepressant	13	68.4	24	51.1		.28
Any neuroleptic	5	26.3	33	70.2		.002
Any atomoxetine	0		2	4.3		1.0

Note: ASD = autism spectrum disorder; CD = conduct disorder; KTEA = Kaufman Test of Educational Achievement; ODD = oppositional defiant disorder.

are differentiated by long-acting vs short-acting stimulants, the difference in the corresponding outbursts' time to calm is negligible (72.3 vs 74.2 minutes), strongly suggesting that it is the extended-release (all long-acting) formulation that results in an approximately 20-minute shortening in outburst duration.

We repeated the analyses comparing TTC1 for children taking IR or ER stimulants, or no stimulant, without adjusting for clustering by child or the differential number of outbursts that the children had (ie, simply treating all outbursts equally). The results of these sensitivity analyses are fully consistent with those shown in Table 3 and described above.

Somewhat surprisingly, the dose of stimulant was not associated with TTC1. Although the MPH-IR dose was comparatively lower than the medication dose of other stimulant preparations (often because short-acting medications were used before converting to ER medications), there was no association between medication dose and TTC1 (Table S2, available online).

Figure 1 presents Kaplan–Meier curves for time to calm separately for those outbursts when the child was on an ER stimulant, an IR stimulant, or no stimulant. Table 2 differentiates MPH from AMP stimulants, revealing that 20% of outbursts when on IR MPH ended within 30 minutes compared to 47.4% when on MAS-IR, whereas there was

TABLE 2 Outbursts, Stimulant Doses, and Association of Time to Calm for Outbursts With Standing Stimulant Medication in Children With Attention-Deficit/Hyperactivity Disorder (ADHD)

Standing stimulant medication	No. of children	No. of outbursts (%)	Adjusted mean stimulant dose mg/kg/d[1]	No. of outbursts with TTC1 (%)	≤30 min %	>120 min %	Adjusted TTC1 mean[2] (95% CI)
No stimulant	17	96 (23.7)	—	91 (22.9)	39.6	28.6	73.1[ab]
Methylphenidate BID	3	10 (2.5)	0.56	10 (2.5)	20.0	40.0	118.1
Methylphenidate TID	19	79 (19.5)	0.77	79 (19.9)	32.9	34.2	75.6[cde]
Immediate-release amphetamine salts	4	19 (4.7)	1.28	19 (4.8)	47.4	10.5	47.8[ac]
Extended-release methylphenidate	26	126 (31.1)	1.48	124 (31.2)	51.6	10.5	52.2[bd]
Extended-release amphetamine	9	75 (18.5)	0.93	74 (18.6)	51.4	13.5	55.2[e]
Total		405 (100)	1.07	397 (100)	44.1	20.7	55.5

Note: Statistical significance: superscript letter "a" identifies 2 means that differ significantly (p < .05, with no adjustment for multiple comparisons); similarly, superscript "b" identifies 2 means that differ significantly, and the same for superscripts "c" through "e." For example, 73.1 is significantly greater than both 47.8 (share "a") and 52.2 (share "b"). BID = bis in die (twice a day); TID = ter in die (three times a day); TTC1 = time to calm.
[1]Primary unit of analysis is a child with multiple outbursts nested within the child; estimate of mean adjusts for differences in the number of outbursts per child and clustering by child.
[2]Covariate-adjusted mean TTC1, controlling for risperidone dose equivalent (RDE) of standing neuroleptic and time of day of the outburst. Global test of significance: $F_{4,389} = 3.64$, p = .006 controlling for RDE and time of day of the outburst. Pairwise comparisons: the differences in mean TTC1 between rows that share the same superscript letter are statistically significant (2-tailed p < .05, unadjusted for multiple comparisons).

little difference between when on MPH-ER (51.6%) and AMP-ER (51.4%) preparations. Less than 15% of extended-release–treated outbursts continued beyond 2 hours compared to more than one-third (34.2%-40.0%) of outbursts when on IR MPH.

DISCUSSION

To our knowledge, this is the first study to examine either outburst duration in children with ADHD or the differential impact of stimulant medications. Compared to children with ADHD without outbursts, children with ADHD and outbursts had a more severe clinical presentation: they were more likely to be hospitalized because of aggression and to have a longer length of stay.

Our primary findings are as follows: (1) the average outburst duration was 17 to 20 minutes shorter for outbursts occurring while the child was taking an ER stimulant, either MPH or AMP based, than for outbursts occurring while the child was taking an IR stimulant or no stimulant; (2) the outburst duration was similar for outbursts while on an IR stimulant and those in whom no stimulant was being taken; (3) among those outbursts while the child was taking an IR stimulant, there was no difference in outburst duration between twice a day and three times a day administrations; (4) almost three-fourths of the PRNs were given to treat aggressive behavior, and it was these outbursts for which ER stimulants were most beneficial, reducing outburst duration by about 30 minutes. Although the average duration was still unacceptably long (57 minutes), at least in children with ADHD, the suggestion is that ER stimulants may specifically improve emotion regulation. In the words of 1 experienced nurse, children on an ER stimulant "ran out of steam sooner."

None of the demographic or clinical characteristics of the children were able to explain ER stimulants' effect. The shortened outburst duration effect was not pharmacological insofar as there was no differential impact conferred on outbursts by time of day (ie outbursts were not shorter in the morning or midday, when the drug should have had its peak effect), and there was no evidence that higher-dosed children responded better than lower-dosed children (although all but 1 child averaged at least 0.4 mg/kg/d). Within the 2- to 4-week hospitalization, there was also no significant effect on outburst duration for outbursts earlier vs later during hospitalization. There was also no evidence of an added benefit of standing α-agonist or neuroleptic dosage on outburst duration.[33]

The lack of benefit of MPH-IR 3 times a day was unexpected, as comparably dosed ER and 3 times a day IR formulations are considered equally effective.[40,41] The longer duration and possibly better effectiveness of AMP has been recognized for years.[42] The importance of all-day coverage with stimulant medication is well recognized.[43] Our data suggest that once-daily smooth release, not just

TABLE 3 Association of Stimulant Duration and Formulation With Time to Calm, Controlling for Potential Confounds

				Covariate-adjusted mean time to calm (min)[1]						
	No. of outbursts / no. of children[2]	**Mean stimulant dose (mg)**	**Mean stimulant dose (mg/kg)**	**No additional covariate**	**Stimulant dose (mg/kg) controlled**	**MPH (vs AMP) controlled**	**α-Agonist controlled**	**Neuroleptic, diphenhydramine, benzodiazepine PRN controlled**	**Days since admitted controlled**	**Reason for PRN controlled**
No stimulant	96 / 17	—	—	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4
Immediate-release	122 / 24	32.7[a]	0.98[a]	69.8[b]	68.0[b]	68.2[b]	67.5[b]	66.8[b]	68.8	68.5
Extended-release	187 / 32	47.6[a]	1.35[a]	52.7[ab]	50.4[ab]	50.8[ab]	50.4[ab]	49.8[ab]	54.0[a]	54.1
No stimulant	96 / 17	—	—	72.4	72.4	72.4	72.4	72.4	72.4	72.4
Short-acting	29 / 7	25.9[a]	0.70[a]	72.0	70.9	68.8	68.3	71.4	70.3	62.9
Long-acting	280 / 37	44.1[a]	1.28[a]	59.2	57.2	52.1	56.2	57.0	60.4	59.6
No stimulant	96 / 17	—	—	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4[a]	72.4
Immediate-release										
short	29 / 7	25.9[a]	0.70[a]	74.2	72.6	73.1	71.2	72.9	72.4	64.1
long	93 / 20	33.3[b]	1.03[b]	72.3[b]	69.7[b]	70.0[b]	70.1[b]	69.5[b]	71.3[b]	70.5[a]
Extended-release	187 / 32	47.6[ab]	1.35[ab]	53.2[ab]	50.2[ab]	51.0[ab]	50.8[ab]	50.3[ab]	54.5[ab]	54.8[a]

Note: Statistical significance: superscript letter "a" identifies 2 means that differ significantly ($p < .05$, with no adjustment for multiple comparisons); similarly, superscript "b" identifies 2 means that differ significantly. In the fourth column, for example, 72.4 is significantly greater than 52.7 (share "a") and, similarly, 69.8 is significantly greater than 52.7 (share "b"); superscript "ab" indicates that 52.7 differs significantly from the 2 other means. AMP = amphetamine; MPH = methylphenidate; PRN = pro re nata.

[1]All estimates of mean time to calm adjust for standing dose of neuroleptic (risperidone dose equivalent), time of day of the outburst, plus the factor listed in the column heading.

[2]The number of outbursts sums to 405; the number of children sums to more than 47 because some children were on different stimulant regimens at the time of different outbursts.

TABLE 4 Association of Stimulant Duration and Formulation With Time to Calm, Stratified by Type of Outburst

		Adjusted mean time to calm (min)[2]		
		Type of outburst		
	No. outbursts /no. children[1]	Aggression (n = 247)	Irritable without aggression (n = 62)	Crying or stress (n =33)
No stimulant	87 / 13	86.9[abcde]	36.1[b]	27.3[d]
Immediate-release	101 / 23	75.9[fgh]	54.3	48.7
Extended-release	154 / 32	57.0[af]	52.8[cg]	41.8[eh]
No stimulant	87 / 13	87.0[abcde]	34.5[b]	27.0[d]
Short-acting	22 / 6	67.1	64.0	Never occurs
Long-acting	233 / 36	64.6[af]	52.3[c]	44.1[ef]
No stimulant	87 / 13	86.5[abcdef]	35.7[b]	26.9[e]
Immediate-release				
Short	22 / 6	67.9	65.1	Never occurs
Long	79 / 19	78.8[ghj]	52.7[c]	49.0
Extended-release	154 / 32	57.1[ag]	53.0[dh]	41.9[fj]

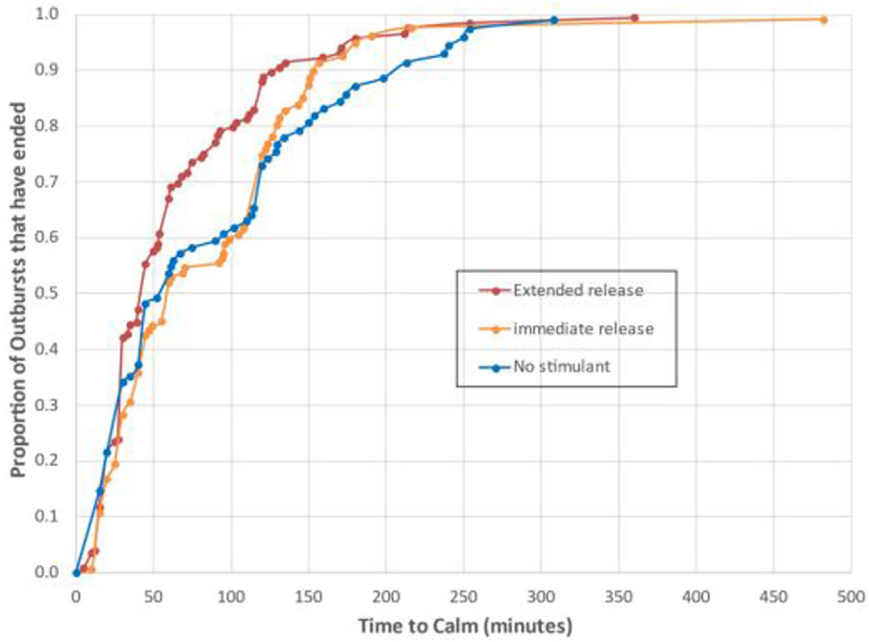
Note: Statistical significance: superscript letter "a" identifies 2 means that differ significantly (p < .05, with no adjustment for multiple comparisons); similarly, superscript "b" identifies 2 means that differ significantly, and the same for superscripts "c" through "j." In the first 3 rows, for example, 86.9 is significantly greater than 57.0 (share "a"), 36.1 (share "b"), 52.8 (share "c"), etc.

[1]*The number of outbursts sums to 342; the number of children sums to more than 47 because some children were on different stimulant regimens at the time of different outbursts.*

[2]*Estimates of mean time to calm adjust for neuroleptic dosage (risperidone dose equivalent) and time of day of the outburst.*

duration of action, may be important not only for ease of use but also for emotion regulation. Although there are several reports demonstrating that short- and long-acting MPH formulations are equivalent to each other in terms of efficacy for treating the core symptoms of ADHD,[41,44,45] we are unaware of data specifically for treating aggression,

FIGURE 1 Kaplan–Meier Curves for Time to Calm of Outbursts When the Child Is On an Extended-Release Stimulant, an Immediate-Release Stimulant, or No Stimulant



and as thorough as the published systematic reviews and network meta-analyses comparing the efficacy and tolerability of pharmacological interventions for ADHD[19,20] are, even they do not examine ER vs IR, emotional symptoms, or aggression.

Our observations need replication, as there are clearly many limitations to this naturalistic study. It was not randomized or controlled. Data were from a single child inpatient unit, potentially limiting generalizability to other ages or settings. One child psychiatrist (L.M.S.) made final treatment decisions, which is both a limitation and a strength. Although there were many outbursts, they represent comparatively few children. Unlike a previous study,[8,46] there was no dedicated person measuring outburst duration. When the inpatient unit was particularly busy and many children were agitated, precise nurse coding of TTC1 could not be guaranteed. The BARS data, however, were very consistent with nursing notes that recorded the child's status after medication was given and whether and when the nurses thought that the medication was effective.

This study specifically examined the effect of stimulant medication on outburst duration, not occurrence or frequency. PRN medication delineated particularly severe outbursts, but there were likely equally severe outbursts that went untreated, especially if they resolved relatively quickly. However, these were not recorded. Therefore, by studying only medicated outbursts, we have probably overestimated the average outburst duration of all outbursts, albeit probably not the aggressive ones.

Better measures of severity of outbursts and medication effectiveness are needed to account for levels of anger, agitation or distress. Both the BARS[35] and the Positive and Negative Syndrome Scale—Excitement Component (PANSS-EC),[47] the measures used in adult studies, were developed to be used with intramuscular medication, for which a drug effect can perhaps be seen more quickly. Greater precision, however, might be obtained from a wearable device that is able to record when the agitation episode starts, when it stops, and how severe it becomes.

The current consensus for treatment of ADHD and co-occurring irritability/aggression/dysregulation is to optimize the child's stimulant medication. Unfortunately, there is no available guidance for using one stimulant medication over another, nor for dosing or choice of formulation. Recourse for the next steps when stimulants are insufficient is also inadequate. Finally, we cannot answer the question of whether we should cease using immediate-release stimulants in children with outbursts. Although data from this study suggest that extended-release stimulants shorten the duration of outbursts, the data were analyzed by outburst, not by child. To answer the question of comparative stimulant effectiveness on outburst duration by child would have required restricting analyses to the 10 children who had outbursts while not on a stimulant and then when taking a stimulant, and/or restricting the analysis to those who had both 1 or more outbursts while on an immediate-release stimulant and also 1 or more outbursts while on an extended-release stimulant, ideally with enough outbursts for each to be able to reliably estimate the differences in time to calm. Ideally, each child would be randomly assigned, in a 3-way cross-over design, to a period of time on no stimulant, a period of time on an immediate-release stimulant, and a period of time on an extended-release stimulant. The present analyses are based on observational data that should be viewed as suggesting what we might expect to find in such a randomized trial. In practice, there are numerous considerations that go into deciding what kind of stimulant medication and preparation a child should be prescribed. The present findings simply support 1 of the ways in which stimulant medication may help emotion dysregulation in some children with ADHD and outbursts.

In conclusion, it is incumbent on us to discover not only how and when stimulants work, but also what makes young people with ADHD and outbursts treatment resistant. Do they differ in severity, in medication response, or is there something else that distinguishes children with ADHD who are extremely volatile with deficits in their frustration tolerance and regulatory skills? We are hampered by our lack of consensus on terminology, rating scales that measure actual aggression, and a way to classify outbursts and the children who have them. We have reported elsewhere, based on a similar sample, that disruptive mood dysregulation disorder did not resolve the diagnostic issue of outbursts.[48] Before we can develop good treatments, we need to determine whether there is a subtype of ADHD with dysregulation,[49] another diagnosis that captures reactive aggression,[50] or if we should use *International Classification of Diseases Eleventh Revision* (*ICD-11*) R code modifiers until the diagnostic question is solved.[3] It may be that each of these is necessary.

This article is part of a special series devoted to addressing aggressive behavior as a focus of psychiatric attention and how its manifestations and treatment needs may vary across psychiatric disorders. The series is edited by Guest Editor Joseph Blader, PhD, Deputy Editor Robert Findling, MD, MBA, and Editor Manpreet K. Singh, MD, MS.

Accepted January 12, 2024.

Lauren M. Spring, Joseph E. Schwartz, and Gabrielle A. Carlson are with the Renaissance School of Medicine at Stony Brook University, Stony Brook, New York.

The authors have reported no funding for this work.

Joseph E. Schwartz served as the statistical expert for this research.

Author Contributions
Conceptualization: Spring, Carlson
Data curation: Spring, Carlson
Formal analysis: Schwartz, Carlson
Investigation: Carlson
Methodology: Spring, Carlson
Project administration: Spring
Supervision: Spring, Carlson
Visualization: Carlson
Writing — original draft: Spring, Schwartz, Carlson
Writing — review and editing: Schwartz, Carlson

Disclosure: Lauren M. Spring, Joseph E. Schwartz, and Gabrielle A. Carlson have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Lauren M. Spring, MD, Department of Psychiatry & Behavioral Health, Stony Brook Medicine, Health Sciences Tower, T-10101 Nicolls Rd., Stony Brook, NY 11794-8101; e-mail: Lauren.Spring@Stonybrookmedicine.edu

2949-7329/© 2024 The Author(s). Published by Elsevier Inc. on behalf of American Academy of Child & Adolescent Psychiatry. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jaacop.2024.01.002

REFERENCES

1. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry. 2003;160(3):430-437. https://doi.org/10.1176/appi.ajp.160.3.430
2. Leibenluft E. Pediatric irritability: a systems neuroscience approach. Trends Cogn Sci. 2017;21(4):277-289. https://doi.org/10.1016/j.tics.2017.02.002
3. Carlson GA, Singh MK, Amaya-Jackson L, *et al*. Narrative review: impairing emotional outbursts: what they are and what we should do about them. J Am Acad Child Adolesc Psychiatry. 2023;62(2):135-150. https://doi.org/10.1016/j.jaac.2022.03.014
4. Copeland WE, Brotman MA, Costello EJ. Normative irritability in youth: developmental findings from the Great Smoky Mountains Study. J Am Acad Child Adolesc Psychiatry. 2015;54(8):635-642. https://doi.org/10.1016/j.jaac.2015.05.008
5. Farquharson Wt, Schwartz JE, Klein DN, Carlson GA. Factors associated with police bringing children to a psychiatric emergency room. Psychiatr Serv. 2023;74(5):488-496. https://doi.org/10.1176/appi.ps.202200028
6. Spring L, Carlson GA. The phenomenology of outbursts. Child Adolesc Psychiatr Clin N Am. 2021;30(2):307-319. https://doi.org/10.1016/j.chc.2020.10.003
7. Evans SC, Corteselli KA, Edelman A, Scott H, Weisz JR. Is Irritability a Top Problem in Youth Mental Health Care? A Multi-informant, Multi-method Investigation. Child Psychiatry Hum Dev. 2023;54(4):1027-1041. https://doi.org/10.1007/s10578-021-01301-8
8. Carlson GA, Potegal M, Margulies D, Gutkovich Z, Basile J. Rages—what are they and who has them? J Child Adolesc Psychopharmacol. 2009;19(3):281-288. https://doi.org/10.1089/cap.2008.0108
9. Blader JC. Attention-deficit hyperactivity disorder and the dysregulation of emotion generation and emotional expression. Child Adolesc Psychiatr Clin N Am. 2021;30(2):349-360. https://doi.org/10.1016/j.chc.2020.10.005
10. Faraone SV, Rostain AL, Blader J, *et al*. Practitioner review: emotional dysregulation in attention-deficit/hyperactivity disorder—implications for clinical recognition and intervention. J Child Psychol Psychiatry. 2019;60(2):133-150. https://doi.org/10.1111/jcpp.12899
11. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014;171(3):276-293. https://doi.org/10.1176/appi.ajp.2013.13070966
12. Cardinale EM, Freitag GF, Brotman MA, Pine DS, Leibenluft E, Kircanski K. Phasic vs tonic irritability: differential associations with attention-deficit/hyperactivity disorder symptoms. J Am Acad Child Adolesc Psychiatry. 2021;60(12):1513-1523. https://doi.org/10.1016/j.jaac.2020.11.02
13. Eyre O, Langley K, Stringaris A, Leibenluft E, Collishaw S, Thapar A. Irritability in ADHD: associations with depression liability. J Affect Disord. 2017;215:281-287. https://doi.org/10.1016/j.jad.2017.03.050
14. Connor DF, Newcorn JH, Saylor KE, *et al*. Maladaptive aggression: with a focus on impulsive aggression in children and adolescents. J Child Adolesc Psychopharmacol. 2019;29(8):576-591. https://doi.org/10.1089/cap.2019.0039
15. Jensen PS, Youngstrom EA, Steiner H, *et al*. Consensus report on impulsive aggression as a symptom across diagnostic categories in child psychiatry: implications for medication studies. J Am Acad Child Adolesc Psychiatry. 2007;46(3):309-322. https://doi.org/10.1097/chi.0b013e31802f1454
16. Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. Can J Psychiatry. 2015;60(2):42-51. https://doi.org/10.1177/070674371506000202
17. Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni RH Jr. Psychopharmacology and aggression. I: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. J Am Acad Child Adolesc Psychiatry. 2002;41(3):253-261. https://doi.org/10.1097/00004583-200203000-00004
18. Pappadopulos E, Woolston S, Chait A, Perkins M, Connor DF, Jensen PS. Pharmacotherapy of aggression in children and adolescents: efficacy and effect size. J Can Acad Child Adolesc Psychiatry. 2006;15(1):27-39.
19. Catala-Lopez F, Hutton B, Nunez-Beltran A, *et al*. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: a systematic review with network meta-analyses of randomised trials. PLoS One. 2017;12(7):e0180355. https://doi.org/10.1371/journal.pone.0180355
20. Cortese S, Adamo N, Del Giovane C, *et al*. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5(9):727-738. https://doi.org/10.1016/S2215-0366(18)30269-4
21. Baweja R, Waxmonsky JG. Updates in pharmacologic strategies for emotional dysregulation in attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am. 2022;31(3):479-498. https://doi.org/10.1016/j.chc.2022.02.003
22. Breaux R, Baweja R, Eadeh HM, *et al*. Systematic review and meta-analysis: pharmacological and nonpharmacological interventions for persistent nonepisodic irritability. J Am Acad Child Adolesc Psychiatry. 2023;62(3):318-334. https://doi.org/10.1016/j.jaac.2022.05.012
23. Fernandez de la Cruz L, Simonoff E, McGough JJ, Halperin JM, Arnold LE, Stringaris A. Treatment of children with attention-deficit/hyperactivity disorder (ADHD) and irritability: results from the Multimodal Treatment Study of Children with ADHD (MTA). J Am Acad Child Adolesc Psychiatry. 2015;54(1):62-70. https://doi.org/10.1016/j.jaac.2014.10.006
24. Galanter CA, Carlson GA, Jensen PS, *et al*. Response to methylphenidate in children with attention deficit hyperactivity disorder and manic symptoms in the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder titration trial. J Child Adolesc Psychopharmacol. 2003;13(2):123-136. https://doi.org/10.1089/104454603322163844
25. Galanter CA, Pagar DL, Davies M, *et al*. ADHD and manic symptoms: diagnostic and treatment implications. Clin Neurosci Res. 2005;5(5-6):283-294. https://doi.org/10.1016/j.cnr.2005.09.008
26. Althoff RR, Ayer LA, Rettew DC, Hudziak JJ. Assessment of dysregulated children using the Child Behavior Checklist: a receiver operating characteristic curve analysis. Psychol Assess. 2010;22(3):609-617. https://doi.org/10.1037/a0019699
27. Waxmonsky J, Pelham WE, Gnagy E, *et al*. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. J Child Adolesc Psychopharmacol. 2008;18(6):573-588. https://doi.org/10.1089/cap.2008.065
28. Waxmonsky JG, Waschbusch DA, Belin P, *et al*. A randomized clinical trial of an integrative group therapy for children with severe mood dysregulation. J Am Acad Child Adolesc Psychiatry. 2016;55(3):196-207. https://doi.org/10.1016/j.jaac.2015.12.011
29. Aman MG, Bukstein OG, Gadow KD, *et al*. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? J Am Acad Child Adolesc Psychiatry. 2014;53(1):47-60. https://doi.org/10.1016/j.jaac.2013.09.022
30. Blader JC, Pliszka SR, Kafantaris V, *et al*. Stepped treatment for attention-deficit/hyperactivity disorder and aggressive behavior: a randomized, controlled trial of adjunctive risperidone, divalproex sodium, or placebo after stimulant medication optimization. J Am Acad Child Adolesc Psychiatry. 2021;60(2):236-251. https://doi.org/10.1016/j.jaac.2019.12.009
31. Gadow KD, Arnold LE, Molina BS, *et al*. Risperidone added to parent training and stimulant medication: effects on attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and peer aggression. J Am Acad Child Adolesc Psychiatry. 2014;53(9):948-959. https://doi.org/10.1016/j.jaac.2014.05.008
32. Childress AC, Sallee FR. Emotional lability in patients with attention-deficit/hyperactivity disorder: impact of pharmacotherapy. CNS Drugs. 2015;29(8):683-693. https://doi.org/10.1007/s40263-015-0264-9

33. Carlson GA, Spring L, Schwartz JE. Does pro re nata oral medication shorten outburst duration in children? J Am Acad Child Adolesc Psychiatry. 2022;61(2):111-114. https://doi.org/10.1016/j.jaac.2021.09.415
34. Kaufman AS, Kaufman NL. Kaufman Test of Educational Achievement. Third Edition ed. Pearson Assessments; 2014.
35. Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. Validation of the Behavioural Activity Rating Scale (BARS): a novel measure of activity in agitated patients. J Psychiatr Res. 2002;36(2):87-95. https://doi.org/10.1016/s0022-3956(01)00052-8
36. Barzman DH, DelBello MP, Forrester JJ, Keck PE Jr, Strakowski SM. A retrospective chart review of intramuscular ziprasidone for agitation in children and adolescents on psychiatric units: prospective studies are needed. J Child Adolesc Psychopharmacol. 2007;17(4):503-509. https://doi.org/10.1089/cap.2007.5124
37. Jangro WC, Preval H, Southard R, Klotz SG, Francis A. Conventional intramuscular sedatives vs ziprasidone for severe agitation in adolescents: case-control study. Child Adolesc Psychiatry Ment Health. 2009;3(1):9. https://doi.org/10.1186/1753-2000-3-9
38. Weisler RH. Safety, efficacy and extended duration of action of mixed amphetamine salts extended-release capsules for the treatment of ADHD. Expert Opin Pharmacother. 2005;6(6):1003-1018. https://doi.org/10.1517/14656566.6.6.1003
39. Leucht S, Samara M, Heres S, Davis JM. Dose equivalents for antipsychotic drugs: the DDD method. Schizophr Bull. 2016;42(Suppl 1):S90-S94. https://doi.org/10.1093/schbul/sbv167
40. Katzman MA, Sternat T. A review of OROS methylphenidate (Concerta((R))) in the treatment of attention-deficit/hyperactivity disorder. CNS Drugs. 2014;28(11):1005-1033. https://doi.org/10.1007/s40263-014-0175-1
41. Pelham WE, Gnagy EM, Burrows-Maclean L, *et al*. Once-a-day Concerta methylphenidate vs three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107(6):E105. https://doi.org/10.1542/peds.107.6.e105
42. Pelham WE, Aronoff HR, Midlam JK, *et al*. A comparison of ritalin and adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics. 1999;103(4):e43. https://doi.org/10.1542/peds.103.4.e43
43. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073-1086. https://doi.org/10.1001/archpsyc.56.12.1073
44. Durand-Rivera A, Alatorre-Miguel E, Zambrano-Sanchez E, Reyes-Legorreta C. Methylphenidate efficacy: immediate vs extended release at short term in Mexican Children with ADHD assessed by Conners scale and EEG. Neurol Res Int. 2015;2015:207801. https://doi.org/10.1155/2015/207801
45. Banaschewski T, Coghill D, Santosh P, *et al*. Long-acting medications for the hyperkinetic disorders. a systematic review and European treatment guideline. Eur Child Adolesc Psychiatry. 2006;15(8):476-495. https://doi.org/10.1007/s00787-006-0549-0
46. Carlson GA, Potegal M, Margulies D, Basile J, Gutkovich Z. Liquid risperidone in the treatment of rages in psychiatrically hospitalized children with possible bipolar disorder. Bipolar Disord. 2010;12(2):205-212. https://doi.org/10.1111/j.1399-5618.2010.00793.x
47. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-276. https://doi.org/10.1093/schbul/13.2.261
48. Margulies DM, Weintraub S, Basile J, Grover PJ, Carlson GA. Will disruptive mood dysregulation disorder reduce false diagnosis of bipolar disorder in children? Bipolar Disord. 2012;14(5):488-496. https://doi.org/10.1111/j.1399-5618.2012.01029.x
49. Karalunas SL, Gustafsson HC, Fair D, Musser ED, Nigg JT. Do we need an irritable subtype of ADHD? Replication and extension of a promising temperament profile approach to ADHD subtyping. Psychol Assess. 2019;31(2):236-247. https://doi.org/10.1037/pas0000664
50. Stepanova E, Langfus JA, Youngstrom EA, *et al*. Finding a needed diagnostic home for children with impulsive aggression. Clin Child Fam Psychol Rev. 2023;26(1):259-271. https://doi.org/10.1007/s10567-022-00422-3