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Stimulant-Responsive and Stimulant-Refractory Aggressive Behavior Among Children with ADHD

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Abstract

OBJECTIVES—The objective of this study was to examine factors that are associated with aggression that is responsive versus refractory to individualized optimization of stimulant monotherapy among children with attention-deficit/hyperactivity disorder (ADHD).

METHODS—Children who were aged 6 to 13 years and had ADHD, either oppositional defiant disorder or conduct disorder, significant aggressive behavior, and a history of insufficient response to stimulants completed an open stimulant monotherapy optimization protocol. Stimulant titration with weekly assessments of behavior and tolerability identified an optimal regimen for each child. Families also received behavioral therapy. Parents completed the Retrospective-Modified Overt Aggression Scale (R-MOAS) at each visit. Children were classified as having stimulant-refractory aggression on the basis of R-MOAS ratings and clinician judgment. Differences that pertained to treatment, demographic, and psychopathology between groups with stimulant monotherapy–responsive and –refractory aggression were evaluated.

RESULTS—Aggression among 32 (49.3%) of 65 children was reduced sufficiently after stimulant dosage adjustment and behavioral therapy to preclude adjunctive medication. Those who responded to stimulant monotherapy were more likely to benefit from the protocol's methylphenidate preparation (once-daily, triphasic release), showed a trend for lower average dosages, and received fewer behavioral therapy sessions than did children with stimulant-refractory aggression. Boys,

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especially those with higher ratings of baseline aggression and of depressive and manic symptoms, more often exhibited stimulant-refractory aggression.

CONCLUSIONS—Among children whose aggressive behavior develops in the context of ADHD and of oppositional defiant disorder or conduct disorder, and who had insufficient response to previous stimulant treatment in routine clinical care, systematic, well-monitored titration of stimulant monotherapy often culminates in reduced aggression that averts the need for additional agents.

Keywords

attention deficit and disruptive behavior disorders; aggression; drug therapy; clinical trial

Psychostimulant medication has long been the mainstay for the effective management of attention-deficit/hyperactivity disorder (ADHD).^{1,2} Stimulant therapy also often ameliorates comorbid disruptive behavior problems^{3,4}; however, the use of antipsychotic agents for severe disruptive behaviors that frequently occur with ADHD, such as aggression, has proliferated.^{5–7} The high incidence and severity of antipsychotic-induced adverse effects among children have made such widespread use a growing concern.^{8–10}

Pharmacotherapy guidelines for ADHD with aggression propose beginning stimulant and behavioral treatments and adding antipsychotic medication only when aggression persists.¹¹ In practice, however, several factors may hasten the initiation of antipsychotic treatment and the premature conclusion or avoidance of stimulant monotherapy: (1) It is unclear how clinicians should establish that aggressive behavior is refractory to stimulant medication alone. (2) It is unknown how frequently stimulant monotherapy promotes remission of severe aggressive behavior among children with ADHD. This uncertainty may undermine the clinician's confidence that protracted efforts to optimize stimulant treatment will prove fruitful. Previous studies that suggested stimulant efficacy for aggression emphasized reductions in rating scale scores of broad-spectrum disruptive symptoms rather than meaningful decreases in aggression per se.⁴ Similarly, previous stimulant trials did not select patients on the basis of severity of pretreatment aggressive behavior. (3) The irritability and brittle anger control that impulsive aggressive children typically show^{12–14} have drawn attention as possible heralds of mood disturbances, such as bipolar spectrum disorders, for which clinicians often prescribe antipsychotic medications and avoid stimulants.^{15–17}

This study addressed these unresolved issues on appropriate stimulant treatment for ADHD that is accompanied by serious aggression among preadolescents. To furnish guidance on stimulant monotherapy that distinguishes responsive from refractory outcomes, we implemented a systematic titration protocol that endeavored to optimize each child's stimulant regimen. To evaluate how frequently serious aggression abates to a clinically meaningful extent, (1) inclusion criteria required that children demonstrate marked, persistent aggressive behavior; (2) aggressive behavior assessment was unalloyed by other disruptive symptoms; and (3) the primary outcome was diminution of aggression so that additional medication was unnecessary. To examine whether mood-relevant symptoms affected stimulant effectiveness, we evaluated whether baseline indices of mood disturbance portended insufficient response.

METHODS

Study Design

Patients participated in the stimulant-optimization lead-in phase to a controlled trial of adjunctive medications for aggressive children with ADHD.¹⁸ This phase endeavored to determine each child's most effective, best tolerated stimulant regimen. Children whose aggression persisted were eligible for the controlled trial. The institutional review boards of

the 2 clinical sites approved the study. Parents or legal guardians provided written informed consent, and children who were older than 8 years gave written assent.

Patients

Inclusion criteria required that boys and girls between the ages of 6 and 13 fulfill (1) diagnostic criteria for ADHD, (2) criteria for oppositional defiant disorder (ODD) or conduct disorder (CD), and (3) obtain parent-reported ratings of clinically significant aggression (per the Retrospective–Modified Overt Aggression Scale [R-MOAS], described in the next section). Eligibility required previous stimulant treatment at a minimum methylphenidate (MPH) dosage of 30 mg/day or equivalent with insufficient response. This criterion sought to exclude individuals with robust responses to initial treatment, for whom the issue of trial persistence versus alternative pharmacotherapy is moot. Stimulant-naïve patients with ADHD are also more apt to show improvements with placebo treatment.¹⁹

Exclusion criteria comprised major depression, bipolar disorder, Tourette syndrome, psychotic disorders, pervasive developmental disorder, mental retardation, and aggressive behavior arising chiefly as a complication of an anxiety disorder (eg, behavioral dys-control only when others interfered with rituals for a child with obsessive-compulsive disorder), contraindications to stimulant treatment, seizure disorders, and pregnancy.

Evaluation Procedures and Measures

Diagnostic evaluation used the Schedule of Affective Disorders and Schizophrenia for School-Age Children (Kiddie)-SADS²⁰, which a clinical child psychologist administered. A child and adolescent psychiatrist conducted a separate clinical diagnostic evaluation. The K-SADS interviewer and clinical assessor conferred to arrive at consensus diagnoses.

Aggressive behavior was assessed by the parent-completed Modified Overt Aggression Scale (R-MOAS)²¹ adapted to acquire retrospective reports covering the preceding week. Parents rate the frequency of 16 aggressive behaviors in 4 areas: verbal aggression; physical aggression toward others; aggression toward oneself; and destruction or hostile misuse of property. Numeric weighting amplifies the seriousness of more harmful behaviors in the total score (eg, physical aggression items garner higher scores than verbal). Parents completed the R-MOAS at baseline and each study visit. Reliability and validity are summarized elsewhere.¹⁸ The R-MOAS, annotated to show scoring, is published as supporting information at Supplemental Information. A baseline score of 24 was required for enrollment.

ADHD symptom severity was quantified by parents' completion of the Conners' Global Index²² (ConnGI-P), which yielded age- and gender-referenced *T* scores for its restless-inattentive subscale. Because the ConnGI-P total score includes the emotional lability subscale, it would have confounded ADHD symptoms with aggression-related difficulties.

Two measures that were administered at baseline evaluated affective symptoms. The Child Depression Rating Scale–Revised (CDRS-R)²³ generates an overall score that is based on parent and child interviews. The Young Mania Rating Scale (YMRS)²⁴ yields clinician ratings for symptoms and associated features of mania. Although major depression and mania were exclusion criteria, these scales permitted analyses concerning the predictive value of subsyndromal affective symptoms for stimulant mono therapy response. Parents completed the Barkley Behavior and Adverse Events Questionnaire–Modified²⁵ (BBAEQ-M) at baseline and each study visit, providing systematic assessment of adverse effects to augment open-ended inquiries.

Stimulant Titration and Treatment Protocol

Children discontinued nonstimulant psychopharmacotherapy with tapering as appropriate to the compound's elimination time course. Children who were taking stimulant medications before enrollment also discontinued this treatment without tapering so that it could be supplanted by the stimulant titration protocol of this study.

Titration procedures resembled those used in other studies that undertook to optimize each child's regimen.^{26–28} Key features were weekly dosage adjustments that took into account rating scale assessment of ADHD symptoms (ConnGI-P, restless-inattentive sub-scale), aggressive behavior (R-MOAS), and adverse effects (BBAEQ-M). When possible, we acquired behavioral ratings from teachers to aid in dosage selection, but inconsistent availability made teacher ratings unsuitable as a study outcome. Parents and children met with investigators weekly to review behavioral and health status and to obtain weight, height, blood pressure, and heart rate. These response and tolerability data guided decisions on adjustment of the child's stimulant dosage for the succeeding week, as described next.

Stimulant monotherapy began with a triphasic-release MPH (MPH-TRI) preparation given once daily (Concerta [Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ]). It is the MPH preparation with the longest duration of action, and, consequently, best resembles the regimens used in previous optimization protocols.^{26–28}

Determination of optimal MPH-TRI dosage ordinarily involved increments from an 18-mg starting dose given shortly after waking but no later than 8:30 AM until (1) there was no room for additional symptomatic improvement, (2) unmanageable or intolerable adverse effects emerged, or (3) a ceiling dosage of 90 mg/day was attained. When 1 of these events occurred, the study physician and a child psychologist reviewed behavioral and tolerability data from preceding weeks to identify the best tolerated dosage associated with greatest overall improvement in ADHD symptoms and aggression. MPH-TRI dosage adjustments were ordinarily in 18-mg increments, but clinicians had discretion to adjust MPH-TRI dosage by 9-mg increments (eg, for children with small stature; when previous history evoked tolerability concerns). When 2 dosage levels yielded similar results, the lower dosage was selected.

Children who experienced problems with sleep, nutrition, or other tolerability issues related to the long duration of action of MPH-TRI but who displayed symptomatic benefit during the day were switched to a biphasic-release MPH preparation (MPH-BI; Metadate CD [UCB, Smyrna, GA]). Starting MPH-BI dosages were ~60% of the effective MPH-TRI dosage. Subsequent dosage adjustments occurred in 10-mg increments/decrements each week on the basis of response and tolerability, to a maximum dosage of 60 mg/day. Candidate regimens for most effective, best tolerated treatment included MPH-TRI dosages the child had previously (viz, MPH-BI may have yielded substantially less benefit than a tolerated dosage of MPH-TRI).

Children who gained little or no symptomatic improvement of ADHD symptoms with MPH could be switched to mixed amphetamine salts, administered once daily as a biphasic-release preparation (Adderall XR [Shire Pharmaceuticals, Wayne, PA]). Starting dosage was approximately one-third of the MPH-TRI dosage or half of the MPH-BI dosage. Subsequent weekly adjustments were by 5-mg increments/decrements but did not exceed a total of 35 mg/day.

The regimen identified as optimal was continued or reinstated for a replication week. When observation during that week confirmed it as the child's optimal dosage, another week elapsed before the stimulant end-point assessment. When behavioral response during the replication week was worse than the response observed previously, additional adjustment to dosage or

agent was permitted until optimal response was again evident and replicated, followed by the end-point assessment.

Concurrent Psychosocial Treatment

All families had behaviorally-oriented psychosocial treatment throughout the trial. Its purposes were (1) to reduce out-come variance from differences in participants' previous exposure to psychosocial interventions, (2) to provide behavioral treatment so that children whose aggression diminished did not go on to additive pharmacotherapy, and (3) to offer individualized support to families. Treatment content was the Community Parent Education (COPE) program,²⁹ modified for incorporation into clinical trials for children with ADHD.³⁰ Advanced graduate students in clinical child psychology provided this treatment.

Response Determination

At the end-point assessment, children who completed the stimulant-optimization phase with R-MOAS scores of < 16 (representing at least a 33% decrease from baseline) were categorized as stimulant monotherapy responders. Previous work with this measure indicated that scores of < 17 were associated with no more than minimal aggressive behavior medication.¹⁸ Those who scored > 16 were classified as refractory, reflecting the persistence of aggressive behavior even though reductions in both aggression and ADHD symptoms from baseline may have occurred.

Data Analysis

Analyses of variance and χ^2 tests compared response groups on demographic and clinical variables. Because the distribution of R-MOAS scores was positively skewed, analyses of variance used the natural logarithm of R-MOAS raw scores. We determined effect sizes for each group's change in aggression (R-MOAS) and ADHD symptom (ConnGI-P) severity by using Dunlap's³¹ method to compute Cohen's *d* for repeated-measures data (d_{corr}).

Logistic regression analyses evaluated child characteristics as predictors of response status. Bivariate associations were calculated between each predictor and outcome, followed by an adjusted model that incorporated all candidate predictors.

Tolerability and adverse effect analyses considered each item of the BBAEQ-M. Items were dichotomized whereby scores of >4, representing moderate severity, counted as positive. χ^2 tests compared the outcome status groups on each with no correction for multiple tests.

RESULTS

Participant Sample

Figure 1 presents the disposition of all 304 initial screenings for this study. Table 1 contains demographic and clinical characteristics of the 65 children (50 boys, 15 girls; mean age: 8.95 years, [SD]: 2.48 years) who started the trial and participated in subsequent assessments to determine their stimulant treatment response.

Changes in Aggression and ADHD Symptoms During Stimulant Treatment

The period between baseline evaluation and final evaluation of stimulant monotherapy response averaged 63.26 days (SD: 23.98 days).

At the end of the stimulant-optimization procedures, 32 (49.3%) of 65 children (95% confidence interval: 37.3%–51.3%) fulfilled response criteria. Figure 2 presents the

distributions of baseline and end-of-stimulant evaluation R-MOAS scores for the whole sample and for outcome status subgroups (responsive versus refractory aggression).

Table 2 shows the means of behavioral measures for aggression response groups and the effect size for changes between baseline and post treatment assessments. The effect size for the reduction in mean R-MOAS scores during the stimulant treatment phase was >5 times as large among the responders as among children whose aggressive behavior was stimulant refractory. Nonetheless, the mean change over time for the latter group was statistically significant.

Children in both response groups showed significant reductions on ADHD symptoms. The effect size for ADHD improvement ($d_{\text{corr}} = 0.97$) was considerably smaller among those with refractory aggression than among responders ($d_{\text{corr}} = 2.02$).

Treatment Characteristics of Remitter and Refractory Groups

Table 3 shows children's optimized stimulant agents and dosages. Children whose aggression responded during stimulant optimization most often achieved stabilization with MPH-TRI:

84% compared with 49% of the refractory patients ($\chi^2_2 = 9.34$, $P = .002$). The average daily MPH-TRI dosage tended to be higher among patients with refractory than nonrefractory aggression (64 vs 52 mg; $t_{41} = 1.83$, $P = .07$). Families of children with stimulant-refractory aggression had significantly more behavioral therapy sessions than other families (3.06 vs 7.28 sessions; $t_{63} = 4.85$, $P < .01$).

Child Factors Associated With Aggression Outcome

Table 4 contains baseline clinical and demographic variables that were examined through logistic regression for their associations with outcome. Odds ratios when response status was regressed onto each predictor singly are presented. Higher baseline R-MOAS, CDRS-R, and YMRS scores predicted a lower likelihood that aggression would remit. Although few in number ($n=4$), all children who had a diagnosis of depressive disorder, not otherwise specified, were in the stimulant-refractory group (Table 1), although none had a history of manic or hypomanic episodes.

In a combined-variable model (Table 4), higher baseline R-MOAS, CDRS-R, and YMRS ratings made independent contributions toward predicting a lower likelihood of response. However, gender emerged as a significant predictor in the combined model (odds ratio: 8.99 [95% confidence interval: 1.33–60.98]; $\chi^2 = 5.06$, $P = .02$). That is, adjusting for the effects of baseline aggression, depression, and manic symptoms, girls were far more likely to experience remission of aggressive behavior with stimulant medication.

Separate computations of parameters for the combined variable model examined boys and girls. Table 4 presents these gender-stratified results. Higher baseline YMRS and CDRS-R total scores jointly predicted less favorable stimulant response status only for boys. Figure 3 illustrates these associations. Two (20%) of the 10 boys with above-median scores on both the YMRS and the CDRS-R fulfilled response criteria, compared with 7 (87.5%) of the 8 boys who were below the median on both. Children whose aggression did not fulfill response criteria nonetheless demonstrated relative improvements on both aggressive behavior ratings and ADHD symptoms (Tables 2 and 3). No child experienced worsening of mood-relevant symptoms on his or her optimized stimulant regimen.

Tolerability and Adverse Effects

We counted a BBAEQ-M item present when the parent rated it for at least moderate intensity. Table 5 displays adverse effect frequencies that were reported for at least 1 child at either baseline or trial end. Group differences in prevalence were assessed at each assessment time

via χ^2 , with P set liberally at .10. Two sleep-related difficulties, initial insomnia and early waking, were more prevalent at base-line among children who would subsequently show remission of aggression.

DISCUSSION

Within a group of children whose chronic aggressive behavior developed in the context of ADHD with comorbid ODD or CD and whose previous treatment history indicated insufficient response to stimulant medication, nearly half attained remission or near-remission of aggressive behavior by the conclusion of rigorously titrated stimulant monotherapy accompanied by psychosocial treatment. Treatment-refractory aggression did not result from less potent therapy. Stimulant responders tended to have more robust response to the first stimulant agent prescribed and at somewhat lower dosages. The stimulant-refractory group also had more family behavioral therapy sessions. Children whose aggression responded adequately had a mean MPH-TRI dosage of 52.33 mg/day, which approaches the labeled maximum dosage of 54 mg for preadolescents.³² This labeling may deter clinicians from prescribing MPH dosages that this and previous research have shown to be efficacious for this patient group.²⁸

Boys were more likely to have aggression that would prove refractory to stimulant monotherapy, particularly those with higher baseline scores of depressive and manic symptom severity. However, optimized stimulant monotherapy did not induce mania or worsen other symptoms of mood disturbance and, notwithstanding inadequate response of aggression, still culminated in improved ADHD symptoms and relative decreases in aggression.

Determining each child's optimal stimulant regimen involved weekly assessments at varying dosages and switches among preparations as needed, an approach that seems uncommon in primary care settings.³³ A medical claims analysis indicated that 44.27% of children who began stimulant treatment experienced no dosage change in 3 months, and the remainder experienced only a modest average increase that was well below regimens that have been shown to be effective for ADHD symptoms.³³ More intensive and methodical approaches to optimal stimulant agent and dosage identification may reduce the need to resort to antipsychotic treatment for severe aggression and behavioral dys-control among children with ADHD. Current pediatric guidelines articulate clearly the overall principle of stimulant dosage escalation as tolerated to achieve optimal response.³⁴ The results of this study illustrate the viability of tactics to do so for children with ADHD, comorbid ODD or CD, and aggressive behavior.

Controlled trials for childhood ADHD show superiority of stimulants over placebo, but placebo response among an estimated 15% to 20% of patients^{2,19} precludes attribution of benefit solely to direct treatment effects. The eligibility criteria of this study included characteristics that have been shown to reduce placebo response, namely previous stimulant treatment (37% less likely), ADHD subtypes that feature hyperactive/impulsive symptoms (57% less likely), and preadolescent age (36% less).¹⁹ In addition, placebo response among children is generally short-lived,^{27,28} and our classification scheme required at least 3 weeks of subthreshold aggression.

CONCLUSIONS

Stimulant medication is the most common pharmacotherapy for children's mental health problems in primary care. Pediatric providers are well-situated to leverage this treatment to affect the course of not only ADHD but also associated conduct disturbances, including severe aggression. Overcoming systemic barriers to optimize ADHD treatment in primary care³⁵ may

yield faster improvements and obviate the need for additional pharmacotherapy with greater health liabilities.

These findings suggest that impulsivity and affective instability are distinct influences on childhood aggression.¹⁴ Youth with greater affective disturbance were more likely to experience incomplete response to stimulant monotherapy. Understanding the high emotional reactivity that impulsive aggressive youth often display remains a high research priority to improve care of this vulnerable patient population.

WHAT'S KNOWN ON THIS SUBJECT

Although stimulant medications frequently alleviate symptoms of ADHD and related behavioral problems, it is unclear how often and with which regimens stimulant treatment culminates in remission of severe aggressive behavior.

WHAT THIS STUDY ADDS

Among aggressive 6- to 13-year-olds with ADHD and previous insufficient stimulant response, individually optimized stimulant monotherapy and behavioral intervention were associated with reductions in aggression that precluded need for additional medications. Boys with higher affect-related disturbances gained less robust benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ODD	oppositional defiant disorder
CD	conduct disorder
R-MOAS	Retrospective–Modified Overt Aggression Scale
MPH	methylphenidate
K-SADS	Schedule for Schizophrenia and Affective Disorders for School-Age Children
ConnGI-P	Conners Global Index, Parent Version
CDRS-R	Child Depression Rating Scale–Revised
YMRS	Young Mania Rating Scale
BBAEQ-M	Barkley Behavior and Adverse Events Questionnaire–Modified

MPH-TRI	triphasic-release MPH
MPH-BI	biphasic-release MPH

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FIGURE 1.
Consolidated Standard of Reporting Trial (CONSORT) diagram showing disposition of all participants screened.

FIGURE 2.

Distributions of baseline and outcome R-MOAS scores for total sample and stimulant-responsive and stimulant-refractory subgroups. Left column presents baseline values, and right column shows scores at the end of stimulant optimization phase. Top row shows all subjects, middle row children whose aggression remitted with stimulant monotherapy, and the bottom row those whose aggression persisted.

FIGURE 3.
Association between stimulant monotherapy aggression-response status and total baseline scores on the YMRS and the CDRS-R.

TABLE 1

Participants' Baseline Demographic and Clinical Characteristics

Parameter	All Patients (<i>n</i> = 65)	Stimulant Responder Group (<i>n</i> = 32)	Stimulant Refractory Group (<i>n</i> = 33)	Tests for Group Differences
Age, mean (SD), y	8.95 (2.48)	9.52 (2.81)	8.39 (2.00)	$F_{1,63} = 3.40; P = .07$
Male gender, <i>n</i> (%)	50 (77)	25 (78)	25 (76)	NSD
Race/ethnicity				NSD
White	47 (72)	22 (69)	25 (76)	
Hispanic	5 (8)	4 (13)	1 (3)	
Black	8 (12)	4 (13)	4 (12)	
Other	5 (8)	2 (6)	3 (9)	
Guardian's relationship to child, <i>n</i> (%)				NSD
Biological parent	56 (89)	28 (90)	28 (87)	
Adoptive parent	6 (9)	2 (7)	4 (13)	
Grandparent	1 (2)	1 (3)	0 (0)	
Diagnoses in addition to ADHD, <i>n</i> (%)				
ODD	61 (94)	31 (97)	30 (91)	NSD
CD	4 (6)	1 (3)	3 (9)	NSD
Anxiety disorder	19 (29)	12 (38)	7 (21)	NSD
Depressive disorder, not otherwise specified	4 (65)	0 (0)	4 (12)	$\chi^2_1 = 4.13; P = .04$
Behavioral symptom severity, mean (SD)				
CBCL total, T	74.61 (6.67)	73.80 (6.90)	75.91 (6.26)	NSD
CBCL externalizing, T	72.49 (7.71)	71.03 (8.08)	73.91 (7.17)	NSD
CBCL internalizing, T	66.62 (10.62)	65.69 (11.70)	67.52 (9.55)	NSD
ConnGI-P restless/inattentive, T	79.08 (9.05)	77.90 (10.68)	80.15 (7.11)	NSD
R-MOAS total	52.34 (32.53)	44.16 (29.03)	60.27 (34.18)	$F_{1,63} = 4.19; P = .05$

NSD indicates no significant difference; CBCL, Child Behavior Checklist.

TABLE 2

Behavioral Outcomes Open Stimulant Monotherapy

Measure	Aggression Responders (<i>n</i> = 32)			Aggression Refractory Group (<i>n</i> = 33)			Group × Time Interaction	
	Baseline	End Stimulant	Lead-in	Effect	Baseline	End Stimulant		Lead-in
R-MOAS total, mean (SD)	44.16 (29.03)	5.12 (2.05)		$F_{1,31} = 163.78^a$ ES: $d_{\text{corr}} = 2.58$	60.27 (34.18)	46.09 (26.07)		$F_{1,32} = 5.81^b$ ES: $d_{\text{corr}} = 0.46$
ConnGI (restless/impulsive scale)	77.91 (10.68)	56.47 (10.53)		$F_{1,30} = 139.42^a$ ES: $d_{\text{corr}} = 2.02$	80.15 (7.11)	70.39 (11.71)		$F_{1,33} = 21.84^a$ ES: $d_{\text{corr}} = 0.97$
T score, mean (SD)								

ES indicates effect size.

^a $P < .001$.

^b $P < .01$.

TABLE 3

Medication Treatments of Open Stimulant Monotherapy

Pharmacotherapy	Aggression Responders			Aggression Refractory Group		
	n (%)	Mean (SD), mg	Range	n (%)	Mean (SD), mg	Range
MPH-TRI	27 (84.4)	52.33 (18.00)	18–90	16 (48.9)	63.00 (19.16)	36–108
MPH-BI	2 (6.3)	40.00 (14.14)	30–50	4 (12.1)	27.50 (5.00)	20–30
Mixed amphetamine salts, extended release	3 (9.4)	26.67 (11.55)	20–40	12 (36.4)	25.83 (6.69)	15–40
Dextroamphetamine spanules	0 (0)	NA	NA	1 (3.0)	10 (0)	10

NA indicates not applicable.

TABLE 4

Predictors of Aggressive Behavior Remission After Stimulant Trial

Baseline Predictor	Bivariate Associations: Single Predictors with Odds of Response			Combined Predictors Adjusted Model for Odds of Response			Gender-Stratified Combined Models for Odds of Response		
	OR (95% CI)	χ^2	P	OR (95% CI)	χ^2	P	OR (95% CI)	χ^2	P
Age, y	1.210 (0.981–1.502)	3.39	.07	1.032 (0.759–1.400)	0.04	.840			
Male (n = 50)							1.020 (0.710–1.460)	0.01	.92
Female (n = 15)							0.770 (0.320–1.810)	0.37	.54
Gender (female vs male)	0.875 (0.275–2.780)	0.05	.82	8.992 (1.326–60.981)	5.06	.020			
ConnGI, restless/impulsive T score	0.972 (0.920–1.027)	1.02	.32	0.990 (0.910–1.076)	0.06	.810			
Male (n = 50)							0.957 (0.857–1.070)	0.61	.44
Female (n = 15)							1.028 (0.085–1.240)	0.08	.77
R-MOAS	0.983 (0.966–1.000)	4.29	.06	0.971 (0.947–0.994)	5.97	.010			
Male (n = 50)							0.985 (0.960–1.010)	1.14	.26
Female (n = 15)							0.941 (0.870–1.010)	2.55	.11
Child Depression Inventory–Revised, total	0.929 (0.846–1.020)	2.85	.09	0.830 (0.657–0.956)	5.87	.010			
Male (n = 50)							0.788 (0.640–0.970)	5.22	.02
Female (n = 15)							0.778 (0.370–1.620)	0.45	.50
YMRS, total	0.839 (0.722–0.974)	6.24	.01	0.630 (0.526–0.886)	8.21	.004			
Male (n = 50)							0.611 (0.430–0.880)	7.15	.01
Female (n = 15)							0.849 (0.400–1.820)	0.18	.67

TABLE 5

Adverse Effect Rates

Adverse Effect	Baseline				χ^2 (P)	Stimulant Monotherapy End Point				
	Aggression Responder Group		Aggression Refractory Group			Aggression Responder Group		Aggression Refractory Group		
	n	%	n	%		n	%	n	%	
Abdominal pain	1	1	3	9		0	0	1	3	
Anxiety or nervousness	4	15	7	22		4	13	8	26	
Enuresis	2	6	1	3		1	3	1	3	
Bite fingernails	4	15	8	25		4	13	5	16	
Bruises easily	1	3	1	3		1	3	0	0	
Crying	3	11	8	25		3	10	5	16	
Insomnia, initial	6	22	15	47	3.88 (.05)	6	20	11	38	
Decrease appetite	6	22	5	16		3	20	10	32	
Diarrhea	1	3	0	0		1	3	1	3	
Insomnia, middle	2	7	2	9		1	3	3	9	
Dizzy	1	3	2	6		0	0	1	3	
Dry mouth	1	4	3	10		1	3	1	3	
Headache	5	19	1	3	3.80 (.05)	1	3	0	0	
Increase appetite	2	7	4	13		0	0	1	3	
Irritability	10	37	16	50		4	13	12	39	5.07 (.03)
Low energy	3	11	2	7		1	3	1	3	
Nightmares	1		2	6		0	0	2	6	
Rash	1	3	0	0		0	0	1	3	
Restlessness	0	0	0	0		0	0	3	9	3.05 (.09)
Sadness	3	11	7	22		3	10	6	19	
Shaking	1	3	0	0		1	3	1	3	
Stares into space	2	7	3	9		1	3	2	6	
Stomachache	2	7	2	7		2	7	3	10	
Heart races	1	3	1	3		1	3	1	3	
Less talkative	3	11	2	6		2	6	2	6	
Overly talkative	10	37	8	25		3	10	5	16	
Tics	2	6	2	6		2	7	1	3	

Adverse Effect	Baseline				Stimulant Monotherapy End Point			
	Aggression Responder Group		Aggression Refractory Group		Aggression Responder Group		Aggression Refractory Group	
	<i>n</i>	%	<i>n</i>	χ^2 (<i>P</i>)	<i>n</i>	%	<i>n</i>	χ^2 (<i>P</i>)
Tired	1	3	1	3	1	3	1	3
Trouble waking	1	3	0	0	1	3	0	0
Tremors	1	3	0	0	0	0	2	6
Lack of interest	2	6	2	6	1	3	5	16
Unusually happy	3	9	3	9	6	7	6	2.81 (.10)
Early waking	3	11	7	22	3	10	3	9