

Risperidone Added to Parent Training and Stimulant Medication: Effects on Attention-Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, and Peer Aggression

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Objective: In this study, we aimed to expand on our prior research into the relative efficacy of combining parent training, stimulant medication, and placebo (Basic therapy) versus parent training, stimulant, and risperidone (Augmented therapy) by examining treatment effects for attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) symptoms and peer aggression, symptom-induced impairment, and informant discrepancy. **Method:** Children (6–12 years of age; $N = 168$) with severe physical aggression, ADHD, and co-occurring ODD/CD received an open trial of parent training and stimulant medication for 3 weeks. Participants failing to show optimal clinical response were randomly assigned to Basic or Augmented therapy for an additional 6 weeks. **Results:** Compared with Basic therapy, children receiving Augmented therapy experienced greater reduction in parent-rated ODD severity ($p = .002$, Cohen's $d = 0.27$) and peer aggression ($p = .02$, Cohen's $d = 0.32$) but not ADHD or CD symptoms. Fewer children receiving Augmented (16%) than Basic (40%) therapy were rated by their parents as impaired by ODD symptoms at week 9/endpoint ($p = .008$). Teacher ratings indicated greater reduction in ADHD severity ($p = .02$, Cohen's $d = 0.61$) with Augmented therapy, but not for ODD or CD symptoms or peer aggression. Although both interventions were associated with marked symptom reduction, a relatively large percentage of children were rated as impaired for at least 1 targeted disorder at week 9/endpoint by parents (Basic 47%; Augmented 27%) and teachers (Basic 48%; Augmented 38%). **Conclusion:** Augmented therapy was superior to Basic therapy in reducing severity of ADHD and ODD symptoms, peer aggression, and symptom-induced impairment, but clinical improvement was generally context specific, and effect sizes ranged from small to moderate. Clinical trial registration information—Treatment of Severe Childhood Aggression (The TOSCA Study); <http://clinicaltrials.gov/>; NCT00796302. *J. Am. Acad. Child Adolesc. Psychiatry*, 2014;53(9):948–959. **Key Words:** ADHD, risperidone, stimulant drug, aggression, multiple drug therapy



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The use of multiple medications for the clinical management of the same psychiatric disorder or target symptom is generally discouraged in best practices guidelines, particularly drug combinations that involve atypical antipsychotics, because of concerns about weight gain and metabolic syndrome. Conversely, many

clinicians would argue that dual-drug therapy is justifiable in the case of medications with different mechanisms of action or for children who have comorbid conditions that have different pathologies and recommended therapies or who have not responded optimally to conventional mono-drug therapies. Unfortunately, psychiatric symptoms are rarely pathognomonic; boundaries between disorders are often ambiguous; risk factors are generally nonspecific; and etiologies are poorly understood. In the absence of controlled trials demonstrating that multiple drug therapy for the same disorder is harmful, the practice has become commonplace, despite a lack of evidence supporting efficacy for most applications.¹⁻³ A case in point is children with attention-deficit/hyperactivity disorder (ADHD), many of whom have co-occurring oppositional defiant disorder (ODD) or conduct disorder (CD), and in some cases, exhibit clinically severe physical aggression. Not only is this combination of symptoms seriously disabling for the child, but it can have significant consequences for family, school, and community. The clinical management of such patients poses many challenges for clinicians, not the least of which are selecting an appropriate intervention plan and dealing with a host of psychosocial issues.

Stimulant medications are a well-established and highly effective treatment for ADHD symptoms, and there is considerable evidence that they suppress ODD symptoms in children with ADHD and ODD.^{4,5} Moreover, direct observation studies conducted in public school settings indicate that stimulants are highly effective in suppressing a wide range of aggressive behaviors including physical aggression in children with ADHD.^{6,7} Parent training in child behavior management skills is also effective for controlling these same symptoms and behaviors,⁸ and, when used in combination with stimulants, results in even greater therapeutic improvement.^{9,10} Nevertheless, the extraordinary heterogeneity in the ADHD clinical phenotype is widely appreciated, and there is considerable controversy as to whether every child with ADHD who exhibits serious physical aggression can be adequately managed with these treatments either alone or in combination. One common practitioner strategy for child patients who show some benefit with stimulant medication is to add a second drug, such as risperidone.¹ Although research indicates that risperidone is effective for some ADHD symptoms (hyperactivity) in

child patients with autism spectrum disorders (ASD)¹¹ and suppresses a wide range of oppositional/aggressive behaviors in children with disruptive behaviors and below-average IQ,¹² there is very little research into the efficacy of dual-drug therapy or its effect on ADHD, ODD, or CD symptoms among youth without ASD or subaverage IQ. One notable exception is a study of clonidine added to stimulant medication for children with ADHD and co-occurring ODD or CD and elevated T scores (≥ 70) on the Child Behavior Checklist (CBCL)¹³ Aggression subscale.¹⁴ A larger percentage of children receiving stimulant and clonidine than stimulant and placebo were treatment responders as assessed with the Conduct subscale of the parent-completed Conners Behavior Checklist.¹⁵

To address these concerns, we conducted a multi-site, 9-week clinical trial (Treatment of Severe Childhood Aggression [TOSCA]) that compared the relative efficacy of parent training in child behavior management techniques and stimulant medication and placebo (hereafter referred to as Basic therapy) versus parent training and stimulant medication and risperidone (Augmented therapy). In addition to engaging in serious physical aggression, each child met diagnostic criteria for ADHD with co-occurring ODD/CD. The initial publication describing results for the primary hypotheses¹⁶ reported that Augmented treatment was superior to Basic treatment in reducing the severity of disruptive behaviors (Cohen's $d = 0.43$) as measured by the primary outcome measure, the parent-completed Nisonger Child Behavior Rating Form Disruptive total (NCBRF D-total).¹⁷ Moreover, there was little evidence of increased risk of adverse events (AEs) at the end of the acute treatment phase for children receiving Augmented treatment. The present article expands on our previous report by addressing several new topics, including the following: (a) drug effects for DSM-IV-defined ADHD, ODD, and CD symptoms and for interpersonal peer aggression; (b) caregiver reports of symptom-induced impairment; (c) teachers' ratings of treatment effects to include school functioning; and (d) informant discrepancy (i.e., differences in parents' versus teachers' ratings of drug response). In addressing these issues, we sought to determine whether Augmented therapy was more effective for the treatment of the aforementioned disorders and reduction in disorder-specific impairment. In addition, we examined whether symptomatic improvement observed in the home was evident in the school setting. As

academic functioning is a major concern in children with ADHD, we also evaluated teachers' perceptions of drug effects on global ratings of test/quiz performance, homework, and classroom participation.

METHOD

Participants

Participants were 168 children between 6 and 12 years of age (mean = 8.9 ± 2.0) recruited at 4 different sites (Columbus, Cleveland, Pittsburgh, and Stony Brook). Descriptively, participants were primarily boys (77%) of average IQ (mean = 97.1 ± 14.1) and white/European geographic ancestry (53%) and living with working parents (mothers = 52%, fathers = 53%) who had at least some college education (mothers = 66%; fathers = 35%), and relatively low family incomes of \$40,000 or less per year (57%) (Table S1, available online).

Inclusion criteria were evidence of serious physical aggression as defined by parent-report to a blinded clinician of level 3 or greater Overt Aggression Scale–M (OAS-M)¹⁸ rating of assault against objects (broke several things in anger), others (assault resulting in serious physical injury to another), or self (cut, bruised, burned self but only superficially; Table 1) and severe disruptive behavior ($\geq 90^{\text{th}}$ percentile NCBRF D-Total); DSM-IV criteria for any subtype of ADHD plus ODD ($n = 124$) or ODD and CD ($n = 44$); and a rating of at least moderately ill by a blinded clinician (severity score ≥ 4 Clinical Global Impression [CGI]).¹⁹ Exclusion criteria included full-scale IQ < 70 ; pregnancy; medical consideration (seizures, abnormal liver function, first-degree family history of type 2 diabetes); lifetime history of pervasive developmental disorder (PDD), psychotic disorder, eating disorders, or substance abuse disorder; current major depressive disorder (MDD) or bipolar disorder (BD); attempted suicide; or evidence of child abuse. Participants needed to be free of psychotropic medicines for 2 or 4 weeks for short- and long-acting drugs, respectively. The study was approved by the institutional review board of each investigative site and a multisite data safety and monitoring board (DSMB); parents/guardians signed consent forms; and study participants gave assent before enrollment.

TABLE 1 Number (%) of Children Who Received Level 3 Parental Ratings of Assaults Against Objects, Other People, and Self From the Overt Aggression Scale

Time	Objects	Others	Self
Screen	130 (77)	155 (92)	14 (8)
Baseline	106 (63)	148 (88)	15 (9)

Note: Data are frequencies with percentages in parentheses.

Procedure

At the completion of the baseline assessment, the primary caregiver started parent training, which continued throughout the 9-week intervention, and all children began an open trial of stimulant monotherapy, usually Osmotic Release Oral System (OROS) methylphenidate. If children were unable to tolerate medication or unable to swallow pills, an alternative stimulant was offered. During the first 3 weeks, the primary clinician adjusted stimulant to achieve an optimal therapeutic response defined as a CGI-Improvement score of 1 by a blinded clinician and a parent-rated NCBRF D-Total score < 15 (within 0.5 SD of the normative mean). If participants did not show a sufficient clinical response at week 3, or if they showed deterioration at week 4 through week 6 (i.e., dropped below a blinded CGI of 1 or had a NCBRF D-Total > 15), the second agent (risperidone or placebo) was added to the treatment package. Randomization was determined at baseline ($n = 84$ for each condition), stratified by site, and balanced by ODD and CD. We adopted the strategy of randomizing at baseline owing in part to National Institute of Mental Health (NIMH) review committee concerns about attrition.²⁰ The second medication was adjusted to achieve an optimal therapeutic response, and all participant assessments were conducted by blinded evaluators without knowledge of treatment assignment or adverse events. More details regarding the background, methods, design, patient recruitment and retention, adverse events, responder criteria, and data analysis models are provided by Farmer *et al.*²⁰ and Aman *et al.*¹⁶

The mean week 9 dose of methylphenidate was 45 ± 15 mg/day (Basic) and 46 ± 17 mg/day (Augmented) ($p = .88$). For the second medication, mean doses were 1.9 ± 0.7 mg/day (placebo) and 1.7 ± 0.6 mg/day (risperidone) ($p = .07$). Stimulant was administered in the morning, and risperidone/placebo were given morning and evening (supper or bedtime). To monitor adherence, staff conducted pill counts, and caregivers completed daily medication logs that were reviewed by staff on a weekly basis.

Fourteen children (Basic = 3; Augmented = 11) dropped out before they completed week 3 and therefore did not receive the second medication. An additional 8 children were classified as clinical responders by the end of week 3 (Basic = 3; Augmented = 5) and did not take the second medication.

For various reasons, including difficulties synchronizing the clinical trial with the child's school year, parent-school conflicts, and divergent levels of teacher involvement across sites, teachers' ratings were available for a subsample of children. Teachers' ADHD Symptom Checklist-4 (ADHD-SC4) ratings were available for 117 children; at least one-half of the teacher data were missing for 50 (43%) of these children. Children who did and did not have teacher ratings were not different in demographic characteristics, rate of ODD

or CD, severity of NCBRF ratings, therapy group assignment, or parents' ratings of treatment effects.

Measures

Main Outcomes. The ADHD-SC4²¹ is a 40-item treatment response measure that includes *DSM-IV*-referenced scales for the symptoms of ADHD and ODD as well as the Peer Conflict Scale,^{21,22} a 10-item measure of interpersonal peer aggression based on the ADHD School Observation Code.²³ Individual items are rated on a scale from 0 (never) to 3 (very often). The Symptom Severity score (dimensional) is the sum of all item scores for a given subscale. To facilitate comparison of results across scales, we report the mean item rating for all symptom severity scores. Numerous studies show that the ADHD-SC4 has satisfactory psychometric properties and is a sensitive indicator of drug effects in children with ADHD.^{21,24} The ADHD-SC4 was completed by parents and teachers at baseline and weekly throughout the 9-week trial.

The Child and Adolescent Symptom Inventory-4R (CASI-4R)²⁵ assesses a broad range of *DSM-IV*-defined disorders and was administered at initial diagnostic evaluation (parents only), baseline, and week 9. Parent and teacher versions contain 169 and 120 symptom items, respectively, and both include the ADHD-SC4 symptom categories as well as CD. Symptom severity scores are calculated similarly to the ADHD-SC4, but the CASI-4R has additional scoring algorithms including the Symptom Count Cutoff (categorical), which indicates whether or not the child meets *DSM-IV* criteria for the prerequisite number of symptoms. Ratings of "often/very often" and "never/sometimes" indicate the presence or absence of a symptom, respectively. The last item in each CASI-4R symptom scale assesses impairment: "How often do the behaviors in [this symptom category] interfere with youth's ability to do schoolwork or get along with others?" For the ADHD subscale, there is 1 impairment item for all subtypes. Impairment severity is rated on a 4-point scale, and the Impairment Cutoff score (categorical) is a frequency rating of "often" or "very often." The Clinical Cutoff score (categorical) indicates whether or not a child meets both Symptom Count Cutoff and Impairment Cutoff for a specific disorder. The teacher version of the CASI-4R has a global classroom functioning scale comprising 3 items (tests/quizzes, homework, class participation), each rated from poor (0) to superior (4). Numerous studies indicate that CASI-4R scales demonstrate satisfactory psychometric properties.²⁶

Subsidiary Outcomes. Items in the ADHD-SC4 ADHD, ODD, and Peer Conflict scales can be further subdivided into component symptom dimensions. For example, the ADHD scale is composed of 3 symptom subscales: inattention (9 items), hyperactivity (5 items), and impulsivity (4 items). Prior research^{27,28} indicates that the ODD scale consists of at least 2 symptom dimensions, anger/irritability (3 items), and noncompliance (5 items). The anger/irritability dimension is very

similar to *DSM-5* disruptive mood dysregulation disorder (DMDD). The Peer Conflict scale generates 3 indices of aggression: physical (e.g., hits, trips, pushes), nonphysical (threatening gestures, verbal threats), and object (destroys things).

Statistical Analyses

A constrained longitudinal data analysis (cLDA) model,²⁹ in which both baseline and post-baseline values for parent-rated mean ADHD-SC4 symptom severity scores are treated as dependent variables, was used in the intention to treat (ITT) population. This included all 168 randomized participants, and contained children randomized to Augmented therapy but who did not receive it or who dropped out before end of week 3 ($n = 16$). Fixed effects included those for time, group, time-by-group interaction, site, and disorder type. An unstructured variance-covariance matrix was assumed for the repeated measures within each subject. Empirically based sandwich estimators were obtained to assess the group differences at week 9 (endpoint), given their robustness against the deviations from model assumptions.³⁰ For the CASI-4R CD subscale, baseline and week 9 (endpoint) measures with last observation after week 3 carried forward (LOCF) were analyzed by a cLDA model with fixed effects for time, group, site, and disorder. Because of concerns about missing data, teachers' ADHD-SC4 ratings were modeled similarly to parents' ratings, with the exception that teachers' ratings were analyzed for changes in behavior from baseline to week 9 (endpoint) with last observation after week 3 carried forward. There was no treatment group bias in missing teacher data. In these exploratory analyses, a straightforward correction for multiple comparisons would risk excessive type 2 error; nevertheless, given the possibility of type 1 error, we adopted a more conservative p value of .025 for the 4 primary within-informant outcomes. Analyses of subsidiary outcomes were conducted for the express purpose of isolating more homogeneous traits for consideration in future research. Effect sizes (Cohen's d) were calculated comparing the 2 treatment arms by using a 2-sample t test of change score at week 9 (endpoint) (i.e., change from baseline to week 9 for participants with complete LOCF data). Model assumptions were assessed by examination of residuals. Some variables were square root transformed to accommodate the assumption of normality. Fisher's exact test (comparison of treatment groups) and McNemar's test (different informant, same children) were used to calculate significant group differences in categorical variables (cutoff scores). All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Primary Outcomes (Dimensional)

According to parents' ADHD-SC4 symptom severity ratings, Augmented therapy was superior

to Basic therapy in reducing ODD but not ADHD symptom severity (Table 2). Teachers' ratings indicated that Augmented therapy was more effective for reducing ADHD but not ODD symptom severity. Augmented therapy was also associated with a significantly greater reduction in the severity of parent- but not teacher-rated peer aggression at week 9. For both informants, group differences in CASI-4R CD severity ratings were not significant.

Subsidiary Outcomes (Dimensional)

Analyses of ADHD-SC4 ODD component symptom dimensions indicated significant treatment effects (Augmented > Basic) for parents' severity ratings of anger/irritability and noncompliant

behavior but not for any of the 3 core symptom domains of ADHD (Table 3). For teachers' ADHD ratings, Augmented therapy was superior in reducing the severity of impulsivity symptoms, and findings for inattention symptoms were marginally significant ($p = .06$; Cohen's $d = 0.38$), but there were no significant differences for teacher ODD subscales.

According to parents' ratings, Augmented was superior to Basic therapy for improving physical aggression and object aggression, and nonphysical aggression was marginally significant ($p = .053$; Cohen's $d = 0.14$) (Figure 1). Teachers' ratings evidenced beneficial treatment effects for object aggression ($p = .03$; Cohen's $d = 0.47$) (Augmented > Basic).

TABLE 2 Mean (SD) Attention-Deficit/Hyperactivity Disorder–Symptom Checklist (ADHD-SC4) Item Severity Scores for Parent Training, Stimulant, and Placebo (Basic) Versus Parent Training, Stimulant, and Risperidone (Augmented)

Symptoms	Baseline		Week 3		Week 9		p^a	p^b	Estimate (CI) ^b	ES ^c
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)				
Parent Ratings										
ADHD							.051	.129	0.15 (−0.04, 0.34)	0.13
Basic	84	2.4 (0.5)	82	1.3 (0.8)	71	1.0 (0.7)				
Augmented	84	2.3 (0.6)	75	1.3 (0.7)	66	0.8 (0.5)				
ODD							.002	.014	0.27 (0.06, 0.49)	0.27
Basic	84	2.4 (0.5)	82	1.4 (0.9)	71	1.1 (0.8)				
Augmented	84	2.3 (0.6)	75	1.5 (0.8)	66	0.8 (0.6)				
CD ^d							NA	.145*	0.06 (−0.02, 0.13)	0.09
Basic	84	0.6 (0.4)	NA	NA	77	0.2 (0.2)				
Augmented	84	0.5 (0.4)			73	0.1 (0.2)				
Peer Conflict Scale							.175	.022*	0.14 (0.02, 0.26)	0.32
Basic	84	1.5 (0.9)	82	0.8 (0.8)	71	0.6 (0.7)				
Augmented	83	1.5 (0.9)	75	0.8 (0.8)	66	0.3 (0.4)				
Teacher Ratings										
ADHD							NA	.021	0.35 (0.05, 0.65)	0.61
Basic	46	1.6 (0.6)	39	0.8 (0.7)	48	0.8 (0.6)				
Augmented	40	1.8 (0.8)	34	0.9 (0.7)	38	0.6 (0.5)				
ODD							NA	.120*	0.17 (−0.04, 0.38)	0.34
Basic	46	1.2 (1.0)	38	0.4 (0.6)	48	0.4 (0.6)				
Augmented	40	1.5 (1.1)	34	0.6 (0.8)	38	0.4 (0.6)				
CD ^d							NA	.087*	0.14 (−0.02, 0.31)	0.14
Basic	45	0.4 (0.4)	NA	NA	39	0.1 (0.2)				
Augmented	37	0.6 (0.6)			30	0.1 (0.3)				
Peer Conflict Scale							NA	.163*	0.15 (−0.10, 0.40)	0.29
Basic	46	0.7 (0.8)	38	0.2 (0.5)	48	0.2 (0.3)				
Augmented	40	0.9 (0.9)	34	0.3 (0.6)	38	0.2 (0.4)				

Note: CD = conduct disorder; ES = effect size (Cohen's d); ODD = oppositional defiant disorder, NA = not applicable.

^a p Values for treatment-by-visit interaction.

^b p Values and estimates (CI) represent results of mixed model for comparison of therapies at Week 9 (parents' ratings) or change from baseline to week 9 (teachers' ratings).

^cEffect size for baseline to week 9 change.

^dFrom Child and Adolescent Symptom Inventory–4R.

* p Values, estimates (CI), and effect sizes represent results from square root transformation on specified Child and Adolescent Symptom Inventory–4R measures.

TABLE 3 Mean (SD) Item Severity Scores for Attention-Deficit/Hyperactivity Disorder-Symptom Checklist (ADHD-SC4) ADHD and Oppositional Defiant Disorder (ODD) Symptom Subscales for Parent Training, Stimulant, and Placebo (Basic) Versus Parent Training, Stimulant, and Risperidone (Augmented)

Disorder	Baseline		Week 3		Week 9		p^a	p^b	Estimate (CI) ^b	ES ^c
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)				
Parent Ratings										
ADHD										
Attention							.034	.156	0.15 (-0.06, 0.36)	0.11
Basic	84	2.5 (0.6)	82	1.4 (0.8)	71	1.1 (0.7)				
Augmented	84	2.4 (0.6)	75	1.4 (0.8)	66	0.9 (0.6)				
Hyperactivity							.329	.237	0.13 (-0.08, 0.33)	0.15
Basic	84	2.3 (0.8)	82	1.2 (0.9)	71	0.8 (0.8)				
Augmented	84	2.2 (0.8)	75	1.2 (0.9)	66	0.6 (0.6)				
Impulsivity							.475	.243	0.14 (-0.10, 0.39)	0.08
Basic	84	2.3 (0.7)	82	1.4 (0.9)	71	1.1 (0.9)				
Augmented	84	2.1 (0.9)	75	1.3 (0.8)	66	0.8 (0.7)				
ODD										
Anger/irritability							.001	.026	0.27 (0.03, 0.50)	0.19
Basic	84	2.3 (0.7)	82	1.4 (0.9)	71	1.1 (0.9)				
Augmented	84	2.2 (0.7)	75	1.4 (0.8)	66	0.7 (0.6)				
Noncompliance							.005	.015	0.28 (0.05, 0.50)	0.30
Basic	84	2.4 (0.5)	82	1.4 (0.9)	71	1.1 (0.8)				
Augmented	84	2.3 (0.6)	75	1.5 (0.8)	66	0.8 (0.6)				
Teacher Ratings										
ADHD										
Inattention							NA	.060	0.33 (-0.01, 0.68)	0.38
Basic	46	1.8 (0.8)	39	1.0 (0.8)	48	1.0 (0.7)				
Augmented	40	2.0 (0.8)	34	1.1 (0.8)	38	0.8 (0.6)				
Hyperactivity							NA	.218	0.24 (-0.15, 0.63)	0.30
Basic	46	1.3 (0.8)	38	0.5 (0.7)	48	0.4 (0.5)				
Augmented	40	1.5 (1.0)	34	0.7 (0.8)	38	0.5 (0.6)				
Impulsivity							NA	.011*	0.29 (0.07, 0.51)	0.75
Basic	46	1.4 (0.9)	38	0.7 (0.9)	48	0.7 (0.8)				
Augmented	40	1.7 (1.0)	34	0.9 (0.9)	38	0.5 (0.6)				
ODD										
Anger/irritability							NA	.317	0.19 (-0.19, 0.57)	0.17
Basic	46	1.2 (1.0)	38	0.4 (0.7)	48	0.5 (0.7)				
Augmented	40	1.4 (1.2)	34	0.6 (0.9)	38	0.4 (0.7)				
Noncompliance							NA	.175	0.29 (-0.13, 0.70)	0.23
Basic	46	1.2 (1.0)	38	0.4 (0.6)	48	0.4 (0.7)				
Augmented	40	1.5 (1.2)	34	0.6 (0.8)	38	0.4 (0.6)				

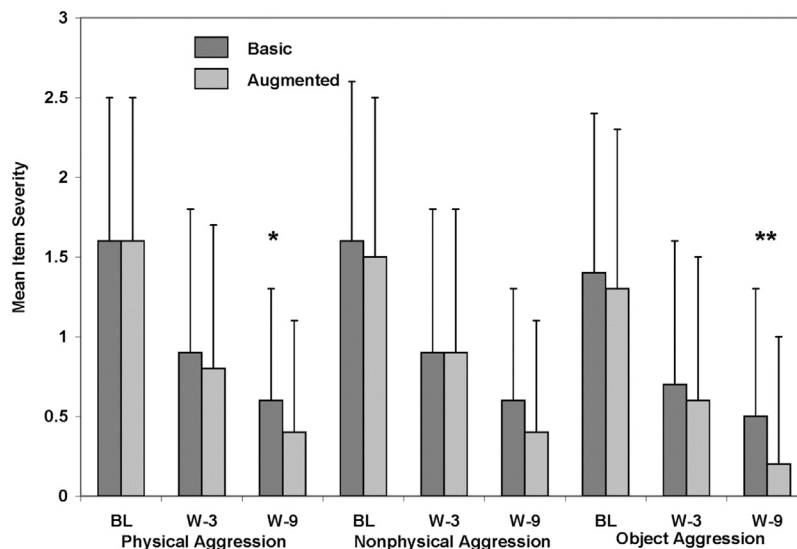
Note: ES = effect size (Cohen's d); NA = not applicable.
^a p Values for treatment-by-visit interaction.
^b p Values and estimates (CI) represent results of mixed model for comparison of therapies at week 9 (parent's ratings) or change from baseline to week 9 (teacher's ratings).
^cEffects size for baseline to week 9 change.
* p Values, estimate (CI), and effect sizes represent results from square root transformation on specified ADHD-SC4 and measures.

Symptom-Induced Impairment (Categorical)

Treatment groups were compared for the percentage of children who met CASI-4R Impairment Cutoff criteria at week 9. Analyses were limited to children who met Impairment Cutoff at baseline, which is indicated in Figure 2. A larger percentage of children receiving Basic (47%) therapy met

CASI-4R Impairment Cutoff criteria for at least 1 targeted disorder at week 9 than did Augmented (27%) therapy according to parents' ratings ($\phi = -0.20$). With regard to specific disorders, Basic therapy was associated with a higher rate of ODD symptom-induced impairment at week 9 (Basic = 40%, Augmented = 16%, $\phi = -0.26$).

FIGURE 1 Mean (SD) Peer Conflict Scale severity scores (parents' ratings) for parent training, stimulant, and placebo (Basic) versus parent training, stimulant, and risperidone (Augmented). Note: BL = baseline; W-3 = Week 3; W-9 = Week 9. * $p < .05$; ** $p < .01$.



Teachers' ratings did not indicate treatment group differences for Impairment Cutoff, but ADHD was marginally significant (Basic = 50%, Augmented = 20%, $p = .09$, $\phi = -0.31$).

Informant Discrepancy in Base Rates (Categorical)

To examine informant discrepancy in base rates, we calculated the percentage of all children who met CASI-4R Impairment Cutoff Criteria for targeted disorders at baseline. Parents ($n = 166$) compared with teachers ($n = 82$) rated a larger percentage of youth in the total sample as impaired by ODD symptoms and peer aggression at baseline (Figure 3). When we limited analyses to children for whom we had both parent and teacher report ($n = 82$), parents' ratings indicated higher baseline Impairment Cutoff rates for ADHD ($p = .033$), ODD ($p = .0001$), and any disorder ($p = .05$) than teachers' ratings.

Outcome Criterion (Categorical)

The use of different CASI-4R categorical scoring algorithms to assess treatment effects resulted in different inferences about efficacy. For example, the superiority of Augmented over Basic therapy was significant for parent CASI-4R ODD Impairment Cutoff (Figure 2). However, group differences were not significant for Symptom Cutoff ($p = .31$, $\phi = -0.10$) and only marginally significant for Clinical Cutoff ($p = .06$, $\phi = -0.18$).

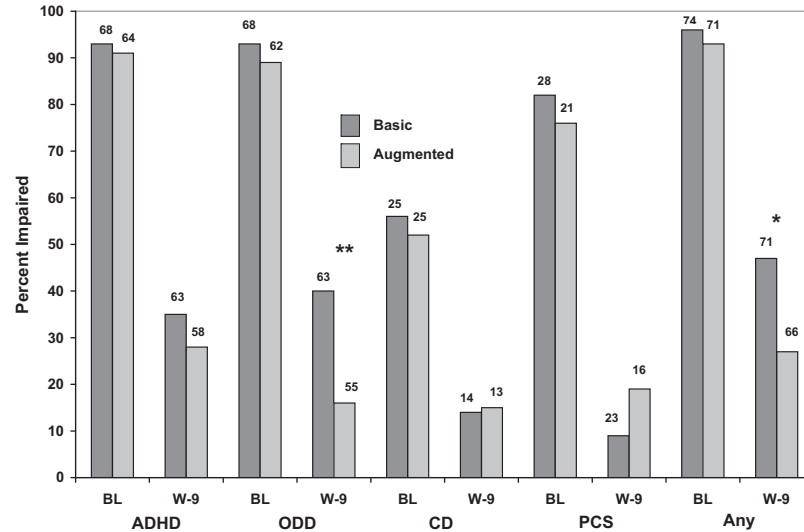
Classroom Functioning

CASI-4R teacher ratings of classroom functioning indicated marked improvement (higher mean item scores at week 9 than at baseline), but differences between treatments were marginally significant ($F = 3.33$, $p = .071$, Cohen's $d = 0.45$). Augmented therapy resulted in greater improvement than Basic therapy: baseline (Basic: mean = 1.5 ± 0.7 ; Augmented: mean = 1.3 ± 0.7) and week 9 (Basic: mean = 1.6 ± 0.8 ; Augmented: mean = 1.8 ± 0.7).

DISCUSSION

The TOSCA study involved a particularly challenging subgroup of children with ADHD who had co-occurring ODD/CD and clinically serious physical aggression. Participants were randomly assigned (at baseline) to receive Basic versus Augmented therapy if they did not show an optimal response to an initial 3-week open trial of parent training plus stimulant medication. In general, parent training plus stimulant medication was associated with marked reductions in ADHD and ODD symptoms and peer aggression at week 3, with Augmented therapy evidencing superior gains in therapeutic improvement by week 9. Consistent with the extant literature, the magnitude of treatment effects varied as a function of type of symptom and informant (setting), but significant treatment group differences were generally in the low-to-moderate range.

FIGURE 2 Treatment group differences in percentage of children who received parent Child and Adolescent Symptom Inventory–4R (CASI-4R) impairment cutoff scores for attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), Peer Conflict Scale (PCS), or any of these types of symptoms (any) at week 9 (endpoint). Note: Analyses limited to children rated impaired at baseline. Basic = parent training, stimulant, and placebo; Augmented = parent training, stimulant, and risperidone. BL = baseline; W-9 = Week 9. * $p < .05$; ** $p < .01$.



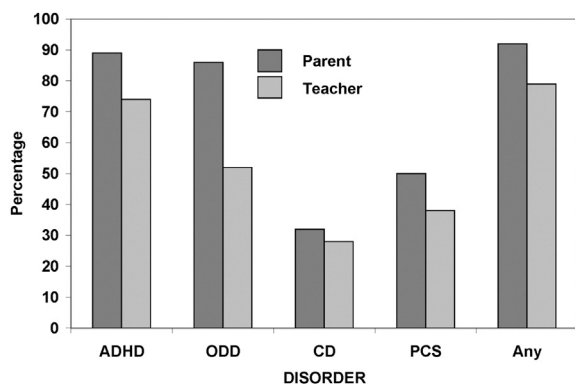
According to teachers' (but not parents') ratings, children receiving Augmented therapy experienced greater therapeutic improvement in ADHD symptoms (Cohen's $d = 0.61$), particularly impulsivity, which likely reflects heterogeneity in the pathophysiology of ADHD traits. As most children were rated both by parents and teachers as being impaired by ADHD symptoms at baseline, this result supports the efficacy of Augmented therapy for school-based (but not home-based) ADHD; however, as previously noted, findings for teachers' ratings are based on a subgroup of children. There is voluminous literature indicating greater sensitivity of teachers' versus parents' ratings of drug response for the symptoms of ADHD, ODD, peer aggression, and even chronic tic disorder in children with ADHD and ADHD with ODD,^{4,5,31} and this was also the case in the present study with regard to ADHD symptoms.

According to parents' (but not teachers') ratings, Augmented therapy was associated with less severe ODD symptoms at week 9 compared with Basic therapy (Cohen's $d = 0.27$). Clinical improvement was not limited to reductions in symptom severity. A smaller percentage of children who were impaired by ODD symptoms at baseline were impaired at week 9 if they were receiving Augmented (16%) rather than Basic

(40%) therapy. As all children in the study met Kiddie-SADS³² criteria for ODD,¹⁶ these findings suggest that Augmented therapy is an effective treatment for parent-defined ODD in children with co-occurring ADHD and severe aggression. Augmented therapy was superior in suppressing anger/irritability symptoms of ODD. It is noteworthy that CASI-4R ODD anger and irritability symptoms are very similar to the symptoms of DSM-5–defined DMDD,³³ but a diagnosis of DMDD also requires persistent disruption in mood between outbursts and mild-to-moderate impairment in a second setting. Although TOSCA screening criteria excluded current (but not lifetime) MDD and BD, all other mood-related disorders (or symptoms), including chronic anger and irritability, were not excluded. Moreover, prior research indicates that anger/irritability is associated with anxiety and depression.^{27,28,34} Regardless, these results suggest that 1 or more components of Augmented therapy may be relevant for future research involving children with DMDD.

Many children with ADHD engage in atypically higher rates of peer aggression, an important characteristic of CD and, although less well appreciated, a common clinical feature of ODD.^{27,28} In the present study, parents' ratings indicated that Augmented therapy was superior

FIGURE 3 Percentage of all children who received parent ($n = 166$) versus teacher ($n = 82$) Child and Adolescent Symptom Inventory–4R (CASI-4R) impairment cutoff scores for attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), Peer Conflict Scale (PCS), or any of these types of symptoms (any) at baseline.



to Basic therapy in suppressing peer aggression (Cohen's $d = 0.32$), to include physical (Cohen's $d = 0.22$) and object (Cohen's $d = 0.16$) aggression, and ratings of nonphysical (verbal/symbolic) aggression were marginally significant ($p = .053$; Cohen's $d = 0.14$). Treatment effects were cross-situational, as teachers' ratings were significant for object aggression (Cohen's $d = 0.47$). Collectively, these results are particularly noteworthy, as the amelioration of aggressive behavior was a major objective of the TOSCA study. Others have also found divergent drug effects for different types of peer aggression,^{6,7} which supports the multidimensionality of aggression and heterogeneity in its pathogenic antecedents.

Informant Discrepancy

Several decades of research have shown that ratings of child psychopathology from different informants generally evidence only modest agreement. This is likely explained in part by differences in raters and their perspectives and the settings in which children are assessed, and the child's natural ability to adjust phenotypic traits to changing environmental features (behavioral plasticity), which appears to vary as a function of child genotype.^{28,35-38} Our finding that parents' but not teachers' ratings of ODD symptoms differentiated treatment groups is likely explained by the use of parent report to confirm the ODD/CD inclusion criterion. For example, more children met CASI-4R impairment

criteria for ODD at baseline according to parents' (86%) than teachers' (52%) ratings. In community-based and referred samples, rates of ODD are similar for both informants, but overlap is minimal.^{27,28,39} Therefore, it seems plausible that perceived differences in initial symptom severity may partially explain informant discrepancy in treatment effects, that is, there was less "room for improvement" in teachers' ratings.

Informant discrepancy poses potential challenges for clinical management as well as nosology. Prior research,²⁸ for example, indicates that the associated clinical features of ODD vary depending on whether the child is identified as ODD by parent or teacher, but not both (source-exclusive), and CASI-4R impairment status may have interacted with or moderated clinical response in the home versus school setting. Our findings for a group of children with largely source-exclusive ODD indicating significant improvement in parent-rated (but not teacher-rated) symptoms with Augmented therapy support this interpretation. Equally important, our results appear to strike at the heart of a common bias that youth with non-cross-situational pathology are more likely to have environmentally induced problems, and therefore are poorer candidates for pharmacotherapy.²⁸

This study has several strengths, including the use of multiple sites, rigorous assessment battery, state-of-the-art data monitoring, and a sample large enough to detect even small-to-moderate treatment effects. Nevertheless, the generalization of results to everyday clinical practice is bounded by sample characteristics and methodology. As previously noted,¹⁶ this is not a "typical" sample of children with ADHD. All of these children had ODD and were considered to be very physically aggressive according to their parents, and their families were generally of below-average income. For example, according to parent OAS report, in the 30 days before evaluation, 97% of the children assaulted (or would have if not prevented) another person, resulting in serious physical injury. Participants who dropped out or who were found to be clinical responders in weeks 1 to 3 did not contribute to the treatment signal for those receiving Augmented treatment. In addition, we did not control for parental psychopathology, which could have influenced perceptions of behavioral change. To this list we would add the following: the caregivers of all participants had access to parent training throughout the 9-week

trial; all treatments were provided free of charge; and families were reimbursed for time and travel expenses and were available for weekly clinic visits for 9 weeks. There were too few female children to assess potential gender differences in response to treatment, and our findings may not generalize to less severely impaired children, preschoolers, teenagers, or children with intellectual disability.

Teacher ratings were available for only a subgroup of children, which has implications for statistical power. For example, although effect sizes for significant treatment group differences based on parents' ratings were often comparable to teachers' ratings, the latter were generally nonsignificant. When we limited our analyses of parent ratings to children who also had teachers' ratings, the former remained significant. Many children did not meet teacher-rated symptom or impairment criteria for ODD or peer aggression; therefore, our results do not speak to the efficacy of Augmented therapy for teacher-defined syndromes other than ADHD.

With regard to the broader issue of clinical necessity, we offer the following interpretive caveat. As we and others have noted,^{16,20,40} had TOSCA adopted a longer initial open trial of parent training plus stimulant medication or a different criterion for improvement, it is possible that a smaller percentage of children would have received Augmented therapy. For example, most children receiving Basic therapy were able to complete the 9-week trial (i.e., did not deteriorate to a clinically unacceptable degree). Nevertheless, the Basic therapy group did receive regular dose increments of placebo during weeks 4 to 8 and at a level consistent with the Augmented therapy group, suggesting less than optimal functioning. This is consistent with the high rate of perceived impairment in the Basic therapy group at endpoint. It also warrants repeating that the duration of Augmented therapy was a maximum of 6 weeks, and pending analyses of intermediate (3-month) and long-term (12-month) outcomes may lead to different conclusions about clinical utility.

Findings also address 2 treatment assessment strategies that may warrant consideration in future research as well as in everyday clinical practice. Consistent with the results of others,⁴¹ a single-item caregiver rating of impairment was as effective in detecting differences between treatment groups as a multi-item symptom

severity score. In addition, caregiver-impairment ratings were a more sensitive indicator of clinical improvement than CGIs completed by blinded clinicians.¹⁶ Rates of psychiatric conditions based on symptom cutoff (number of symptoms), impairment cutoff (child's ability to do schoolwork or to get along with others), or clinical cutoff (symptom cutoff plus impairment cutoff) generally show modest agreement.³⁸ As the results of this study indicate for parents' ratings of ODD, this also applies to conclusions about relative improvements from treatment, which underscores the limitations of relying on a single measure to determine efficacy in clinical trials and routine patient management.

TOSCA results suggest that augmentation with risperidone for pediatric patients with ADHD and co-occurring ODD/CD who are receiving an ongoing regimen of parent training and stimulant medication may result in added therapeutic benefit for some cases, with a seemingly modest increased risk of adverse events,¹⁶ at least during the short term. Importantly, as the distinguishing subject selection criterion in this study was clinically significant physical aggression, parents reported reduced physical aggression directed toward peers and objects with Augmented therapy. Teacher ratings indicated less severe ADHD symptoms with Augmented therapy. Although the breadth of clinical improvement was encouraging, effect sizes were generally small for the added benefits of Augmented therapy, probably because of the large improvement already attained by the Basic multimodal treatment. The fact that perceptions of relative efficacy were setting specific highlights the importance of obtaining treatment response information from multiple informants. The clinical severity of the study sample is underscored by the fact that at week 9, almost one-half of the children receiving 2 evidence-based treatments (Basic) and more than one-fourth of those receiving 3 treatments (Augmented) continued to exhibit symptoms that their parents perceived as interfering with social or academic functioning. Thus these findings should not be generalized beyond severe cases of irritability and aggression with ADHD. Although they provide new evidence to inform clinical practice, their application still requires thoughtful personalization of the treatment plan for individual patients. *ε*

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TABLE S1 Demographic Characteristics of Children Receiving Parent Training, Stimulant, and Placebo (Basic) Versus Parent Training, Stimulant, and Risperidone (Augmented)

Characteristic	Total (N = 168)		Basic (n = 84)		Augmented (n = 64)	
Gender, male, n (%)	129	(76.8)	64	(76.2)	65	(77.4)
Disorder, n (%)						
CD	44	(26.2)	22	(26.2)	22	(26.2)
ODD	124	(73.8)	62	(73.8)	62	(73.8)
Age, y at screening, mean (SD)	8.89	(2.01)	8.75	(1.98)	9.03	(2.05)
IQ at screening, mean (SD)	97.1	(14.1)	97.0	(13.9)	97.2	(14.4)
Race/ethnicity (n, %)						
African American	58	(34.5)	30	(35.7)	28	(33.3)
Multiracial	17	(10.1)	10	(11.9)	7	(8.3)
White	89	(53.0)	41	(48.8)	48	(57.1)
Other ^a	4	(2.4)	3	(3.6)	1	(1.2)
Hispanic origin	9	(5.4)	5	(6.0)	4	(4.8)
Non-Hispanic origin	157	(93.5)	78	(92.9)	79	(94.0)
Unknown	2	(1.2)	1	(1.2)	1	(1.2)
Child's type of school						
Regular public (or private parochial)	145	(86.3)	73	(86.9)	72	(85.7)
Other ^b	23	(13.7)	11	(13.1)	12	(14.3)
Mother's employment						
SAH	21	(12.5)	10	(11.9)	11	(13.1)
Other ^c	59	(35.1)	28	(33.3)	31	(36.9)
Working full-/part-time	88	(52.4)	46	(54.8)	42	(50.0)
Father's employment						
SAH	1	(0.6)	1	(1.2)	0	(0.0)
Other ^c	75	(44.6)	38	(45.2)	37	(44.0)
Working full-/part-time	89	(53.0)	42	(50.0)	47	(56.0)
Unknown	3	(1.8)	3	(3.6)	0	(0.0)
Mother's education						
Some high school or less	16	(9.5)	4	(4.8)	12	(14.3)
High school graduate or GED	40	(23.8)	16	(19.0)	24	(28.6)
Some college or more	111	(66.1)	63	(75.0)	48	(57.1)
Not in household/unknown	1	(0.6)	1	(1.2)	0	(0.0)
Father's education						
Some high school or less	7	(4.2)	3	(3.6)	4	(4.8)
High school graduate or GED	49	(29.2)	23	(27.4)	26	(31.0)
Some college or more	59	(35.1)	29	(34.5)	30	(35.7)
Not in household/unknown	53	(31.5)	29	(34.5)	24	(28.6)
Household income						
<\$20,000	61	(36.3)	33	(39.3)	28	(33.3)
\$20,001-\$40,000	35	(20.8)	16	(19.0)	19	(22.6)
\$40,001-\$60,000	24	(14.3)	9	(10.7)	15	(17.9)
\$60,000-\$90,000	21	(12.5)	12	(14.3)	9	(10.7)
>\$90,000	21	(12.5)	10	(11.9)	11	(13.1)
Unknown	6	(3.6)	4	(4.8)	2	(2.4)

Note: CD = conduct disorder; ODD = oppositional defiant disorder; SAH = stayathome.
^a"Other" category included Asian American, Native American, and unknown.
^b"Other" category included home school, special class for children with learning disabilities, special class for children with emotional disabilities, or other (open-ended response).
^c"Other" category included: unemployed, disabled, retired, student, not in household, or other (open-ended response).