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What Does Risperidone Add to Stimulant and Parent Training for Severe Aggression in Child Attention-Deficit/Hyperactivity Disorder?

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Abstract

Objective—Although combination pharmacotherapy is common in child/adolescent psychiatry, there has been little research evaluating it. We tested the value of adding risperidone to concurrent

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psychostimulant and parent training (PT) in behavior management for children with severe aggression

Method—We randomized 168 children age 6–12 years (mean 8.89 ±2.01) with severe physical aggression to a 9-week trial of PT, stimulant, and placebo (*Basic* treatment; n=84) or PT, stimulant, and risperidone (*Augmented* treatment; n=84). All had diagnoses of attention-deficit/hyperactivity disorder (ADHD) and either oppositional defiant (n= 124) or conduct disorder (n= 44). Children received psychostimulant (usually OROS methylphenidate) for 3 weeks, titrated for optimal effect, while parents received PT. If there was room for improvement at the end of Week 3, either placebo or risperidone was added. Assessments included parent ratings on the Nisonger Child Behavior Rating Form (NCBRF; Disruptive-Total subscale = Primary outcome) and Antisocial Behavior Scale (ABS); blinded clinicians rated change on the Clinical Global Impressions (CGI) scale.

Results—Compared to *Basic* treatment (PT + stimulant[STIM][44.8±14.6 mg/day] + placebo [1.88±0.72]), *Augmented* treatment (PT + STIM[46.1±16.8 mg/day] + risperidone[1.65±0.75]) showed statistically significant improvement on the NCBRF Disruptive–Total subscale (treatment-by-time interaction p= 0.0016), the NCBRF Social Competence subscale (p= 0.0049), and ABS Reactive Aggression (p= 0.01). CGI scores were substantially improved for both groups but did not discriminate between treatments (CGI-I ≤ 2, 70% for *Basic* treatment vs. 79% for *Augmented* treatment). Prolactin elevations and gastrointestinal upset occurred more with *Augmented*; other adverse events differed modestly from *Basic* treatment; weight gain within the *Augmented* treatment group was minor.

Conclusions—Risperidone provided moderate but variable improvement in aggressive and other seriously disruptive child behavior when added to PT and optimized stimulant treatment. Clinical trial registration information—Treatment of Severe Childhood Aggression (The TOSCA Study); http://clinicaltrials.gov/; NCT00796302.

Keywords

disruptive behavior disorders; parent training; physical aggression; psychostimulants; risperidone

Physical aggression in childhood is associated with serious negative consequences later in life. Many longitudinal studies have followed children from early childhood to evaluate the impact of early disruptive behavior disorders (DBDs) and/or aggressive behavior.[1–4] Such DBD and aggression have been linked to (a) adult smoking, alcohol use, hard drug use, physical aggression, and risky sexual behavior;[1] (b) frequent occurrences on police registers, repeated/serious crimes, involvement in confrontational and destructive offenses;[2] (c) presence of generalized anxiety disorder (35%), social phobia (20%), obsessive compulsive disorder (21%), depression (23%), bipolar disorder (46%), attention-deficit/hyperactivity disorder (ADHD) (62%), physical aggression, and substance abuse;[3] (d) nonviolent offending, and violent delinquency.[4] Thus, DBD and aggressive behaviors are not only problematic at the time of first occurrence in the child's life, but they are also important early warning signs of potential deleterious consequences later in life. Therefore, evidence-based attempts to attenuate these problems early in life are clearly warranted.

Concomitant pharmacotherapy is rising quickly in child and adolescent psychiatry, and this is especially the case for children with DBDs. For example, in a nationally representative sample of child psychiatric patients, 50% of the children with ADHD and 61% of the children with DBDs were taking combination pharmacotherapy.[5] In another nationally representative sample of 3,466 youth, subsuming 27,979 visits to U.S. physicians, the most commonly reported diagnostic categories were DBDs and ADHD (49%).[6] Multiclass prescriptions rose from 14% (1996–1999) to 20% (2004–2007) of patient visits that included

psychotropic medication (57% increase in combination therapy over 8 years).[6] When risperidone was prescribed, concomitant psychotropic prescribing occurred 62% of the time.[6] The combination of ADHD medication plus antipsychotic medication was about 6 times more likely to occur than other multiclass combinations. Thus, augmented pharmacotherapy has become a fact of life in child psychiatry, despite the lack of controlled studies of combined pharmacotherapy.[5–7] One of the most contentious issues in the treatment of children with disruptive behavior problems is the increasing use of multiple concurrent medications, especially the addition of atypical antipsychotic agents, because little is known about the safety and efficacy of such regimens.[6]

Aggressive behavior is one of the most prominent targets for the use of augmented pharmacotherapy in children. Of the medicines that have been assessed for managing aggression in youth, there is abundant evidence that psychostimulants, such as methylphenidate, can be helpful.[8,9] This is not surprising given that ADHD and aggression often co-occur in children. Connor *et al*.[8] conducted a meta-analysis of 28 stimulant studies involving aggressive behavior in children with ADHD. They reported a wide range of effect sizes (ES) for overt aggression (CI= 0.70–1.02; ES range= 0.24–2.12). Furthermore, the presence of ODD or CD led to significantly diminished ES in managing overt aggression. This raises the possibility that DBDs may be linked to diminished psychostimulant effect on aggression and poses the question of what to do when children show unsatisfactory psychostimulant response.

Risperidone has been shown consistently to reduce disruptive behavior in children. Findling *et al*.[10] reported less aggression after 10 weeks of risperidone versus placebo for 20 children with CD. Two large trials (Ns=110, 118) of risperidone in children with subaverage IQs (IQ <85) and high scores on the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (NCBRF) showed highly significant reductions on the Conduct Problem subscale; an approximately 45% decline accompanied risperidone compared to about a 15% decline with placebo.[11, 12] Large follow-up studies (Ns=107, 504) showed maintained improvements over a year in previously medicated children, new gains in previously unmedicated children, and generally good tolerability (although weight gain was a problem for some).[13, 14]

Hence, psychostimulants and atypical antipsychotics are a commonly used form of augmented pharmacotherapy, and each effectively reduces DBD symptoms. However, very little research has tested their combined efficacy despite their common joint use in the community for children with DBDs. In a pilot study of risperidone versus placebo for 25 aggressive children with ADHD, Armenteros et al.[15] studied 25 children with ADHD and overt aggression; only children with affective/impulsive aggression were enrolled. They added risperidone or placebo to constant doses of stimulants that were begun 3 weeks before study entrance. No significant differences in parent or teacher ratings of aggression were found after 4 weeks of combined risperidone or placebo augmentation. Although the paper reported a statistically significant difference in response rate (≥30% improvement on the parent-rated aggression scale) favoring risperidone, our re-analysis of that finding was not statistically significant (Fisher's Exact Test, p=0.22; Yates' chi-square, p=0.24). It is possible that, with only 25 subjects, the study was under powered.

Other studies of atypical antipsychotics added to stimulants lacked proper controls. Kronenberger *et al*.[16] assessed the effects of open-label quetiapine over 9 weeks among 24 youth whose aggression was not adequately controlled after 3 weeks of OROS methylphenidate. All measures of aggression showed marked reductions from baseline to the end of methylphenidate monotherapy and further substantial statistically significant reductions when quetiapine was added. However, with this design, it is impossible to

separate the effects of quetiapine alone from the placebo effect and the passage of time. Thus, there is a dearth of properly controlled and well-powered studies of combined stimulant and antipsychotic treatment in children with severe physical aggression and comorbid DBDs.

In this study, we evaluated risperidone's contribution to the control of childhood DBDs (specifically, CD or ODD) with severe aggression and comorbid ADHD, when combined with ongoing psychostimulant (STIM) therapy and parent training (PT) in behavior management. We included PT due to its well-established efficacy in reducing childhood disruptive behaviors, [17] particularly in combination with stimulant treatment in ADHD.[18] Thus the design of the study was closely aligned with recommendations from an expert panel's Treatment Recommendations for Antipsychotics for Aggressive Youth (TRAAY).[19] We predicted immediate reduction of DBD behaviors with initial stimulant treatment. Further, we predicted that the combination of PT and psychostimulant + risperidone (PT + STIM + RIS) would produce significant improvement, exceeding that of PT + psychostimulant + placebo (PT + STIM + PBO).

Method

Design

As both psychostimulants (STIM) and parent training (PT) are established treatments for ADHD and aggressive behavior, we termed this *Basic treatment*. We attempted to *augment* these effects by adding risperidone (RIS) for half of the participants. This was a four-site, randomized, double-blind, placebo-controlled study of PT and STIM (*Basic* treatment) compared with PT, STIM, and RIS (called "Augmented" hereafter) for the treatment of disruptive behavior in children with ADHD and ODD or CD. PT + STIM were initiated at the end of baseline (BL) assessment. If subjects failed to show a sufficient clinical response (defined below) at 3 weeks or if they deteriorated between 4 and 6 weeks, the second agent (RIS or PBO) was added to the treatment package. Subjects were randomized in a 1:1 ratio at baseline and the randomization was stratified by site and balanced for comorbid disruptive-disorder diagnosis (CD vs. ODD) through a web-based centralized randomization system. The clinical sites were Ohio State University, Case Western University, the University of Pittsburgh, and Stony Brook University. More details regarding the background, methods, design, and variables are provided by Farmer *et al*.[9]

Ratings of global behavioral response were made by blinded evaluators who were not permitted to ask about adverse events (AEs) or to know treatment assignment. Primary clinicians rated AEs, made titration adjustments, and were responsible for breaking the blind if subjects, due to nonresponse, exited study treatment at the end of the acute trial (9 weeks). During Weeks 3 to 8, a clinical responder was defined a priori as having a blinded evaluator-determined Clinical Global Impressions–Improvement (CGI-I) score[20] of 1 (very much improved)and a parentrated NCBRF–Typical IQ (TIQ) Disruptive Behavior total (NCBRF D-Total) score of ≤15 (within 0.5 sd of the normative mean).[21] This stringent definition of responder was used to make sure that any youngster who had room for further improvement was given the chance to receive the second medication. This provided a rigorous test of the added value of combined pharmacotherapy and encouraged the ideal target of behavioral normalization, especially in the case of serious childhood aggression. For the purposes of statistical evaluation at study endpoint, a clinical responder was defined in the more usual way, as having a reduction to the NCBRF D-Total of ≥25% and a CGI–I of 1 (very much improved) or 2 (much improved).

Subjects

***Inclusion criteria* were as follows—**(i) ages 6–12 years, inclusive; (ii) *DSM-IV* DBD diagnosis (CD or ODD); (iii) *DSM-IV* diagnosis of ADHD (any subtype); (iv) evidence of serious physical aggression as rated on the Overt Aggression Scale–M[22] (score ≥3 on assaults against other people, objects, or self); and (v) evidence of seriously disruptive behavior as determined by parent or guardian rating ≥ 27 (90th %ile) on the NCBRF D–Total. In addition, a CGI–Severity score of ≥4 ("Moderately ill" or higher) for aggression was required by blinded clinicians. Participants needed to be free of psychotropic medicines for 2 weeks for most drugs (such as most antidepressants, alpha agonists, beta blockers, anxiolytics, mood stabilizers, oral antipsychotics, and antihistamines), and 4 weeks for depot antipsychotics or fluoxetine. This rule was occasionally relaxed (to as little as 3–7 days) for extreme cases who could not tolerated being unmedicated the full time, as approved by the cross-site steering committee.

***Exclusion criteria* included—**(i) full-scale IQ below 71; (ii) pregnancy or a history of seizure disorder, other neurological or medical disorder for which medication may present a considerable risk; (iii) abnormal liver function; (iv) pervasive developmental disorder, schizophrenia, other psychotic disorders, or eating disorders; (v) hypomanic/biphasic score of ≥36 as rated by child's parent on the General Behavior Inventory (see below) and, if positive, confirmed by clinician as indication of mood disorder; (vi) current or history of major depressive disorder or diagnosis of bipolar disorder; (vii) current use of psychotropic medications from which discontinuation would present a significant risk; (viii) active substance use disorder; (ix) evidence of current child abuse or neglect; (x) history of suicide attempt in the past year or current suicidal ideation; and (xi) family history of Type II Diabetes in 2 or more first-degree relatives (owing to potential weight gain with risperidone).

The study was approved by the IRB of each investigative site; parents/guardians signed consent forms, and study participants gave assent before enrollment.

Procedure

Thereafter, families were involved in the following visits and assessments. A schedule of measures appears in Farmer *et al*.[9]

1. Screening visit(s)—occurred within 4 weeks of BL. During screening, we completed a physical exam, conducted clinical laboratory tests and an ECG, and interviewed parents regarding the child's medical history. IQ was assessed with the Kaufman Brief Intelligence Test–2;[23] and clinicians interviewed both child and parent using the Schedule for Affective Disorders and Schizophrenia for school-aged children (K-SADS-PL)[24] to establish the presence of ADHD and ODD or CD and to rule out bipolar disorder, schizophrenia, and other exclusionary conditions. Parents rated their child on the General Behavior Inventory[25] to ensure further that children with bipolar disorder were detected.

Clinicians completed the Overt Aggression Scale–Modified (OAS-M) a 7-item instrument from both parent and child report.[22] Questions assess aggression on the dimensions of assaults against (a) objects, (b) others, and (c) self, on rating subscales ranging from 0 (no events) to 5 (severe events). Children receiving a score of at least 3, both at screen and at BL, qualified for inclusion. Providing some notion of initial severity, a score of 3 for assaults against objects is anchored with "Breaks objects, smashes windows," whereas a score of 3 for assaults against others is characterized as "Attacks others, causing mild injury (bruises, sprains, welts, etc.)."

Parents also rated their child on the NCBRF–TIQ ("TIQ" referring to "Typical IQ version;" called NCBRF hereafter) at screen, BL, and Weeks 3 through 9.[21] The NCBRF provides one prosocial subscale (Positive/Social) and six problem behavior subscales: (a) Conduct Problem, (b) Oppositional Behavior, (c) Hyperactive, (d) Inattentive, (e) Overly Sensitive, and (f) Withdrawn/Dysphoric.[21] The NCBRF has excellent internal consistency, distinguishes between controls and subjects with DBDs, and its predecessor (for children with developmental disabilities) was highly drug-sensitive. Conduct Problem and Oppositional Behavior map closely to *DSM-IV-TR* symptoms of CD and ODD; they were scored together to form a variable called the D(isruptive)-Total. The D-Total was the primary outcome measure for this study. The Hyperactive and Inattentive subscale scores were combined to form an ADHD-Total.

In order to qualify, a child also required a Clinical Global Impressions–Severity (CGI-S)[20] score of at least 4, reflecting the presence of consistent ADHD, disruptive, and physically aggressive/destructive behavior. Anger, defiance, and aggressive speech were not enough to qualify children for the study. Subjects had to display behavior that was physically harmful to others, themselves, or the environment around them. We established interrater reliability on the CGI-S and CGI-I subscales by discussion at Investigators Meetings, subsequent "gold standard" test vignettes, and repeated recertifications of blinded evaluators.

The subjects were assessed on the following safety measures at screening and all visits thereafter: (a) Barnes Akathisia Scale,[26] a clinician-completed scale utilizing both objective observation/clinical judgment and the patient's subjective experience of restlessness; (b) The Simpson-Angus Rating Scale checks for extrapyramidal side effects (rigidity, dystonia, and abnormal glabellar reflex) of antipsychotics;[27] (c) The Abnormal Involuntary Movement Scale (AIMS),[28] a standardized clinician-rated review of tremor, dyskinesia, and other possible antipsychotic neuromotor side effects.

2. Baseline (BL) and subsequent visits—At BL and thereafter, we collected the following assessments: vital signs, height, weight, open-ended elicited AEs and specific side effects ratings by parents and primary clinicians, plus concomitant medications. The CGI-I was obtained at all visits, whereas CGI-S was completed at end of Weeks 3 and 9. Finally, parents completed the Antisocial Behavior Scale (ABS)[29] at BL and Week 9 or end-point. The 28-item ABS has a Proactive Aggression subscale (5 proactive items and 5 covert antisocial items) and a Reactive Aggression subscale (6 items).[29] This instrument was used to differentiate affective and proactive subtypes of aggression and to assess treatment effects on both.

Beginning with BL, we administered a 9-session course of PT with up to 2 optional booster sessions using an empirically established program for children (the Community Parent Education Program [COPE]).[30] Fidelity was monitored through audio tapes, reviewed by the Pittsburgh site, and by regular conference calls. The COPE's focus on strategies for managing impulsive behavior, including reactive aggression, made it a good fit for this protocol.

From BL through Week 3, primary clinicians openly titrated psychostimulant medication to optimal effect balancing benefit and side effects, usually in the form of Osmotic Release Oral System (OROS) methylphenidate (Concerta). For smaller children (<25 kg), dosage was titrated clinically using the following daily doses: 18 mg (7 days), 36 mg, 54 mg (maximum maintenance dose). For larger children (>25 kg), dosage was increased every 3–4 days using the following daily doses: 18, 36, 54, 72 mg.[9] Subjects unable to tolerate OROS methylphenidate or unable to swallow pills were offered an alternative (at comparable doses) from the following, of which the capsule contents could be sprinkled onto food:

mixed amphetamine salts (Adderall), dextromethylphenidate extended release (Focalin XR), or lisdexamphetamine dimesylate (Vyvanse).

If residual symptoms remained, randomized placebo or risperidone was then added to treatment at Weeks 4 through 6. For children < 25 kg, risperidone was dosed between 0.5 to 2.5 mg/day; for children >25 kg, dosing ranged from 0.5 to 3.5 mg/day.[9] The risperidone titration schemes allowed for dose increases every 3–7 days, following a schedule that specified maximum dose increases over 29 days of titration; doses could always be held constant or reduced if satisfactory clinical response occurred or if indicated by AEs.

Statistical Analysis

Primary/Secondary analyses—For the primary outcome NCBRF D-Total score, a constrained longitudinal data analysis (cLDA) model, in which both BL and post-BL values were treated as dependent variables, was used in the intention-to-treat (ITT) population (all randomized subjects).[31] The outcome was square root transformed to accommodate the assumption of normality. Fixed effects in the final model included those for time, group, time × group interaction, site, and disorder type. Other interaction effects such as effects for site × time × group, site × time and site × group were explored and none of them was statistically significant. An unstructured variance covariance matrix was assumed for the correlated measures within each subject. Empirically-based sandwich estimators were obtained to assess the group differences at Week 9.[32] Although mixed models can be used in the presence of missing data, the missing at random assumption is not directly testable. Thus, various sensitivity analyses were conducted to examine the robustness of results. Secondary longitudinal outcome variables, such as subscales other than the D-Total of the NCBRF and weight, were modeled in a similar fashion to the D-Total. Dichotomous rates of response to treatments were compared between groups by Fisher's exact tests. For the ABS proactive and reactive aggression subscales rated by parents, BL and post-BL measures were analyzed by cLDA model with fixed effects for time, group, site, and disorder. As their distribution was non-normal, prolactin levels were compared using Wilcoxon ranked sum test. The secondary outcome variables were corrected for multiplicity by using Bonferroni corrections at the scale level (α= 0.0125 for NCBRF [4 subscales]; α =0.025 for CGI [2 subscales]; α =0.025 for ABS [2 subscales]). We used Cohen's d to estimate effect size (ES); we calculated ES using complete cases, a subset of the ITT. All analyses were conducted in SAS (version 9.2, SAS Institute Inc., Cary, NC).

Power Analysis—With a two-sided α of 0.05, we had 80% power to detect an ES of 0.5 with complete data from 128 subjects (64 per group). To allow for average attrition of 20%, we concluded that 160 patients (80 per group) were needed, although the ITT analysis includes all subjects.

Data Management—The Data Coordinating Center used Teleform® (HP Autonomy) to generate data collection instruments and a secure SQLserver database to provide storage and access services. SharePoint was used as the study collaboration portal. A patient recruitment website was developed using Drupal.

Results

Subjects, Failure To Use Second Medication (RIS), and Dosage

One hundred sixty-eight subjects (84 per treatment group) were randomized before starting *Basic* (STIM + PT). Figure 1 contains the CONSORT diagram showing disposition of subjects. Subject characteristics appear in Table 1. As would be expected for youth with DBDs, about 75% of the sample were boys.[33] The large majority of the sample (73.8%) had

ODD; the others had CD but would have qualified for ODD except for CD pre-emption of diagnosis. IQ was virtually identical for the two groups, and most demographic variables were similar between groups. Household incomes were relatively low, and parental education (especially for fathers) was also low. Thus, this sample largely comprised lower socioeconomic status families, although there was also a significant minority from the middle class (Table 1).

Fourteen subjects (3 from the *Basic* treatment group and 11 from the *Augmented* group) dropped out before completing the third week of the study, before the opportunity for adding the second drug. With our analytic model, these participants did not appreciably affect the statistical outcomes. Eight subjects were clinical responders by the end of Week 3 and did not take the second medication (3 from the *Basic* treatment group and 5 from the *Augmented* group). Thus, 22 subjects either dropped out before they had an opportunity to benefit from *Augmentation* or were deemed not to need it. Treatment dropouts were generally lost to further follow-up.

The mean Week 9 methylphenidate dose for the *Basic* group was 44.8±14.6 mg/day, as compared with 46.1 ±16.8 mg/day for the *Augmented* group (p=0.88). For the second drug, the subjects receiving PBO had a mean Week 9 "dose" of 1.9±0.72 mg/day, as compared with 1.7 + 0.75 mg/day of risperidone for those taking active drug (*Augmented*) (p=0.07).

Primary Outcome

The results for the NCBRF D-Total appear in Table 2 and Figure 2. As determined by the linear mixed effects model, the group-by-time interaction was statistically significant (p= 0.0016), indicating that the *Augmented* group D-Total scores decreased more over time than the *Basic* treatment group. At Week 9, the difference between groups was statistically significant (p= 0.0143), with an ES of 0.43. Using change from Week 3 to Week 9, the ES was 0.50 (most ESs appear in Table 2). We conducted a sensitivity analysis for ES by excluding those who never experienced the second drug (14 pre–Week-3 dropouts and 8 PT + STIM responders). ES relative to Baseline was 0.51 and relative to Week 3 was 0.62.

Other NCBRF and ABS Outcomes

Findings for the other NCBRF and ABS variables also appear in Table 2. The results for the Positive-Social subscale of the NCBRF revealed a significant group-by-time interaction (p= 0.005): parents rated *Augmented* children as increasingly more socially competent than those with *Basic* treatment, ES = 0.35 (ES=0.46 from Week 3 to Week 9). Analyses of the ABS showed no significant treatment effect for the Proactive subscale and a significant treatment-by-time effect for the Reactive subscale (p= 0.0105, ES = 0.29). Thus, *Augmented* reduced reactive ("hot") aggression more than did *Basic* treatment, whereas treatment effects on proactive ("cold") aggression were not significantly different.

CGI and Responder Status

End-point CGI-I scores—No significant difference was observed between groups on CGI-I scores at endpoint; within the *Basic* group, 58 (70%) were "much or very much improved," 22 (26%) were minimally improved, and three (4%) as unchanged or worse. Within the *Augmented* group, 63 (79%) were much/very much improved, 11 (14%) were minimally improved, and six (7%) were unchanged/worse (p= 0.09). Similarly, no significant effect of risperidone augmentation was observed on CGI-S. At end-point, for those receiving *Basic* treatment, 49 (59%) were rated as "normal/borderline/mildly ill," and 34 (41%) were "moderately/markedly/severely ill." For *Augmented* treatment, the figures were 56 (72%) and 22 (28%), respectively (p= 0.10). Our a priori definition of responder (reduction on D-Total of ≥25% and CGI-I of 1 or 2) was met by 70% of *Basic* treatment

subjects and 79% of *Augmented* therapy subjects. This difference failed to reach significance (Fisher's exact test, $p = 0.09$). The following percentages of children met the stringent definition of responder (parent-rated D-Total score of ≤15 and CGI-I of 1: [a] Weeks 4-8 means were 19.8% for *Basic* treatment and 32.9% for *Augmented*; [b] end-point 33.7% for *Basic* and 34.2% for *Augmented* [N.S.]).

Adverse Events (AEs)—No serious AEs related to study treatments were noted. We report only AEs for Weeks 4– 9, (when the second medication was used) in Table 3. After subtracting the 22 subjects who were not given the second medication, AE data were available for 80 *Basic* treatment and 73 *Augmented* participants. AEs occurring in 9 or more subjects per group are presented in Table 3. Trouble falling asleep ($p = 0.02$) was more common in the *Basic* treatment, whereas gastrointestinal upset ($p = 0.03$) occurred more commonly with augmentation.

Abnormal Laboratory Tests—There were four clinically significant abnormal lab values, 2 with risperidone (triglyceride of 389 and prolactin of 112 [we adopted convention of reporting any prolactin >100 as abnormal]) and 2 with placebo (fasting glucose of 144 and fasting insulin of 24). We analyzed prolactin concentrations at screen and endpoint for 77 children assigned to *Basic* treatment and 75 children assigned to *Augmented* treatment. Although the values were very similar at screen (5.7 ± 3.9 and 5.9 ± 3.0 μg/L, respectively), the values at endpoint were significantly different (*Basic* treatment, 7.1 ± 9.3; *Augmented*: 36.0 ± 27.5; Wilcoxon Ranked Sum test, $p < 0.0001$). Using upper limits of >18.0 ng/mL for boys and >30 ng/mL for girls, we found that 46 of 68 children (68%) assigned to *Augmented* had elevated prolactins, compared with 4 of 73 (5%) assigned to *Basic* treatment. None were considered to be causing sexual or other AEs.

Weight—Mean (±SD) kg weights for the two groups were as follows: *Basic* treatment: BL, 33.2±12.9; Week 9, 32.0±10.9; *Augmented*: BL, 36.0±14.5; Week 9, 37.8±15.5; F (8, 1311) $p = <.0001$. Body mass index [BMI] percentiles were: *Basic* treatment, BL=67.2%ile; Week 9=56.5%ile; *Augmented*, BL=66.6%ile; Week 9=67.0%ile ($p = <.0001$). Thus, analysis of BMI data suggested that the weight gain in the *Augmented* group was associated with overall growth, as BMI percentile did not change appreciably over the course of the trial.

Discussion

Three positive clinical findings resulted from this study. First, the primary outcome, NCBRF D-Total score, improved more with *Augmented* than with *Basic* treatment (ES = 0.43 relative to baseline, 0.50 relative to Week 3, when need for further clinical improvement was determined and risperidone or PBO was added). Second, there was a significant interaction on the ABS, with scores improving more on the Reactive subscale for *Augmented* therapy than for *Basic*, but not so on the proactive scale. Third, improvement on the Social Competence subscale of the NCBRF was significantly better with *Augmented* treatment. Conversely, clinician ratings of improvement on the CGI-I did not show a statistically significant advantage with *Augmented* treatment. Together, the findings indicate that risperidone, when added to optimized stimulant treatment and parent training, provides a moderate advantage in parental ratings of disruptive behavior for children with serious aggression and additional disruptive behaviors.

Our primary finding was not consistent with that of Armenteros *et al*.,[15] who found no significant advantage for parent-rated aggression when risperidone was added to stimulant. The inconsistency might be explained by differences in study design, choice of primary outcome measure (ours did not emphasize aggression *per se*), or severity of DBDs in study samples. The ESs (0.43 and 0.50) for Augmentedf treatment in this study were more modest

than ESs of 0.82 and 0.75 reported in Aman *et al*. and Snyder *et al*., respectively.[11,12] This study extends well beyond those investigations in terms of total exposure to intervention because all participants in the present study received 2 evidence-based treatments, PT + STIM, before commencing placebo or risperidone. In these earlier studies, any STIM was maintained, but there was no effort to titrate it to optimal effect; no PT was provided; and STIM effect was included in the baseline score.

It is also interesting to compare CGI findings across studies. Aman *et al*.[11] reported 8% of the placebo group and 54% of the risperidone group were much/very much improved. Snyder et al.[12] reported 6% of placebo and 48% of risperidone subjects as much/very much improved. Conversely, in this trial, 70% of *Basic* treatment and 79% of *Augmented* treatment subjects were rated with CGI-I scores of 1 (very much improved) or 2 (much improved) with far more children benefiting from the overall treatment package provided in the current study. Indeed, the entry criteria in the current study were more exclusive (in terms of greater severity of aggressive behavior), as compared with previous studies, which increased the opportunity for improvement for all children. In addition, we observed marked benefits conferred by *Basic* (PT + STIM), even before risperidone was added. Despite nominal differential impact on the CGI, we observed statistically significant improvement on NCBRF D-Total, NCBRF Social Competence, and ABS Reactive Aggression. Hence, from the perspective of parent ratings, risperidone produced better results than placebo.

This is one of the first augmented treatment studies in child psychiatry even though augmented treatment has become widespread in practice.[5,9] The question that naturally arises is whether such co-therapy is worth the added expense, inconvenience, and potential risks that may accompany use of more than one drug. In attempting to answer this, it is important to keep in mind the following: First, risperidone was added only *after* stimulant therapy was optimized and *after* PT was begun. Second, problem behavior, as assessed by the NCBRF D-Total, had declined by about 42% by Week 3. Indeed, the pre–post effect size at Week 3 for all participants was 1.25 for NCBRF D-Total and 0.81 for Social Competence, creating very substantial reductions overall before introducing augmentation. In a study of methylphenidate monotherapy in children with CD,[34] clinician ratings of improvement reached 68% (similar to our control treatments) showing that stimulants often have robust effects on antisocial behavior. Third, even compared to continuance of stimulant and PT for the last 6 weeks, *Augmented* therapy was of further benefit (about 21% additional reduction on the NCBRF D-Total [ES= 0.50]). Fourth, a meta analysis of 45 randomized clinical trials targeting aggression in children[35] found a mean ES of 0.56 for monotherapy. As previously noted, our ESs for the ITT sample when risperidone was added to 2 other treatments were 0.43 (relative to Baseline) and 0.50 (relative to Week 3), and our sensitivity ESs were 0.51 and 0.62, respectively. Finally, DBDs, especially when accompanied by aggressive behavior, are often associated with severe later psychosocial problems and impairments such as substance abuse, sexual promiscuity, violent crime, accidents, depression, suicide attempts, spousal abuse, abusive parenting, and incarcerations,[36] making the price of ineffective treatment potentially very high (although continued treatment through childhood and adolescence is likely needed to affect long-term outcomes). Hopefully, these findings will help to inform clinical decisions regarding the utility of short-term augmented treatment. They do not speak to the issue of medium- and long-term usefulness. We have exploratory moderator analyses planned for these data, which may better identify prime candidates for augmented treatment. We already have some indication that the risk-benefit ratio is more favorable for “hot” reactive aggression than for “cold” proactive aggression.

The finding of enhanced Social Competence is reassuring, suggesting that our participants were engaging in more socially appropriate behavior with *Augmented* treatment and that the treatment was not simply suppressing all behaviors, including those that are considered

adaptive. Further, the observation of *Augmented* therapy having significantly greater effect on the ABS Reactive subscale than *Basic* treatment is in line with prevailing thought in the field.[37] This suggests that a principal mechanism of drug effect is on the impulsive, unplanned disruptive actions of these children rather than on callous, planned aggression. As such, the findings help to verify a widely held clinical belief in the field for which there has been little empirical evidence one way or the other.[38]

Figure 2 shows a trend for D-Total scores to converge after Week 5 and diverge again by Week 9. We were unable to find a potential cause for this observation, including attrition or any tendency of children receiving higher risperidone doses to benefit less. PT was completed by Week 9, and it may have contributed to the regained improvement at Week 9.

Children receiving *Augmented* treatment gained more weight than those receiving *Basic* treatment. This appeared to be due more to *Basic* subjects losing weight than to *Augmented* subjects gaining weight. Indeed, the mean weight gain for the *Augmented* group was only 0.38 BMI percentile, using CDC norms. As expected, there was a significant increase in prolactin concentrations with *Augmented* therapy (above the threshold of normal in 65% of cases); those increases were not associated with sexual side effects in this short study. Finally, gastrointestinal upset was significantly greater with *Augmented* treatment (16.4% vs. 5.0%). We are preparing a separate paper to evaluate AEs in detail.

There were several limitations in this study. First, we were assessing a treatment strategy rather than a treatment combination per se. Consequently, when subjects dropped out or were found to be clinical responders in Weeks 1–3, they did not contribute to the medication signal for participants assigned to *Augmented* treatment. Second, to alleviate subject burden, we did not require parent ratings on the NCBRF in Weeks 1 and 2. This proved to be unfortunate because it prevented us from modeling the trajectory for participants who dropped out before Week 3, and hence, we did not fully benefit from the mixed effects regression model. An additional concern was the absence of a statistically significant advantage on CGI-I responder analysis. This finding might be explained by a lag or difference in clinician appreciation of improvements in overall functioning, versus parent ratings of specific behaviors, during a fairly short interval. It is also possible that group differences in dimensional scores of disruptive behavior are not translated into differences in overall functioning, perhaps diminishing any perceived added clinical benefit from risperidone. Finally, we did not measure or control for parental psychopathology, which might have influenced the effect of parent training; however, with 168 subjects, randomization should have distributed the effect of parental psychopathology evenly across groups.

Some of these limitations could obscure the signal from addition of risperidone, which showed a moderate statistical advantage when compared to *Basic* treatment. Although many children with severe aggressive behavior benefit sufficiently from stimulant coupled with PT, an important subgroup continues to experience a degree of behavioral dysregulation. The results of this study provide some reassurance that further behavioral benefit may be obtained from addition of risperidone in cases where there is a suboptimal response to first line PT + STIM, as per TRAAY guidelines.[19] It is important to note that these results were obtained with children selected for severity of aggression and disruptive behavior, and the risk–benefit ratio may well be diminished for children with milder disruptive behavior or no physical aggression.

The discrepancies between our a priori selected primary outcome variable (parent ratings of disruptive behavior), and the blinded clinician ratings of improvement, warrant consideration by clinicians and clinical researchers. A common standard for clinical

improvement is a CGI-I of 1 or 2, which in this study did not distinguish significantly between the groups. Moreover, based on our rigorous criteria for clinical responder (CGI-I=1 and parent-rated D-Total ≤15) in Week 3, equal percentages of children in each group benefited from treatment at end-point (33.7% vs. 34.2%), although there was a mean 13% advantage for Combined treatment for the intermediate Weeks 4 through 8. The discrepancy in outcomes between the primary NCBRF D-Total and secondary CGI scores suggest that the blinded clinicians may have missed some important evidence of clinical benefit noted by parents. These discrepant results, observed in many studies, are difficult to interpret due to complete confounding of reporter with measure type. However, they do underscore the potential importance of not relying on one source of information when evaluating response to treatment in the clinical setting. Consistent with our results, TRAAY guidelines,[19] recommend the use of standardized assessment instruments to help clinicians make more systematic and objective clinical decisions, especially when combined treatment is being considered. Our findings suggest that practicing clinicians may need to use similar rating scales in order to detect improvement.

In conclusion, the findings suggest that after experiencing marked improvements from behavior therapy and optimized STIM, children with DBD and ADHD who have continuing aggression and other disruptive behaviors can experience further improvement with added risperidone. Given the clinical severity of this child population, these findings provide evidence for an additional treatment should it be deemed necessary. It is important to emphasize, however, that these results are based on a relatively brief 6-week trial with possible subsequent waning of efficacy of risperidone or the emergence of problematic adverse events (e.g., weight gain and metabolic disturbance) and that the true implications of this study for informing clinical practice will be more fully realized when analyses of our 3-month follow-up assessment are completed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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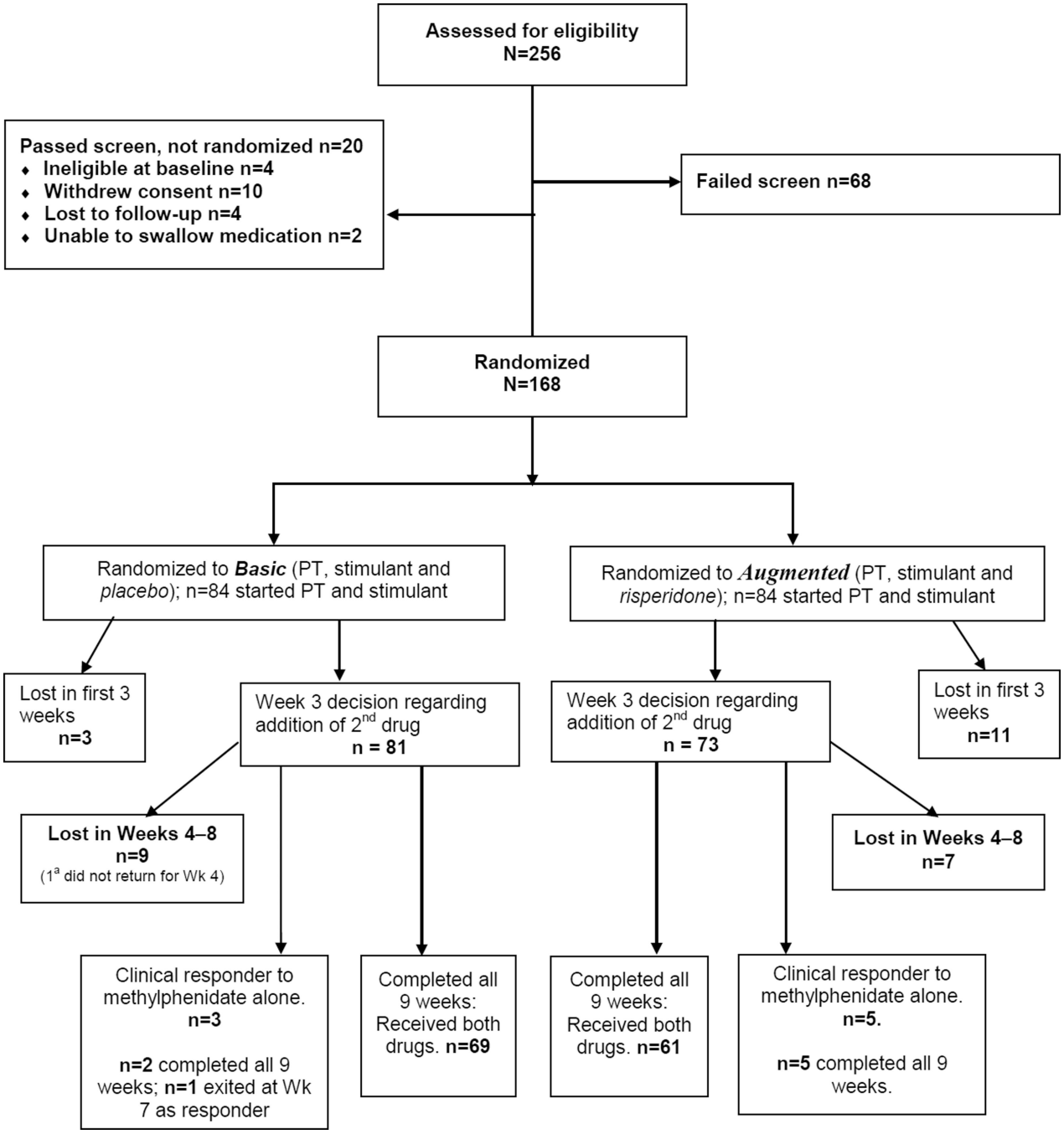

Figure 1.

CONSORT diagram showing subject allocation and subject attrition. Note: All 168 subjects were retained in the mixed model analysis regardless of whether they exited the study before Week 9, failed to respond, or were clinical responders to *Basic* (parent training [PT] + stimulant [STIM]). [a] Although 2nd medication was dispensed, subject was lost to follow-up with no Week 4 assessments.

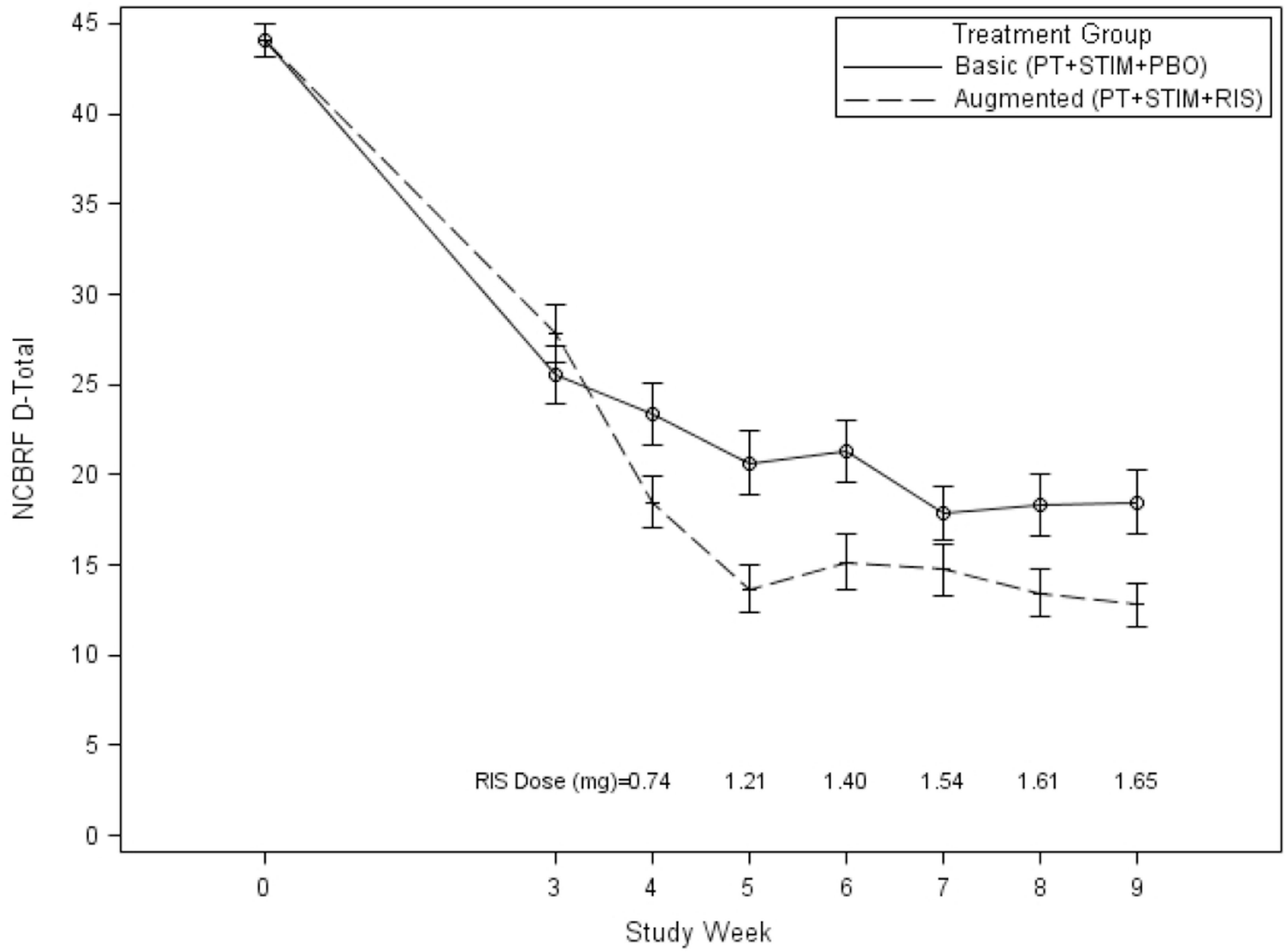

Figure 2.
Nisonger Child Behavior Rating Form (NCBRF) Disruptive Behavior Total (D-Total) score as a function of treatment condition and study visit. Note: Mean doses for risperidone are provided above the X axis.

Table 1

Demographic Features of Participants

Characteristic	Overall (N=168)	Basic (n=84)	Augmented (n=84)
Gender, male, n (%)	129 (76.8)	64 (76.2)	65 (77.4)
Disorder, n (%)			
Conduct Disorder	44 (26.2)	22 (26.2)	22 (26.2)
Oppositional Defiant Disorder	124 (73.8)	62 (73.8)	62 (73.8)
Age, years at screening, m (SD)	8.89 (2.01)	8.75(1.98)	9.03 (2.05)
IQat screening, m (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 (86.90)	72 (85.7)
Other[b]	23(13.7) *1*	11(13.1)	12 (14.3)
Mother's Employment			
Homemaker	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			
Homemaker	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 orGED	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 orGED	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)

Characteristic	Overall (N=168)	Basic (n=84)	Augmented (n=84)
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: Basic = parent training + stimulant + placebo ; Augmented = parent training + stimulant + risperidone . All comparisons were nonsignificant, except Mother's Education, where mothers in the *Basic* treatment had more schooling (Fisher's Exact test, p=0.021).

[a] *Other* category for Race included: Asian, American Indian and Alaska Native, 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 (openended response).

Table 2

Results for Comparisons on Nisonger Child Behavior Rating Form (NCBRF)-Typical IQ (TIQ) and Antisocial Behavior Scale

Variable	Baseline m(SD)	Week 3 m(SD)	Week 4 m(SD)	Week 5 m(SD)	Week 6 m(SD)	Week 7 m(SD)	Week 8 m(SD)	Week 9 m(SD)	*p* value[a]	Estimate (CI)[a]	Effect Size[b]	Effect Size[c]
NCBRF												
D-Total												
n's: Basic	84	82	80	75	74	73	69	71				
n's: Augmented	84	75	71	69	70	68	67	66				
Basic	43.5 (10.3)	24.9(15.3)	22.4(15.1)	20.1(15.7)	20.7(14.6)	16.8(12.8)	17.8(15.0)	17.8(15.4)	0.0143[d]	0.67	0.43	0.50
Augmented	42.1(10.4)	25.9(15.2)	17.1(12.5)	12.1(10.1)	13.8(12.1)	13.0(11.2)	11.7(10.2)	10.7(9.0)		(0.14, 1.20)		
Overly Sensitive												
Basic	6.2 (3.4)	4.6(3.1)	4.1 (3.4)	3.5(3.3)	3.4(2.9)	2.9(2.5)	2.8(3.0)	2.5(2.9)	0.1977	0.51	0.15	0.16
Augmented	6.3(3.2)	3.9(3.1)	2.9 (2.6)	2.2(2.5)	2.2(2.1)	2.4(2.3)	2.0(2.4)	1.9(2.2)	(−0.27,1.30)			
Positive Social												
Basic	9.1(4.2)	13.6(4.7)	13.9(5.6)	14.4(5.9)	15.2(6.5)	15.4(5.9)	15.0(6.2)	15.5(6.6)	0.0112	−2.82	0.35	0.46
Augmented	10.0(3.7)	13.8(5.6)	16.0(6.0)	18.0(6.5)	17.1(6.9)	17.6(6.9)	17.7(7.4)	18.7(6.8)	(−4.99,−0.65)			
ADHD												
Basic	25.3 (6.0)	13.7(8.8)	12.7(8.6)	11.4(8.2)	11.2(7.5)	10.1 (8.0)	10.1 (7.7)	9.5 (7.8)	0.1557	1.61	0.19	0.26
Augmented	24.7(6.1)	14.2 (7.7)	10.6(7.5)	7.8(6.7)	8.4(7.3)	7.4(5.7)	6.8 (5.4)	7.0(6.1)	(−0.62,3.83)			
Withdrawn-Dysphoric												
Basic	13.3(8.0)	8.3 (6.7)	7.1(7.1)	7.0 (8.2)	6.5 (6.3)	5.5(6.1)	5.6(6.3)	5.0(6.5)	0.3565[d]	1.19	0.13	0.003
Augmented	13.7(8.0)	7.8(5.8)	5.4(5.8)	4.0 (5.0)	4.6 (4.8)	4.4(4.6)	3.7(4.3)	3.6 (4.4)	(−0.21,0.58)			
ABS												
n's: Basic	84	—	—	—	—	—	—	77				
n's: Augmented	84	—	—	—	—	—	—	75				
Proactive Behavior												
Basic	20.2(4.6)	—	—	—	—	—	—	15.1(4.3)	0.0935	0.87	0.16	
Augmented	19.6(4.3)	—	—	—	—	—	—	14.0(3.4)		(−0.15,1.88)		
Reactive Behavior												
Basic	15.9(1.8)	—	—	—	—	—	—	12.3(3.1)	0.0105	1.16	0.29	
Augmented	15.5 (2.4)	—	—	—	—	—	—	11.0(2.7)		(0.27,2.04)		

Notes: Basic = parent training + stimulant + placebo ; Augmented = parent training + stimulant + risperidone; ABS= Antisocial Behavior Scale.

[a] *p* values and estimates (CI) represent results of linear mixed model for comparison of therapies at Week 9

[b] Effect size for Baseline to Week 9.

[c] Effect size for Week 3 to Week 9.

[d] *p* values, estimate (CI), and effect sizes represent results from square root transformation on specified NCBRF measures.

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Table 3

Adverse Events Reported In Weeks 4 to 9 for Nine or More Subjects Per Group

	basic (n=80)		Augmented (n=73)		
Variable	**n**	**%**	**n**	**%**	***p* value[a]**
Trouble falling asleep	29	36.3	14	19.2	0.0205
Rhinorrhea	14	17.5	11	15.0	0.8273
Cough	20	25.0	14	19.2	0.4394
Appetite decrease	19	23.8	9	12.3	0.0935
Appetite increase	7	8.8	10	13.7	0.4412
Diarrhea	9	11.3	5	6.8	0.4088
Gastrointestinal discomfort	4	5.0	12	16.4	0.0322
Vomiting	6	7.5	10	13.7	0.2910
Sedation	20	25.0	16	21.9	0.7504
Headache	17	21.3	16	21.9	1.0000

Notes: Basic = parent training + stimulant + placebo ; Augmented = parent training + stimulant + risperidone. Sample size for each group excludes those who dropped out at or before Week 3. One subject within *Basic* treatment took medication between Week 3 and 4 but did not return for assessment, resulting in n=80.

[a] Fisher's Exact Test used to compare incidence of adverse events between groups