Stepped Treatment for Attention-Deficit/Hyperactivity Disorder and Aggressive Behavior: A Randomized, Controlled Trial of Adjunctive Risperidone, Divalproex Sodium, or Placebo After Stimulant Medication Optimization

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Abstract

Objective: Stimulant medications are the most prevalent first-line pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD), but children with aggressive behavior often receive multi-agent treatment. There is sparse evidence for the benefits of adjunctive medications when stimulant monotherapy has proved inadequate, yet the adverse effects of common adjuncts are well-established. This study compared the efficacy in reducing aggressive behavior of risperidone (RISP), divalproex sodium (DVPX), and placebo (PBO) added to stimulant medication among children whose symptoms persisted after individually-optimized stimulant treatment.

Method: This trial enrolled 6–12-year-olds with ADHD, a disruptive disorder, significant aggressive behavior, and prior stimulant treatment. Open, systematically titrated stimulant treatment identified patients with inadequate reductions in aggressive behavior, who were then randomized to receive adjunctive RISP, DVPX, or PBO under double-blind conditions for 8 weeks. Family-based behavioral treatment was offered throughout the trial. The primary outcome was the parent-completed Retrospective-Modified Overt Aggression Scale.

Results: 175 children participated, mean [SD] age 9.48 [2.04] years, 19% female. 151 participants completed the stimulant optimization phase, with aggression remitting among 96 (63%), and 45 were randomized to adjunctive treatment groups. The adjunctive RISP group showed greater reductions in aggression ratings than the PBO group; least squares means difference [ΔLSM], −2.33 (95% confidence interval [CI], −3.83 – −0.82; effect size [ES], −1.32), as did those receiving DVPX (ΔLSM, −1.60; 95% CI, −3.18 – −0.03; ES, −0.91). Mean standardized body mass index scores increased more among RISP-treated patients than those receiving PBO (ΔLSM, 1.54; 95% CI, 0.68 – 2.40; ES = 0.58).

Conclusion: High response rate during the trial's open stimulant optimization phase suggests that rigorous titration of stimulant medication and concurrent behavioral therapy may avert the need for additional medications. Among nonremitters, RISP and DVPX were efficacious adjunctive treatments although RISP was associated with weight gain.

Clinical trial registration information: Effectiveness of Combined Medication Treatment for Aggression in Children with Attention Deficit Hyperactivity Disorder (The SPICY Study); https://www.clinicaltrials.gov; NCT00794625

Keywords

attention deficit and disruptive behavior disorders; aggression; central nervous system stimulants; antipsychotic agents; anticonvulsants

INTRODUCTION

Aggressive behavior is among the most frequent reasons children obtain mental health care.[1–3] The most prevalent psychiatric disorder with which childhood aggressive behavior co-occurs is attention-deficit/hyperactivity disorder (ADHD), usually combined with oppositional defiant disorder (ODD), conduct disorder (CD), or disruptive mood dysregulation disorder (DMDD).[4–6] Impulsiveness is a cardinal element of both ADHD and childhood aggressive behavior, and patients often show deficits in behavioral restraint, cognitive control, and emotion regulation.[5, 7] Recommended pharmacotherapy approaches for aggressive youth with ADHD therefore prioritize treatments that are effective for ADHD, particularly stimulants.[8, 9]

Children with ADHD and behavior disturbances that include aggression often receive other medications adjunctive to stimulants.[10–16] Guidelines recommend that one consider adjunctive treatment when adequate trials of stimulant medication and behavioral interventions yield insufficient improvements.[17–19] Monotherapy trials have shown efficacy for the use of risperidone (RISP) in reducing aggression,[20] and use of risperidone and other second-generation antipsychotics (SGAs) in this context is widespread in U.S. outpatient care.[15, 21–23] However, a study of risperidone vs. placebo added to study-titrated stimulant treatment[24] yielded a smaller effect size than reported in RISP monotherapy trials.

SGAs have metabolic and cardiovascular risks to which youth are especially vulnerable; younger patients are also susceptible to neuromotor adverse effects, perhaps more so than adults.[25–31] The propensity for SGAs to induce rapid weight gain in children is well-documented, and an increased risk for the emergence of insulin resistance has been confirmed.[29, 32] The chronic nature of childhood aggression and behavioral volatility often entails lengthy treatment with medication, and the potential for prolonged exposure to SGAs further heightens concerns.

Despite consensus that first-line pharmacotherapy for ADHD and behavioral interventions should precede adjunctive medications for aggression, trials seldom evaluate cotherapy among patients who are demonstrably underresponsive to these initial treatments. A stepped-treatment trial[33] for children who experienced inadequate response in community care provided an extensive stimulant optimization and behavioral therapy protocol (mean duration 6 weeks). Aggressive behavior remitted among half these participants after this treatment; adjunctive divalproex sodium (DVPX) was more effective than placebo in lowering aggression for the others whose symptoms were refractory to stimulant treatment alone. A trial[24] that compared risperidone vs. placebo added after a briefer stimulant titration and behavioral treatment phase (3 weeks), reported that only 5% had an adequate response to stimulant treatment; however, those randomized to placebo showed further reductions in behavioral disturbances resulting in no difference in responder rates. Ratings of overall disruptive behavior symptoms favored risperidone, however both groups' endpoint scores were within the normal range.[24] These findings suggest that a longer period devoted to stimulant dose optimization and behavioral therapy may be required to determine that these treatments are insufficient for aggressive behavior.

It is important for clinical decision-making (a) to determine the effects of adjunctive treatments among children who are demonstrably under-responsive to thoroughly titrated first-line stimulant treatment; (b) to compare the efficacy of SGAs with alternative adjuncts for those with stimulant-refractory aggression; and (c) to compare adverse effects between these treatments. Stimulant medications are appealing first-line treatments because they have the largest effects sizes for ADHD symptoms, they frequently ameliorate other conduct problems, a regimen's effects are evident right away, treatment can be adjusted rapidly, and their adverse effect profiles are well understood. SGAs ameliorate aggressive behavior, but their effects as adjunctive treatment to thoroughly titrated stimulant therapy is uncertain; moreover, their cardiometabolic and neuromotor risks are worrisome and require they be used sparingly. Among non-antipsychotic mood stabilizers, DVPX may contribute to behavioral stability when children have already gained benefit for ADHD symptoms from stimulant medication. [33] DVPX poses generally lower adverse effect liability for children than SGAs, but determining dose adequacy and safety requires serum levels. It is problematic among post-menarchial women due to its teratogenicity and possible anovulatory and androgenic effects. With these consideration in mind, the present study compared adjunctive risperidone, divalproex sodium, and placebo among 6- to 12-year-olds with ADHD, a disruptive disorder, and chronic aggressive behavior whose aggression did not resolve during an open stimulant optimization phase that also provided family-focused behavioral treatment. We hypothesized both active compounds would be superior to placebo. To increase the likelihood that participants would be candidates for adjunctive medication due to insufficient response after the open stimulant optimization phase, inclusion criteria required prior stimulant treatment during which the trials' behavioral severity criteria were met.

METHOD

Study Design

Figure 1 summarizes the trial's design and procedures. The trial's stepped-care approach began with open-label stimulant medication and behavioral therapy using a protocol to identify patients' most effective, best-tolerated medication dose. Reassessment of aggressive behavior followed. Children whose aggressive behavior persisted were randomized to adjunctive treatment with either RISP, DVPX, or placebo (PBO), in a 2:2:1 ratio, for an eight-week double-blind controlled trial. Stimulant treatment remained constant and behavioral therapy continued. Children whose aggressive behavior remitted at the end of open stimulant optimization discontinued the trial.

Patients

Trial participants were boys and girls between 6 and 12 years old. Diagnostic inclusion criteria were ADHD (any subtype) and either ODD or CD, as defined in DSM-IV-TR. Severity inclusion criteria required parental ratings on the Restless/Inattentive subscale of the Conners Global Index[34] (ConnGI-P) and on the Aggressive Behavior subscale of the Child Behavior Checklist[35] (CBCL) at least 1.5 standard deviations above the mean for the normative reference group corresponding to the child's age and sex. Aggressive behavior severity was measured by the parent-completed Retrospective - Modified Overt Aggression

Scale (R-MOAS). Enrollment required an R-MOAS total score over 24, representing clinically significant aggressive behavior during the preceding week, at both the initial telephone screening and the in-person evaluation. Study enrollment also required recent or current treatment with stimulant medication at a minimum daily total dose equivalent of 30 mg of immediate-release methylphenidate (MPH; e.g., 15 mg of mixed amphetamine salts or dexmethylphenidate, 40 mg of lisdexamfetamine) for at least 30 days.

Exclusion criteria included these disorders as defined in DSM-IV-TR: current or previous major depressive, bipolar I or II, Tourette's, autistic, or any psychotic disorder. IQ below 70 was also exclusionary. A current anxiety disorder was disqualifying if aggressive behavior was chiefly a complication of it (e.g., child with separation anxiety who became aggressive only when separated from attachment figures). Medical exclusions included seizure disorders, pregnancy, and contraindications to treatment with stimulants, RISP, or DVPX.

Recruitment and Enrollment

Three outpatient child and adolescent psychiatry centers recruited study participants from patients currently receiving or seeking care, as well as print and radio advertising. Initial telephone screenings were followed by an evaluation visit when indicated. Parents or legal guardians provided written informed permission, and children >8 years of age gave written assent. Institutional Review Boards at each site approved the protocol and conducted annual reviews.

Assessments and Outcomes

Diagnostic assessment included completion of the Schedule of Affective Disorders and Schizophrenia for School-Age Children[36] (K-SADS) with a parent and the child by a clinical child psychologist or a child and adolescent psychiatrist. A second clinician (child and adolescent psychiatrist or advanced-practice nurse practitioner) conducted a separate clinical diagnostic evaluation and obtained a medical history from the parent. The K-SADS interviewer and the clinical assessor conferred to arrive at consensus diagnoses and eligibility to begin the trial.

The trials' primary outcome, aggressive behavior, was assessed using the R-MOAS. This instrument is adapted from the Overt Aggression Scale[37] so that informants rate the frequency of the child's aggressive behaviors using predefined intervals, rather than clinician estimates of the number of incidents the original version acquires. Items are grouped into four categories of aggression (verbal, physical, toward property, and toward oneself). Scores are weighted to accord larger values to more severe aggressive behaviors. Psychometric data based on a similar cohort are available from an earlier trial.[33] This form and its scoring guide are in Supplement 1, available online.

Secondary outcomes were the two subscales of the CBCL (Aggressive Behavior and Rule-Breaking Behavior) that form its Externalizing broadband component, and the ConnGI. These instruments yield standardized (T) scores based on their normative samples' score distribution.

Other measures served to indicate the baseline severity of the patient sample. These measures were the teacher version of the Conners Global Index,[34] the Teacher Report Form, [35] and the parent-completed Columbia Impairment Scale[38] (CIS).

Safety and adverse effects were assessed using the Barkley Behavioral and Adverse Effect Questionnaires[39] (BBAEQ), amended to include effects associated with RISP and DVPX. Spontaneously reported adverse effects were also recorded and tracked. Height, weight, blood pressure, and pulse were measured at each visit. Standardized body mass index (z-BMI) was based on U.S. growth charts.[40] Motor abnormalities were assessed at visits during the randomized controlled trial (RCT) phase.[41–43] Laboratory tests for patients randomized to adjunctive medications included complete blood cell counts, glucose drawn during a fasting state, serum prolactin, liver enzymes, and trough valproic acid (VPA) levels.

Study Treatments

Stimulant Treatment—On trial entry, non-stimulant pharmacotherapy was discontinued on a washout schedule appropriate to its elimination half-life; the study only enrolled children for whom current treatment was ineffective and the provider concurred that discontinuation was in the child's interest. Open-label stimulant titration was used to identify the child's most effective and best tolerated regimen. This protocol began with MPH in an extended-release tablet whose coating contains the initial dose and later release of two internal drug layers is controlled by a reverse-osmosis mechanism (MPH-OROS) . Dosage adjustments occurred during weekly office visits based upon ConnGI-P (and ConnGI-T when available), R-MOAS, and BBAEQ-M data. Titration usually occurred in 18 mg increments until either (a) ConnGI-P ratings were within one standard deviation of the mean for the child's age and sex, (b) adverse effects contraindicated the dose, or (c) the ceiling dose of 72 mg/d was attained, though clinicians had the option to increase to 90 if indicated and tolerated. When tolerability issues hindered continuation of a clinically more effective dose, reductions by 9 mg could be employed. Because earlier research indicated no association between stimulant dose and weight,[44] titration was driven by response and tolerability rather than a target mg/kg approach.

If tolerability problems attributable to long duration of action occurred (sleep, appetite, etc.), patients could be switched from MPH-OROS to a beaded biphasic methylphenidate preparation (MPH-BI), adjusted by 10 mg per week, with a ceiling dose of 60 mg/d. Participants who experienced insufficient or adverse response to MPH could switch to extended-release mixed amphetamine salts (MAS-XR), titrated in 5 mg increments, with a ceiling dose of 35 mg/d.

Review of response by two clinicians at each site to all regimens determined the child's best dose, which was continued or reinstated for another week to verify its efficacy. A final assessment determined eligibility for trial continuation. (1) Participants whose *aggressive behavior remitted* (RMOAS < 15) concluded the trial. (2) Participants whose aggression persisted and who experienced benefit for ADHD symptoms to warrant stimulant continuation (based on ConnGI-P improvement by at least 2 standard errors and clinical judgment) were randomly assigned to one of the double-blinded adjunctive medication treatment groups.

Randomization and Treatment with Adjunctive RISP, DVPX, or PBO—Group allocation was stratified by site and sex, and random orders using blocks of n=5 within each stratum was generated by a statistician using SAS (SAS Institute, Cary, NC). Investigational pharmacies at each site followed the sequence and dispensed study medications accordingly. Unblinded safety monitors at each site were the only other individuals aware of group assignment.

A compounding pharmacy produced capsules containing RISP (0.25, 0.5, and 1 mg), DVPX (125 and 250 mg), and matching PBOs containing cellulose filler. Medications were dispensed using a "double-dummy" technique; each patient took two sets of capsules, but only one contained active drug corresponding to his/her randomized treatment, or, if randomized to PBO, all capsules contained filler only.

RISP dose started at 0.25 mg each evening for three days, with a morning dose of 0.25 MG added on the fourth day. Further dose adjustments were elective and based on response and tolerability, but dose increases could not exceed 0.5 mg each week. Maximum allowable RISP dose was 2.5 mg in divided doses, achieved by week 5.

DVPX target dosing was weight-based and aimed to achieve approximately 18 mg/kg by the end of the first week (e.g., oral dose for those weighing 18–27 kg was 375 mg daily while for the heaviest weight stratum, 57–68 kg, dose was 1000 mg). Trough valproic acid levels were sent to the site's safety monitor who advised blinded clinicians if a dose increase was permissible or if decrease was required; those on placebo DVPX received sham instructions according to a randomized schedule to preserve blinding. When permitted by VPA level, dose increases by 125 or 250 mg occurred based on clinical response through Week 5. Ceiling VPA level was 110 ml/L. Due to DVPX's teratogenicity, the protocol required that all female participants of child-bearing potential be serum bHCG-negative, be counseled about the risks of pregnancy and that a method of continuous contraception be used for those who were sexually active. However, no individuals of child-bearing potential were randomized.

Cross-site teleconferences occurred week to biweekly throughout the trial during which participants' treatment was reviewed to insure concordance with the protocol.

Family-Based Behavioral Therapy—All families had behaviorally-oriented psychosocial treatment during the stimulant medication optimization phase and the randomized, controlled trial phase. Therapists were licensed social workers or advanced graduate students in clinical child psychology. Families were seen weekly during the same visit that they met with the pharmacotherapy treatment clinicians. Treatment was based on the Community Parent Education Program,[45] a group program adapted for use with individual families. Core components are 1) goal setting; 2) increasing positive interactions with the child and rewarding cooperative behavior and composure; 3) judicious ignoring of low-level misbehaviors; 4) communicating directions and feedback for behavior; 5) a system to reward cooperation and improved frustration tolerance; and 7) handling uncooperative and dyscontrolled behavior. The first author's weekly supervision of therapists emphasized

adherence and cross-site consistency in the application of the program's principles and procedures.

Data Analysis

The primary outcome, R-MOAS total score, was positively skewed (Kolmogorov-Smirnov $D = 0.12$, $p < 0.01$). Analyses therefore used its square-root transformation.

Models for outcomes included the fixed effects of treatment group, time and their interaction. Patients nested within study sites were random effects. Model estimation and statistical tests were computed with PROC GLIMMIX[46] running on SAS® v9.4. Estimates for outcomes are the marginal, least-squares means and standard errors these models generated. Analyses included all subjects who provided at least one post-randomization outcome measurement, following intention-to treat principles. Confidence intervals for the standardized differences were computed using the method for small sample sizes described by Hedges and Olkin.[47, p. 86] Similarly, effect sizes (ES) were determined using Hedge's g, which is interpretively identical to Cohen's d, but its computation includes a correction for small samples ($n < 50$).[48, p. 27] Pooled standard deviations for ES were derived from the groups' baseline scores.

RESULTS

Participants and Progression through Trial Stages

Figure 2 shows the enrollment and trial-completion status of all children screened for participation. Of the 175 who began study treatment, 24 (13.7%) did not complete the open stimulant optimization phase. Among those who did complete it, 96 (63.6%) fulfilled the criterion for remission of aggressive behavior, that is, three consecutive weeks with subthreshold R-MOAS ratings. Forty-five (29.6%) children were eligible for randomization to the adjunctive treatment conditions, and 42 began the blinded treatment to which they were allocated.

Table 1 presents characteristics of the participants who started treatment in the trial. Ninety-two percent exceeded the CIS cutoff for impairment (for reference, 35–40% of youth receiving outpatient mental health care meet this criterion[15]). Almost all (94.3%) received special education services, and 31.4% were in specialized class settings. Twenty-four percent received prior antipsychotic treatment for behavioral disturbances, and 18.3% had at least one crisis that led to presentation at a hospital emergency department or admission to psychiatric inpatient treatment.

Table 1 also shows three background characteristics significantly associated with the likelihood that aggressive behavior would remit during the stimulant optimization phase. The significant overall race/ethnicity effect shown in the last column reflects the higher proportion of black children (65.52%) than white children (46.91%) who completed the open stimulant optimization phase and did not enter the randomized controlled trial because their aggressive behavior remitted (X^2 [1] = 9.62, $p < .002$, for this comparison).

The remitter group had a smaller proportion of children with prior antipsychotic treatment (16.13%) than did the stimulant-refractory group (34.15%). However, children with prior antipsychotic treatment who completed the stimulant optimization phase had equal rates of remission and nonremission (15/29 and 14/29). Stimulant optimization phase non-remitters were also more likely to have had prior psychosocial treatment than remitters (78% vs. 60%).

Study Medication Doses and Psychosocial Treatment Attendance

At the end of their open stimulant optimization treatment, 104 children received MPH-OROS (69% of the aggression remitters, 55% of non-remitters in the RCT, and 29% of non-completers); 17 received MPH-BI (8% of remitters, 13% of non-remitters in RCT, 16% of non-completers), and 42 received MAS-XR (23% of remitters, 33% of non-remitters in RCT, and 25% of non-completers), with X^2 [4] = 3.62, p =.46). The mean (sd) daily dose, in immediate-release methylphenidate equivalence units, was 41.6 (16.12) mg. Dose differences between stimulant optimization phase outcome groups were not significant (F [2, 160] = 1.68, p = .19). Remitters' mean stimulant MPH dose equivalent was 42.03 (14.6), non-remitters RCT participants' mean was 44.25 (16), and non-completers' mean was 37.38 (19.9).

The duration of the stimulant optimization protocol varied because of the individualized nature of the dose optimization approach. Aggression remitters had a shorter stimulant optimization phase compared to those with persistent aggression who entered the RCT (mean [sd], 75.4 [32] days vs. 66.5 [36.4]), but this difference was not statistically significant, F (1,131) = 1.78, p =.18).

Nonremitters who entered the RCT phase had more psychosocial treatment sessions during the stimulant optimization phase than those whose aggression remitted by its end (mean [sd], 4.54 [2.5] vs. 3.48 [2.27]; F [1,123] =5.36, p = .023).

In the RISP group, the mean dose (sd) of active RISP was 1.15 (0.81) mg/d (range, .05 to 3.0 mg/d). In the DVPX group, the mean dose of active drug was 713 (327) mg/d (range, 250 – 1750 mg/d and the mean (sd) serum valproic acid level was 77.75 (25.76) ml/L. The mean number (sd) of total behavioral therapy sessions for children randomized to adjunctive treatment was 8.22 (4.5)

Primary Outcome, Parent Ratings of Aggressive Behavior

Figure 3 presents each study treatment group's least-squares mean R-MOAS scores obtained at Baseline, Stimulant Optimization Endpoint, and, for children randomized to adjunctive treatments, their group's controlled trial endpoint. The figure also shows the Baseline and Stimulant optimization endpoint values for children who experienced remission of aggressive behavior with after open stimulant optimization to indicate that the magnitude of improvement for randomized patients remained substantially less even after adjunctive treatments.

Table 2 contains outcomes and statistical analysis results, also with stimulant optimization phase responders included for comparison though excluded from statistical tests. The

treatment group-by-time interaction for RMOAS scores was significant (F[2, 105] = 2.77, p = .03). Pairwise comparisons of the group's least-squares means at the RCT endpoint indicate larger reductions for both active treatments relative to placebo. However, the difference from placebo was larger for the risperidone group (−2.328; t[105] = −3.07, p < .003) than for the DVPX group (−1.6; t[105] = −2.02, p < .046), the latter excluding zero from its confidence interval only marginally.

Secondary Outcomes

CBCL scales showed a similar pattern. Significant group-by-time interactions reflected greater average reductions for the risperidone group compared to the placebo group for Aggressive Behavior and Rulebreaking Behavior scores. DVPX differed reliably from placebo on the Aggressive Behavior scale.

The aggression-remission criterion (R-MOAS < 15) was met by 69% of the RISP group, 40% of the DVPX group, and 37% of the PBO group (Fisher's exact test [49] p = .023).

The overall group-by-time interactions for the Conn-GI Emotional Lability and CDRS depression ratings were not significant. As shown in Table 2, however, between-group contrasts showed significant superiority for risperidone over placebo.

Table 2 shows that Columbia Impairment Scale ratings had a significant effect for time, reflecting improved mean scores overall, with no difference between treatment groups.

Tolerability

Standardized BMI scores increased significantly for the RISP group relative to the PBO and DVPX groups (Table 2). Weight gain in the RISP group averaged 2.23 kg, while those receiving DVPX and PBO averaged 0.65 kg and 0.02 kg, respectively.

There were no serious adverse events during this study. Table S1, available online, shows the rates of adverse events. During the stimulant optimization phase, there was one investigator-initiated discontinuation due to medication intolerance. During the controlled trial of adjunctive treatments, two children experienced adverse events that led to early discontinuation. One RISP-treated patient developed neutropenia and one DVPX-treated patient developed widespread skin rash; both resolved upon drug discontinuation and treatment by a separate, safety monitor physician. Two other patients, one each in the DVPX and PBO groups, exited the trial early because of symptom worsening. Study medications were judged unlikely to have caused their behavioral deterioration, but their clinical condition precluded continuing blinded treatment.

DISCUSSION

Among patients randomized to an adjunctive treatment because of inadequate response to open stimulant optimization, RISP showed an appreciable advantage over placebo on the primary outcome of aggressive behavior, the two CBCL externalizing behavior subscales, and on rates of remission of aggressive behavior. DVPX's effect size over PBO was smaller but also statistically significant for reduced aggression and disruptive behavioral symptoms

more broadly. Weight and z-BMI changes in the RISP group were significantly greater compared with PBO. The high rate of remitted aggressive behavior during the stimulant optimization phase reduced the RCT's sample size, decreasing the trial's power for the comparison of RISP and DVPX and rendering it inconclusive in comparing their efficacy and non-BMI safety profiles. After stimulant medication optimization, aggression remitted for 55% of enrollees and 63.6% of completers. This is noteworthy because participants were selected for their prior non-response to stimulant medication and elevated indices of severity (prior psychiatric emergencies, special education services, multi-medication treatment, etc.) were prevalent. By requiring prior stimulant treatment at moderate doses and high baseline severity, we aimed to increase the likelihood that enrollees would represent patients who need adjunctive medications because of inadequate response to first-line treatment. Nevertheless, a methodical approach to establishing these participants' most beneficial stimulant regimen frequently culminated in behavioral improvements that made additional medications unnecessary. It is therefore important for future trials to plan for diminished sample sizes that may result when rigorous first-line treatment is followed by high rates of response that obviates the need for adjunctive medication. Although difficult and costly to conduct, stepped-care trials are necessary to determine the value of medication polytherapy, which is clinically pervasive but has very limited evidentiary support for children and adolescents.

We found that black children were more likely than white children to experience remission of aggressive behavior during the stimulant optimization. Bearing in mind studies reporting that black children less often receive appropriate evaluation and treatment for ADHD,[50–53] it seems possible that regular contact during our trial's lead-in treatment might have rectified deficiencies in prior care to which white children were less exposed. Other data suggest racial differences in parent ratings on common structured assessment tools, leading to inflated scores for black youth, which might yield baseline assessments that overestimate severity.[54] These and other factors associating race and ethnicity with treatment outcomes indicate the importance of performing studies adequately powered to examine them.

Because the trial's stimulant optimization phase provided open treatment, there is a risk that attributing its high aggression remission rate to its specific approach may be inaccurate. However, placebo and nonspecific effects stem largely from patients' expectancies of a new medication or setting.[55, 56] This study involved medications that children took at enrollment or earlier and most families had previous behavioral therapy in the same location as the trial sites. It is thus unlikely that this study's open stimulant optimization phase embodied these elements of novelty that would have fostered expectancies favoring nonspecific effects. Moreover, placebo effects are generally small in childhood ADHD,[57] and negligible among children who have had prior stimulant treatment[58, 59]

Another trial reported remitted aggression among just 4.5% of a similar patient population who completed a 3-week stimulant lead-in,[24] suggesting that our more extensive titration and psychosocial treatment phase contributed to a more favorable outcome with first-line treatment. Because non-remitters attended more psychosocial therapy sessions than remitters, there is no evidence that underuse of that modality diminished behavioral response. Our study also based stimulant dose titration on weekly parent ratings of ADHD

symptoms and adverse effects, allowed a wider range of doses, switched stimulant products for insufficient improvement of ADHD symptoms as well as for tolerability problems, and determined response based on three consecutive weekly assessments on a given regimen. Nevertheless, this trial was not designed to parse the contributions of the lead-in phase's components. Further study is required to determine more conclusively the specific impact of well-monitored, measurement-based delivery of first-line treatments and other aspects of trial involvement.

Other study limitations include its short time frame for what are typically chronic problems that require extended treatment; we did not conduct systematic follow-up assessments of participants who discontinued because of satisfactory response during the initial stimulant optimization and behavior treatment phase. The trial's outcomes were confined mainly to parent-reported behavior. Impairments outside the home setting are nevertheless significant for children with ADHD and conduct problems. Because we limited the patient cohort to children with ADHD and aggressive behavior our findings may not generalize to those who have significant conduct problems but do not have ADHD. Although we observed RISP's propensity to raise BMI, our sample did not enable us to estimate the less common incidence of neuromotor adverse effects. We did not require that female participants be prepubertal, but just about all were. We recognize that DVPX's teratogenicity disfavors its use among those who might become pregnant, and its potential association with hyperandrogenism and anovulation is also a deterrent. These factors restrict the generalizability of our findings for the treatment of postpubertal female individuals.

Our findings confirm that RISP and DVPX may benefit patients with aggression refractory to first-line stimulant and behavioral treatments. However, Figure 3 shows that those receiving these adjunctive treatments remained more symptomatic than those who remitted with stimulant alone. It is unclear if insufficient response of aggression to stimulant medication denotes a distinct pathophysiology, a more pernicious course, or greater overall disorder severity. We did not find, however, that baseline indices of severity distinguished those experiencing robust stimulant response from others. It is possible that stimulant refractoriness marks a mechanism of disorder that eludes stimulants' effect of enhanced synaptic availability of dopamine and norepinephrine. It is tempting, if simplistic, to suspect that these youngsters have greater mood-related (i.e., "bottom-up") psychopathology, while strong stimulant responders have disturbances more restricted to impulse dyscontrol (i.e., "top-down" regulatory deficits). Disruptive mood dysregulation disorder (DMDD) is a clinical phenotype thought to involve a primary abnormality of mood that features severe behavioral outbursts alongside persistent and pervasive irritable or angry mood. However, our group reported earlier that children with these characteristics, as well as comorbid ADHD, were just as likely to benefit from stimulant medication as those without persistently negative mood. [60] Antidepressant controlled trials for DMDD are limited. One inpatient stepped-care trial in which either adjunctive citalopram or placebo was added to methylphenidate showed an advantage for citalopram on Clinical Global Impressions (CGI) Improvement ratings and modestly larger change in CGI Severity scores.[61]

Our results reinforce the clinical value of optimizing first-line stimulant pharmacotherapy for impaired youngsters with ADHD through measurement-based titration and family-based

behavioral therapies, practices that remain uncommon in routine care.[62, 63] Given the adverse effect liabilities of adjunctive medications, it is important to improve ADHD care so that clinicians initiate antipsychotic and other co-therapies as sparingly as possible. For those who do not experience sufficient benefit from thoroughly-implemented initial treatments, this study adds to the emerging evidence base that such adjunctive medications may be helpful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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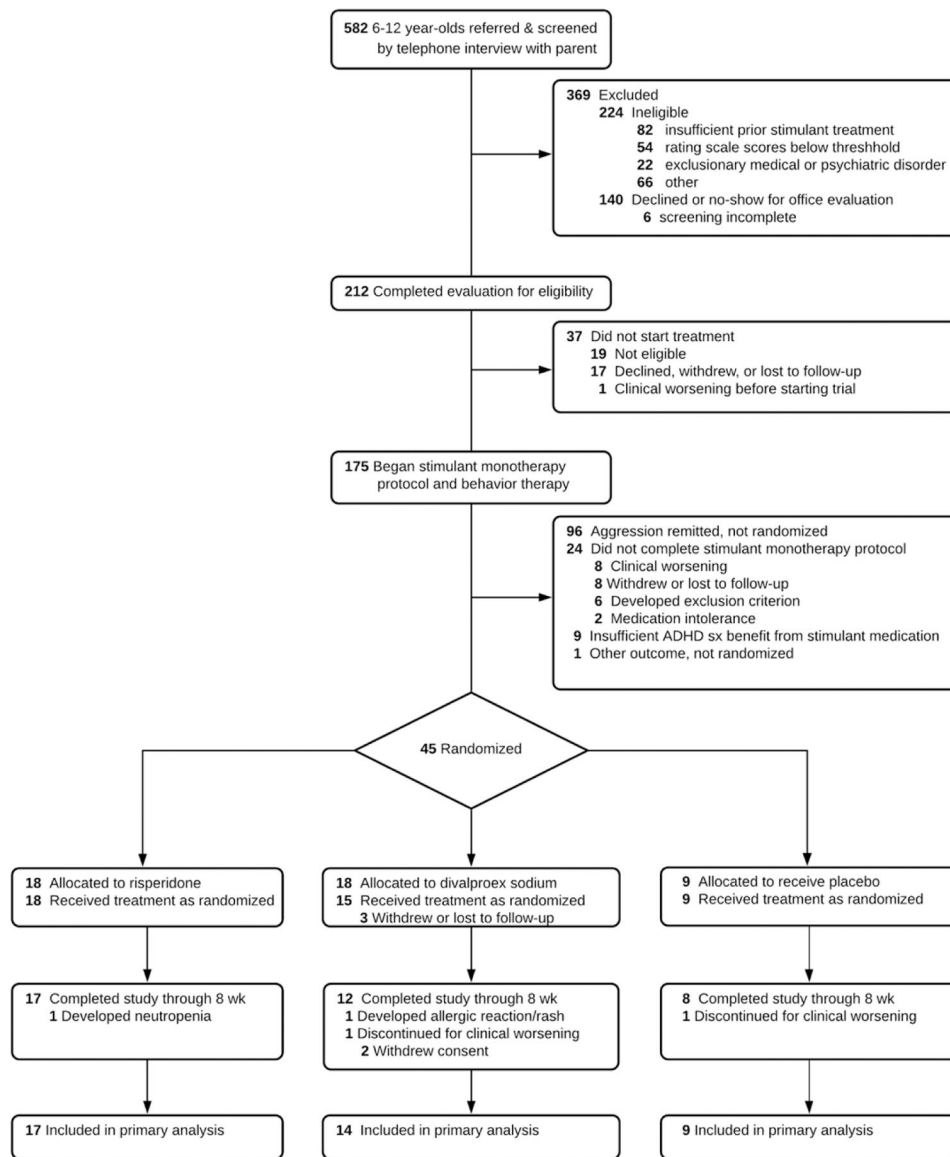
Figure 1:

Schematic of Stepped-Treatment Trial Design and Procedures

Note: BBAEQ-M = Barkley Behavior and Adverse Effects Questionnaire - Modified; BP = blood pressure; ConnG R/I = Conners Global Improvement Index Restless-Inattentive subscale; DVPX = divalproex sodium; EKG = electrocardiogram. EPS = extrapyramidal symptoms; HR = heart rate; mg/d = milligrams per day; mg/wk = milligrams per week; R-MOAS = Retrospective - Modified Overt Aggression Scale; RCT = randomized controlled trial; RISP = risperidone; SD = standard deviation; SE = standard error; sxs = symptoms; VPA, valproic acid.

Enrollment

Consent/assent; clinical & diagnostic assessments; baseline measures.

No Meds Baseline

1-2 Weeks

Washout period for nonstimulant medications as needed.

Open Stimulant Optimization

Variable Duration, Mean [SD] , 69 [35.5] days

- Dose or product adjustments weekly. See text for dosage increments/decrements.
- Titrate until: (A) ConnGI *T* score < 65; (B) tolerability problems arise; (C) ceiling dose attained.
- If B or C, reduce dose or switch agent.
- Treat with best-tolerated regimen with greatest score reduction and confirm response. If not confirmed, adjust dose accordingly until response is stable over two weeks.

Family-based behavioral therapy

R-MOAS, ConnGI, BBAEQ-M, BP, HR, height and weight at each visit

Response Determination

| *If:* | R-MOAS < 18 (aggression remitted) |
| *then:* | **Discontinue from trial** |

Otherwise...

| *If:* | ConnGI R/I decreases > 2 SE (improved ADHD sxs warrant stimulant continuation) |
| *then:* | **Eligible for RCT** |

Otherwise...

| *If:* | ConnGI R/I decreases < 2 SE (insufficient stimulant benefit to warrant continuation) |
| *then:* | **Discontinue from trial** |

Blinded RCT of Adjunctive Risperidone, Divalproex Sodium, or Placebo

Pre-RCT Tx	Days 1-3	Days 4-7	Weeks 2-5	Weeks 5-7	Week 8
	RISP 0.25 DVPX, < 27 kg: 250 DVPX, > 27 kg: 500	RISP 0.5 DVPX, < 27 kg: 375 27-40 kg: 500 40-57 kg: 750 > 57 kg: 1000	*Dose escalation based on response (CGI-S > 3)* RISP increase 0.5 mg per wk up to 2.5 mg/d DVPX increase 125/250 mg/wk, max VPA 110 ml/L	Continuation	Trial Endpoint
All labs and EKG			VPA level after Week 1 and each dose change	Week 4 All Labs		All labs and EKG
Family-based behavioral therapy continues					
R-MOAS, ConnGI, BBAEQ-M, BP, HR, height and weight, EPS assessments, at each visit .					

Figure 2:
CONSORT Flow Chart
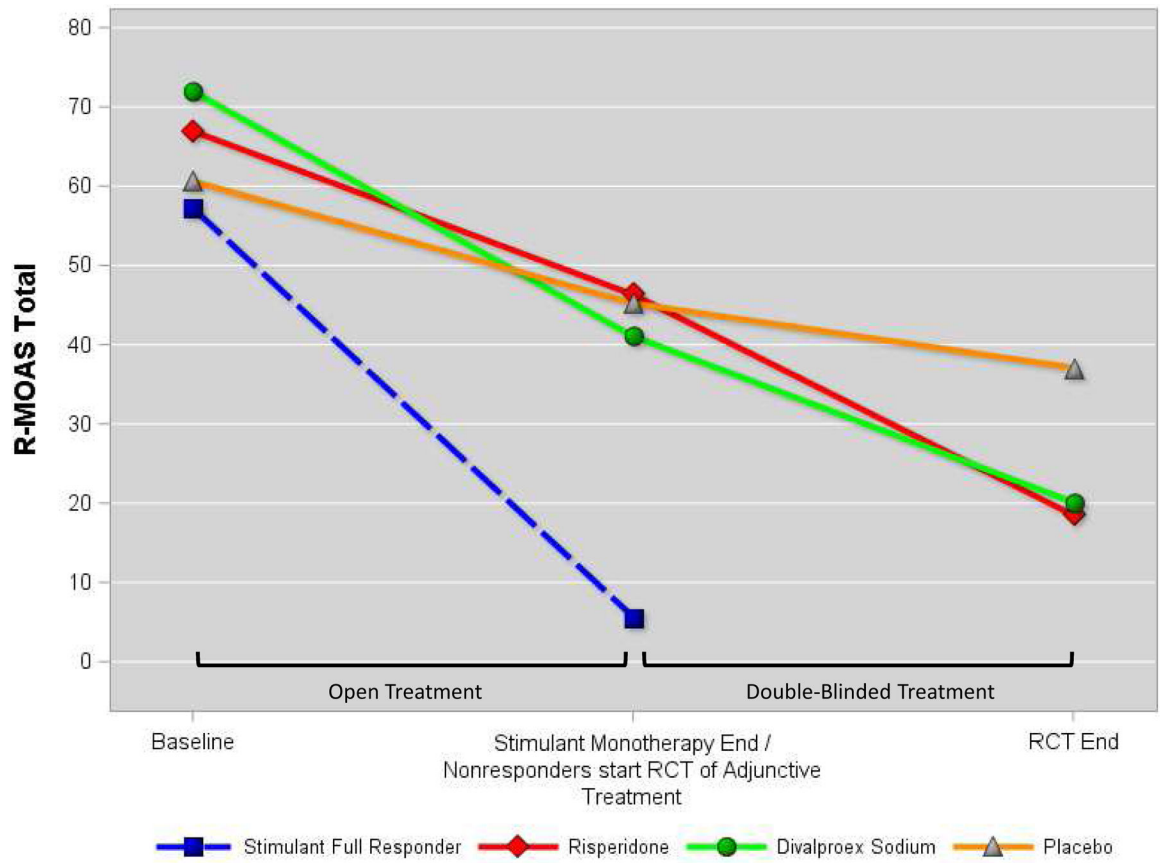
Figure 3:
Treatment Groups' Retrospective-Modified Overt Aggression Scale Scores

TABLE 1:

Characteristics of Patient Sample by Stimulant Optimization Trial Outcome Status

	Complete Sample (n = 175)	Stimulant Optimization Phase Aggression Remitters (n = 96)	Stimulant Optimization Non-Remitters Randomized to RCT (n = 45)	Stimulant Optimization Non-Completers or No Benefit (n = 34)	F or χ^2 (p)[a]
Demographic Characteristics					
Age in years, Mean (SD)	9.47 (2.04)	9.38 (2.11)	9.63 (2.02)	9.53 (1.93)	0.26 (0.77)
Female / Male participants, No. (%)	34 / 141 (19.4 / 80.6)	20/76 (20.8 / 79.2)	7/49 (15.6 / 84.4)	7/27 (20.6 / 79.4)	0.58 (0.76)
Race/Ethnicity, Number (%)[b]					
Black	29 (16.57)	19 (19.79)	3 (6.67)	7 (20.59)	12.69 (0.04)
Hispanic	53 (30.29)	33 (34.38)	8 (17.78)	12 (35.29)	
Other	12 (6.86)	5 (5.21)	5 (11.11)	2 (5.88)	
White	81 (46.29)	39 (40.63)	29 (64.44)	13 (38.24)	
Parents' Marital Status, No. (%)					
Divorced/Separated	38 (21.71)	22 (22.92)	7 (15.56)	9 (26.47)	2.30 (0.91)
Married	96 (54.86)	50 (52.08)	28 (62.22)	18 (52.94)	
Never married	35 (20.00)	20 (20.83)	9 (20.00)	6 (17.65)	
Other or Unknown	6 (3.43)	4 (4.17)	1 (2.22)	1 (2.94)	
Adults in home, No. (%)					

	Complete Sample (n = 175)	Stimulant Optimization Phase Aggression Remitters (n = 96)	Stimulant Optimization Non-Remitters Randomized to RCT (n = 45)	Stimulant Optimization Non-Completers or No Benefit (n = 34)	F or χ^2 $(p)^a$
1	45 (26.01)	25 (26.04)	10 (22.73)	10 (30.30)	2.55 (0.68)
2	98 (56.65)	51 (53.13)	28 (63.64)	19 (57.58)	
3 or more	30 (17.34)	20 (20.83)	6 (13.64)	4 (12.12)	
Clinical Characteristics					
Comorbid Disorders[c] (other than ADHD), No. (%)					
Oppositional defiant disorder	148 (84.57)	82 (85.42)	39 (86.67)	27 (79.41)	0.90 (0.64)
Conduct disorder	27 (15.43)	14 (14.58)	6 (13.33)	7 (20.59)	0.90 (0.64)
Anxiety disorder	62 (35.43)	40 (41.67)	13 (28.89)	9 (26.47)	3.67 (0.18)
Depressive disorder	36 (20.57)	17 (17.71)	10 (22.22)	9 (26.47)	1.28 (0.50)
Tic disorder	6 (3.42)	3 (3.13)	1 (2.22)	2 (5.88)	0.84 (0.73)
Elimination disorder	19 (10.86)	9 (9.38)	6 (13.33)	4 (11.76)	0.53 (0.76)
Learning disorder	39 (22.29)	25 (26.04)	6 (13.33)	8 (23.53)	2.89 (0.21)
Clinical Severity, Mean (SD)					
Retrospective-Modified Overt Aggression Scale, total score	62.79 (31.75)	57.96 (29.79)	67.71 (33.24)	69.94 (33.69)	2.56 (0.08)
Conners Global Index Restless/Inattentive, T score	84.79 (7.63)	85.15 (7.34)	83 (9.28)	86.15 (5.60)	1.90 (0.15)
Conners Global Index Emotional Lability, T score	82.4 (9.16)	82.04 (9.14)	81.60 (9.64)	84.47 (8.50)	1.12 (0.33)
Child Behavior Checklist, Total Problems, T score	71.82 (5.63)	71.87 (4.78)	71.47 (6.69)	72.15 (6.40)	0.15 (0.86)
Child Behavior Checklist, Internalizing Problems, T score	61.39 (8.26)	60.62 (8.09)	61.69 (8.93)	63.15 (7.75)	1.21 (0.30)
Child Behavior Checklist, Aggressive Behavior, T score	76.95 (8.99)	75.96 (8.56)	78.18 (8.35)	78.12 (10.77)	1.29 (0.28)
Child Behavior Checklist, Rule Breaking Behavior, T	72.37 (6.44)	72.29 (6.61)	71.87 (5.43)	73.24 (7.26)	0.45 (0.64)

	Complete Sample (n = 175)	Stimulant Optimization Phase Aggression Remitters (n = 96)	Stimulant Optimization Non-Remitters Randomized to RCT (n = 45)	Stimulant Optimization Non-Completers or No Benefit (n = 34)	F or χ² (p)[a]
Teacher Conners Global Index, Restless/Inattentive, *T* score	75.63 (13.88)	75.28 (14.17)	73.96 (15)	78.20 (12.03)	0.62 (0.54)
Teacher Conners Global Index, Emotional Lability, *T*	69.59 (17.36)	68.37 (17.62)	67.54 (18.55)	74.88 (14.89)	1.51 (0.23)
Columbia Impairment Scale, Total Impairment Score	29.89 (9.35)	29.43 (8.98)	30.09 (10.55)	30.94 (8.90)	0.34 (0.71)
Columbia Impairment Scale, Severe Impairment (total score >=16), No. (%)	161 (92.53)	87 (90.63)	41 (93.18)	33 (97.06)	1.54 (0.59)
Teacher Report Form, Total Problems, *T* score	66.08 (9.91)	66.49 (10.28)	61.88 (10.53)	69.04 (6.53)	3.43 (0.04)
Teacher Report Form, Internalizing Problems, *T* score	58.71 (9.39)	58.85 (9.69)	56.50 (10.94)	60.50 (6.19)	1.11 (0.33)
Teacher Report Form, Aggressive Behavior, *T*	67.73 (12.11)	68.64 (12.95)	63.29 (11.46)	69.42 (9.14)	2.08 (0.13)
Teacher Report Form, Rule Breaking Behavior, *T*	62.49 (8.05)	62.93 (8.28)	58.38 (6.47)	65.29 (7.45)	5.01 (0.01)
Prior Treatments & Services, No. (%)					
Special in-class school services	110 (62.86)	60 (62.50)	29 (64.44)	21 (61.76)	0.07 (0.95)
Specialized class or school setting	55 (31.43)	32 (33.33)	14 (31.11)	9 (26.47)	0.55 (0.78)
Prior antipsychotic treatment	42 (24.00)	16 (16.67)	15 (33.33)	11 (32.35)	6.28 (0.04)
Prior mood stabilizer treatment	6 (3.43)	2 (2.08)	2 (4.44)	2 (5.88)	1.28 (0.47)
Prior alpha-2-agonist treatment	33 (18.86)	18 (18.75)	8 (17.78)	7 (20.59)	0.10 (0.93)
Prior selective serotonin reuptake inhibitor treatment	17 (9.71)	8 (8.33)	7 (15.56)	2 (5.88)	2.53 (0.33)
Prior psychiatric emergency department visit or hospitalization	32 (18.29)	17 (17.71)	9 (20)	6 (17.65)	0.12 (0.96)
Prior psychosocial treatment	109 (62.29)	58 (60.42)	35 (77.78)	16 (47.06)	8.10 (0.02)

Note:

[a] Tests of frequencies are based on likelihood-ratio X^2.

[b] For consistency with text's description of this result, values in parentheses for stimulant optimization outcome columns are percentages of each row. The Complete Sample column shows percentages of each race/ethic group in the sample.

[c] Because the trial began before criteria for Disruptive Mood Dysregulation Disorder were established for DSM-5, it was not evaluated with the KSADS.

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TABLE 2

Trial Outcomes

| | Group Means Across Assessments Least-Squares Means (SD)[a] | | | | | | | | | | | Fixed Effects F (df=105) P | | | Between-Group Contrasts[b] Differences in Least-Squares Means [95% CI] Effect Size[c] Significance test | | |
| | Stimulant responders[d] | | Risperidone adjunctive to stimulant | | | Divalproex sodium adjunctive to stimulant | | | Placebo adjunctive to stimulant | | | | | | | | |
	Baseline	Stim optim end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Tx	Time	Tx by Time	RISP-PBO	DVPX-PBO	DVPX-RISP
R-MOAS, square-root	7.42 (1.93)	1.91 (1.94)	7.91 (1.62)	6.57 (1.61)	3.33 (1.90)	8.16 (1.58)	6.12 (1.63)	3.95 (1.91)	7.56 (1.90)	6.43 (1.90)	5.41 (1.95)	0.49 .62	58.34 <.001	2.77 .03	−2.33 [−3.83, −0.82] −1.52 t=−3.07, p=.003	−1.60 [−3.18, −0.03] −0.91 t=−2.02, p=.046	0.72 [−0.59, 2.04] 0.45 t=1.09, p=.277
CBCL Aggressive Behavior, T	75.81 (8.96)	61.16 (9.11)	77.25 (6.89)	72.62 (6.85)	61.75 (8.19)	78.67 (6.59)	72.21 (6.86)	63.88 (9.09)	77.83 (7.64)	73.03 (7.64)	71.36 (8.17)	1.30 .28	42.38 <.001	2.72 .03	−9.11 [−14.86, −36] −1.25 t=−3.15, p=.002	−7.48 [−13.93, −1.03] −1.03 t=−2.30, p=.023	1.63 [−3.90, 7.16] 0.24 t=0.58, p=.560
CBCL Rulebreaking Behavior, T	72.42 (7.34)	63.64 (7.47)	71.83 (7.34)	69.02 (7.47)	60.07 (4.11)	72.51 (4.09)	68.68 (4.92)	63.96 (3.94)	71.85 (4.11)	69.85 (5.48)	68.07 (4.63)	2.74 (4.63)	48.83 (4.95)	5.04 .07	−7.58 [−11.08, −4.09] <.001 t=−4.31, p=.000	−3.87 [−7.79, 0.06] <.001 t=−1.96, p=.053	3.72 [0.35, 7.08] −1.73
CBCL Internalizing Behavior, T	60.45 (9.06)	51.05 (9.21)	61.82 (7.07)	57.53 (7.04)	49.60 (8.36)	61.90 (6.75)	59.18 (7.01)	51.21 (9.20)	61.68 (7.78)	59.38 (7.78)	57.57 (8.30)	1.07 0.35	22.91 <.001)	1.78 0.14	−7.11 [−12.83, −1.39] −0.95 t=2.19, p=.031	−6.37 [−12.80, 0.05] −0.85	0.74 [−4.77, 6.25] 0.106

| | Group Means Across Assessments Least-Squares Means (SD)[a] | | | | | | | | | | | Fixed Effects F (df=105) P | | | Between-Group Contrasts[b] Differences in Least-Squares Means [95% CI] Effect Size[c] Significance test | | |
| | Stimulant responders[d] | | Risperidone adjunctive to stimulant | | | Divalproex sodium adjunctive to stimulant | | | Placebo adjunctive to stimulant | | | | | | | | |
	Baseline	Stim optim end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Tx	Time	Tx by Time	RISP-PBO	DVPX-PBO	DVPX-RISP
Conn-GI, Restless & Inattentive, T	85.25 (14.09)	58.43 (14.15)	82.01 (8.32)	68.84 (8.26)	60.25 (9.70)	83.66 (8.06)	65.54 (8.32)	64.27 (9.71)	84.21 (9.67)	70.61 (9.67)	68.97 (9.89)	1.17 / .31	75.33 / <.001	1.63 / .17	-6.73 [-14.19, 0.73] / -0.75 / t = -2.47, p = .015	-1.89 [-9.71, 5.93] / -0.21 / t = -1.97, p = .052	4.84 [-1.68, 1.37] / 0.59 / t = 0.27, p = .791
Conn-GI, Emotional Lability, T	81.9 (11.92)	55.37 (12.00)	80.86 (9.21)	71.87 (9.10)	55.23 (11.01)	81.80 (9.05)	70.55 (9.46)	64.28 (11.26)	79.36 (10.94)	75.76 (10.94)	68.34 (11.35)	1.87 / .16	33.05 / <.001	2.34 / .06	-11.91 [-21.80, -2.01] / -1.18 / t = -2.39, p = .019	-2.68 [-13.02, 7.67] / -0.26 / t = -0.51, p = .609	9.23 [0.69, 17.78] / 1.01 / t = 2.14, p = .034
Child Depression Rating Scale	34.53 (21.47)	25.98 (21.49)	36.62 (14.16)	32.14 (14.14)	26.18 (14.75)	37.61 (13.06)	33.74 (13.16)	29.58 (14.29)	37.52 (12.08)	33.86 (11.82)	35.12 (12.16)	1.89 / .16	12.82 / <.001	1.63 / .17	-7.62 [-13.58, -1.67] / -0.58 / t = -2.48, p = .015	-5.51 [-12.06, 1.03] / -0.42 / t = -1.46, p = .148	2.11 [-3.34, 7.56] / 0.15 / t = -0.90, p = .369
Columbia Impairment Scale	29.29 (10.23)	16.24 (10.48)	31.08 (8.06)	24.48 (8.02)	20.16 (9.85)	30.93 (7.87)	26.05 (7.94)	23.62 (11.17)	29.96 (9.52)	28.09 (9.42)	25.37 (9.80)	0.64 / .53	11.50 / <.001	0.79 / .54	-3.97 [-10.96, 3.03] / (-0.4) / (0.336)	-1.22 [-9.14, 6.70] / (-0.13)	2.75 [-4.09, 9.58] / (0.336)

	Stimulant responders [d]		Risperidone adjunctive to stimulant			Divalproex sodium adjunctive to stimulant			Placebo adjunctive to stimulant			Fixed Effects F (df=105) P			Between-Group Contrasts [b] Differences in Least-Squares Means Effect Size [c] [95% CI] Significance test		
	Baseline	Stim optim end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Baseline	Stim optim end	RCT end	Tx	Time	Tx by Time	RISP-PBO	DVPX-PBO	DVPX-RISP
															t = -1.13, p =.263	t = -0.31, p =.760	t = 0.80, p =.427
Body Mass Index, z-score	0.47 (1.23)	0.18 (1.23)	0.05 (0.96)	-0.18 (0.96)	0.43 (1.00)	0.14 (0.88)	-0.17 (0.89)	-0.17 (0.93)	0.18 (0.84)	-0.18 (0.82)	-0.24 (0.84)	1.57 0.21	8.30 <.001	6.44 <.001	0.74 [0.39, 1.09] 0.815 t = 4.16, p =.000	0.09 [-0.28, 0.46] 0.097 t = 0.47, p =.637	-0.65 [-0.96, -0.34] -0.70 t = -4.18, p =.000
Weight, kg	34.32 (11.91)	34.08 (11.91)	34.68 (8.73)	35.07 (8.71)	37.30 (8.83)	35.13 (7.94)	35.31 (7.96)	35.96 (8.10)	36.05 (6.91)	34.48 (6.81)	34.50 (6.90)	0.24 0.79	2.47 0.09	3.28 0.01	3.18 [1.19, 5.17] 0.404 t = 3.17, p =.002	1.50 [-0.61, 3.62] 0.190 t = 1.41, p =.161	-1.68 [-3.38, 0.02] -0.20 t = -1.96, p =.053

NOTE: CBCL = Child Behavior Checklist; CI = confidence interval; ConmGI = Conners Global Index – Parent Version; DVPX = divalproex sodium; PBO = placebo; R-MOAS = Retrospective – Modified Overt Aggression Scale; RCT = randomized controlled trial; RISP = risperidone; Stim optim end = stimulant optimization phase endpoint; Tx = treatment.

[a] Least-squares means and SDs across assessment times are adjusted for random effect of site.

[b] Contrasts are the differences in least-squares means in RCT endpoints between groups, adjusted for site, baseline and stimulant optimization endpoint assessments.

[c] Effect sizes are Hedge's g, which adjusts Cohen's d for small sample sizes and is interpretively identical to it.

[d] Data for those whose aggressive behavior remitted during stimulant optimization are Presented for reference; they were not included in the mixed effects analyses shown.