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Clinical Implications from the Treatment of Severe Childhood Aggression (TOSCA) Study: A Re-analysis and Integration of Findings

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This article is discussed in an editorial by Dr. Jon McClellan on page xx.

Abstract

Objective—The Treatment of Severe Childhood Aggression (TOSCA) project examined augmentation of stimulant treatment and parent training (PT) with risperidone for severe physical aggression. This article 1) summarizes the clinical implications; 2) re-analyzes the data to examine the utility of four criteria for deciding to augment; and 3) develops a treatment algorithm.

Method—The newly analyzed four criteria for augmenting comprised failure to attain the following after 3 weeks of stimulant and PT treatment: 1) Clinical Global Impressions-Improvement (CGI-I) of 1 and normal score (≤ 15) on the Nisonger Child Behavior Rating Form Disruptive-Total (D-total); 2) CGI-I of 1 or 2 plus 25% D-Total improvement; 3) a D-Total ≤ 15 ; and 4) a CGI-Severity of 3 (mild) or better. Effect sizes were calculated. Prior TOSCA publications were reviewed for clinically relevant findings.

Results—All four criteria resulted in medium or better effect sizes ($d=.59-.72$) comparing risperidone to placebo. Providing risperidone to children who failed to reach a CGI-I=1 plus D-Total ≤ 15 resulted in the greatest benefit. Additionally, a review of clinically relevant data suggests that stimulant plus PT shows further improvement after 3 weeks even without augmentation.

Conclusion—For those children who did not attain a CGI-I of 1 and a D-total score of 15 or below, adding risperidone maximized both the number of children benefitting from treatment and the average amount of benefit. Unless clinical circumstances dictate otherwise, practitioners should delay an antipsychotic for at least a month after optimal stimulant dose is achieved and PT has commenced.

Clinical trial registration information—Treatment of Severe Childhood Aggression (The TOSCA Study); <http://clinicaltrials.gov>; NCT00796302.

Keywords

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

INTRODUCTION

Childhood disruptive behavior disorders (DBDs) and physical aggression are associated with negative outcomes, such as failing to complete high school, adolescent and adult mental health or substance use disorder, legal consequences (e.g., incarceration), unemployment, and risky sexual behavior.^{1,2} A meta-analysis of 28 studies³ found that stimulant monotherapy resulted in a reduction of overt aggression with moderate to large effect sizes in children with attention-deficit/hyperactivity disorder (ADHD) alone. However, when children were diagnosed with ADHD and comorbid conduct disorder (CD) or oppositional defiant disorder (ODD), effect sizes for overt aggression were notably smaller.³ Given the severity of the outcomes associated with DBDs and physical aggression, the use of multiple psychotropic medications to address symptoms unresponsive to stimulant monotherapy is an increasing reality.⁴

The combination of stimulant medication plus parent training in behavior management (PT) is accepted practice for children with DBD, ADHD, and aggression.⁵ The Treatment of Severe Childhood Aggression (TOSCA) study evaluated the superiority of six weeks of PT

+ stimulant + risperidone (i.e., augmented treatment) over PT + stimulant + placebo (i.e., basic treatment) in children age 6–12 years with ADHD and severe aggression.⁶ TOSCA proceeded in three phases: the acute 9-week trial, consisting of 3 weeks of PT and stimulant treatment for everyone followed by 6 weeks of randomized double-blind augmented or basic treatment. The second study drug (risperidone or placebo) was only added for children who did not respond sufficiently to PT and stimulant alone. The results of the acute phase indicated a medium advantage of augmented over basic on the primary outcome measure of disruptive behavior (Cohen's d [effect size] = 0.43, $p = .01$ measured from baseline; $d = 0.50$ measured from week 3).⁶ Figure 1 displays the basic timeline and effect of basic and augmented treatments on the Disruptive-Total score, the primary outcome measure. In a secondary analysis, augmented treatment also improved teacher-rated ADHD symptoms more than placebo.⁷

The second phase of the study was a 12-week blinded extension in which participants who responded to randomized treatment during the acute phase continued the same blinded treatment.⁸ Regardless of randomization (i.e., augmented or basic), improvements in functioning at week 9 were essentially maintained after 21 total weeks of treatment. A slight deterioration in both groups was observed, though this was reasonably explained by regression to the mean in the subsamples, selected for good response. Using a last-observation-carried-forward (LOCF) methodology that included children who dropped from participation or were not included in the extension due to poor response, the augmented group experienced greater improvements from week 3 (when the second medication was introduced) to week 21 (the end of the treatment phase) in positive social behavior ($p = .005$; $d = 0.44$), reactive aggression ($p = .03$; $d = 0.36$), and marginally in disruptive behavior ($p = .058$; $d = 0.29$).⁸

Finally, the study concluded with a 52-week follow-up of all participants.⁹ Mean differences between basic and augmented on the primary outcome measure had attenuated to nonsignificance ($d = 0.34$, $p = .08$); however, more children in the augmented group demonstrated a Clinical Global Impressions–Severity (CGI-S) score of 1 to 3 (mild or better) at follow-up ($p = .02$). Further, exploratory analyses revealed that at 52 weeks, augmented was superior to basic for children who continued to receive the treatment to which they were randomized (basic, $n = 20$; augmented, $n = 23$). This was true for ADHD symptoms ($p = .02$), anxiety symptoms ($p = .04$), and marginally in disruptive behavior ($p = .06$; $d = 0.33$).

Differences in adverse events between basic and augmented were minimal across the acute, extension, and follow-up studies. However, those receiving the augmented treatment demonstrated higher prolactin levels and more gastrointestinal upset than the basic group. Augmented also had significantly more weight gain, largely due to children receiving the basic treatment losing weight from stimulant appetite suppression, which was possibly neutralized for the augmented group by the appetite promotion of risperidone.

One difficulty in the clinical interpretation of the TOSCA results is that the sample for each phase was not identical: only responders participated in the extension, and not everyone in the extension participated in the follow-up, whereas some who had not been in the extension

did return for the follow-up (i.e., all participants were invited back for the follow-up assessment). Further, because treatment was identical up to 3 weeks, the actual baseline of the acute double-blind randomized trial of risperidone augmentation might be considered to be clinical status at end of 3 weeks (see Figure 1). Finally, in order to ensure that children who had room to improve had a chance to receive the augmented treatment, a strict (i.e., difficult to achieve) definition of responder, which identified more children as needing augmented treatment, was used at 3 weeks to determine whether or not the randomized medication would be added. In practice, this could result in children being too liberally classified as nonresponders and unnecessarily medicated. All of this taxes the understanding of clinical implications for casual readers. In this report, we examine whether alternative response criteria, such as more lenient definition of responder resulting in stricter guidelines for determining whether a child should receive augmented treatment, would have resulted in a larger increment of benefit, and we use the extension and follow-up data to shed light on the overall clinical implications.

METHOD

At baseline, 168 children were randomized to either basic ($n=84$) or augmented ($n=84$) groups. Based on the child's response to at least 3 weeks of stimulant and PT, the second medication (risperidone or placebo) was added. Fourteen children dropped out during the first 3 weeks; 10 more met the stringent definition of response and did not receive the randomized medication. Finally, eight participants never received the second medication. This left 136 of the originally randomized children (81%) who received at least one week of either augmented or basic treatment to be included in these analyses.

Participants

Inclusion criteria were as follows: aged 6 to 12 years inclusive, severe physical aggression (i.e., causing significant physical damage to person or property), a diagnosis of ODD or CD, a diagnosis of ADHD, and $IQ > 70$. Exclusion criteria were as follows: diagnosis of a neurological or medical disorder where medication may lead to additional risks (e.g., seizures), atypical liver functioning, pervasive developmental disorder, current use of psychotropic medications that would lead to negative effects if discontinued, evidence of child abuse or neglect, family history of type 2 diabetes in two first-degree relatives, and the following mental health issues: mood disorder (past or current), schizophrenia, other psychotic disorders, eating disorders, or suicidal ideation.

Of the 136 participants included in this analysis, 75% ($n=102$) were boys. A majority of the participants were white ($n=76$, 56%) followed by African American ($n=44$, 32%) and multiracial ($n=10$, 7%). ODD was the more common DBD diagnosis ($n=107$, 73%). Household incomes were low on average, and parental education, particularly for the fathers, was also low. Thus, a substantial proportion came from low socioeconomic backgrounds, although a significant minority were from the middle class. More details on these participants are found elsewhere.^{6,8}

Instruments

Measures relevant to the reanalysis include the Disruptive Total (D-Total) of the Nisonger Child Behavior Rating Form –Typical IQ (NCBRF)¹⁰ and the severity and improvement ratings from the Clinical Global Impressions scale (CGI-S and CGI-I).¹¹ The NCBRF D-Total score is a combination of the Conduct Problem and Oppositional Behavior subscales. The NCBRF has demonstrated high internal consistency coefficients and is sensitive to medication effects. Reliability among CGI raters was established through case vignette discussion and reliability case conferences. Additional details about the sample, instruments, and design are found elsewhere.^{6,12}

Treatment

All participants started PT and stimulant after baseline assessment. PT consisted of the Community Parent Education Program (COPE)¹³ in modified form, which includes nine primary sessions with two optional boosters. The stimulant started at 18 mg of oral osmotic system methylphenidate, titrated over a 2-week period to optimal dose (capped at 54 mg or by limiting side effects), which was maintained through the remainder of the study. Those who could not swallow whole tablets instead received mixed amphetamine salts XR, starting at 10 mg, which could be opened and mixed with soft food. When the second (randomized) medication was added at the end of week 3 or later, risperidone (placebo) was initiated at 0.5 mg hora somni (h.s.) and titrated over the next few weeks to optimal dose (average $1.7 \pm .75$ mg/day). The optimal dose was maintained through week 9 (and into the extension, if the child was a clinical responder).

Criteria for Adding Second Drug

The response criteria for not adding the second drug after at least 3 weeks of PT and stimulant were a CGI-I of 1 (very much improved) and a score of 15 or below on the D-Total, which is within 0.5 standard deviation of the normative mean.⁶ This definition of response was more stringent than the definition used to classify overall response to intervention at week 9: a CGI-I of 1 or 2 and at least 25% improvement on the D-total. The differences in these criteria reflect different purposes: the more stringent definition of response ensured that any participant who had the potential for additional improvement was given the opportunity to receive the second medication, while the endpoint response criteria classified those who did and did not experience a clinically meaningful amount of benefit from treatment. However, the implementation of the more stringent response definition for not adding the second medication may have inadvertently reduced the ability of the study to demonstrate an effect of augmented treatment by providing the second medication to individuals who had already demonstrated sizeable response although not remission. However, this approach was consistent with the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY) guidelines,⁵ given that these children were still exhibiting serious aggressive behaviors compared to the normal population. In the current analyses, we explore the impact of this response definition by calculating the effects of augmented treatment using subgroups classified by three alternative definitions of nonresponder. These definitions were designed to restrict the number of participants who

received the second drug to those most in need, who may show a larger benefit. The three alternative responder definitions that we explored are as follows:

1. Lenient definition: CGI-I of 1 or 2 plus 25% improvement on the D-Total (originally named a priori definition in the original report; it is the definition used to identify a responder at 9 weeks)
2. Low disruptive behaviors as indicated by NCBRF D-Total of 15 or less (corresponding to the mean + ½ SD, based on normative scores; essentially a normal score)
3. A level of global function as indicated by a CGI-Severity score of 3 (mild) or better (CGI-S)

We also repeat the analysis using the stringent responder definition (CGI-I of 1 plus D-Total score 15) for comparison.

Data Analysis—Given that the start of the second medication occurred three weeks after baseline, an analysis of variance (ANOVA) test was used to determine if there was a significant difference in D-Total scores between those who received augmented treatment and those who received basic treatment for each definition between visit 3 and visit 9. Effect sizes were calculated using Cohen's *d*.¹⁴ Only children who received the second medication (i.e., risperidone or placebo) were included in the analysis (*n*=136). In contrast to the initial report,⁶ which used a mixed effects regression model, including all participants, a last-observation-carried-forward (LOCF) approach was used to handle data associated with participants who discontinued treatment prior to the end of the 9-week trial, but only for the children who received the second medication (i.e., placebo or risperidone).

Clinical Implications—Finally, we couple the results of these re-analyses with a review of the results of the initial,⁶ extension,⁸ and follow-up⁹ studies and three secondary reports^{7,15,16} to derive practical implications for further study for clinicians who must follow patients over extended periods. This also provides a quick summary of major outcomes of the TOSCA study program.

RESULTS

Participants who were assigned to groups for failing to meet the original (i.e., stringent) and additional definitions of responders were as follows: stringent (*n*=136), lenient (*n*=83), D-15 (*n*=106), and CGI-S (*n*=109). All four definitions used to determine who should receive the second medication resulted in greater improvements in D-Total for those who received risperidone augmentation. Effect sizes ranged from *d*= .59 to *d*= .72 (Table 1). As expected, the stringent response definition (i.e., CGI-I of 1 plus D-Total score 15) resulted in the most children receiving the second medication (*n*=136), given that each additional group was a subset of the stringent group, which comprised all who got the second drug. Effect size was moderate-to-large in favor of augmented treatment using this definition from visit 3, when risperidone was added (*d*=.72). The CGI-S (*n*=109; i.e., CGI-Severity score of 3 or better) and D-15 (*n*=106; D Total 15) definition applied at week 3 included the second and third highest number of participants respectively. However, the effect sizes for the

augmented treatment for both of these definitions were notably lower than for the stringent definition (D-15, $d=.64$; *CGI-S*, $d=.59$). The definition applied at week 3 that identified the fewest participants ($n=83$) needing the second medication was the most lenient one. Despite only including the 60% of participants with the most variance to show improvement, the effect size of this analysis comparing visit 3 to visit 9 ($d=.65$) was no better than the effect using the stringent definition ($d=.72$). In other words, the average benefit per child was not increased by restricting augmentation with risperidone to the poorest responders to PT + stimulant.

Highlights of Previous Reports

In addition to using the stringent definition of responder to determine whether children should receive the second medication, the following clinical information can be gleaned from the acute trial,⁶ extension,⁸ follow-up,⁹ and secondary TOSCA reports,^{7,15,16} which may be beneficial to practitioners after further validation:

1. Well-titrated stimulant and parent training were highly effective for the treatment of ADHD and ODD or CD (pre-post $d=1.36$), but this was relative to no-treatment baseline, and participants knew that they were being treated with PT and at least one medicine (see Figure 1).
2. Visual inspection of the treatment plot from the acute trial (Figure 1) suggests that the benefit of stimulant and parent training combination continued to increase over a 6-week period (i.e., it had not plateaued at 3 weeks). It is possible that by 6 weeks more children would have met the stringent response criterion and not needed the second drug.
3. A moderate additional boost was obtained from adding an antipsychotic.
4. Risperidone also added significant improvement of ADHD as rated by teachers in school ($d=.61$) but not by parents at home.⁷ The relative lack of structure at home may diminish parents' ability to detect ADHD-specific effects.
5. Good responders to a 6-week trial of either stimulant+PT or stimulant+PT +risperidone continued to do well over the next 3 months with the treatments maintained essentially unchanged.
6. Over a year's time, those who originally added risperidone continued marginally better ($d=.35$, $p=.09$) than those who did not, even though half stopped one or both drugs; in fact, 23% of the augmented were taking no medication compared to 11% of the basic group taking none at a one-year follow-up). This confirms the wisdom of periodic attempts to taper and discontinue the antipsychotic as the child gains impulse control.
7. At 52-week follow-up, 52.6% of those originally receiving only PT and stimulant switched or added treatments. Only 17.1% of those also assigned risperidone added or switched drugs.

8. At 52 weeks, 45% of both groups continued to show impairment in at least one area (ADHD and/or disruptive behavior), with 55% showing no impairment. Thus, prognosis was neither glowing nor hopeless.
9. Side effects of risperidone were remarkably muted from what might be expected from monotherapy trials. More research is needed to determine if the two drugs partially neutralize each other's side effects (e.g., weight gain was minor and extrapyramidal effects were unremarkable; the only dyskinesia was atypical and suspected to be mannerisms rather than dyskinesia).
10. In children with disruptive behavior disorders, high levels of anxiety as assessed by the Child and Adolescent Symptom Inventory – 4 (CASI-4) were related to more substantial aggressive behaviors. More importantly, reduction of anxiety mediated reduction of disruptive behavior by teacher ratings ($p = .001$).¹⁵ Practitioners should check for anxiety in the presence of childhood aggression and consider whether anxiety may be playing a role in symptom presentation in order to inform treatment. Future research should examine the efficacy of using evidence-based psychosocial treatments (i.e., cognitive-behavioral therapy) and/or psychopharmacological treatments (e.g., selective serotonin reuptake inhibitors [SSRIs]) to treat underlying anxiety before resorting to a riskier antipsychotic.
11. Results from moderator analyses indicated that children of mothers with lower education levels (high school or less) did worse in the basic treatment group compared to children of mothers with higher levels of education. This difference was not observed in the augmented group. Given that parent training interventions are often presented in an academic format (i.e., lessons, homework, etc.) it is not surprising that mothers who have had less exposure to or success in these settings do not do as well as those who have higher education levels. Clinicians providing PT should attempt to modify the format of the intervention to be more suitable to parents with lower levels of education if the standard intervention is unsuccessful or less acceptable.

Based on these findings collected from three primary and two secondary TOSCA analyses, the algorithm in Figure 2 is proposed, which may be helpful for practitioners after further validation. Briefly, the algorithm suggests the following choice points. First, once a DBD + significant aggression (i.e., causing physical damage to person or property) are identified, we recommend initiating PT immediately and a 4–6-week trial of a long-acting stimulant preparation following the titration process provided by Greenhill et al.,¹⁷ which suggested the following: 1) start patient on immediate release stimulant medication and monitor for side effects; 2) if no improvement in core ADHD symptoms is noted after one to two weeks, increase dose of immediate release stimulant until sufficient response is achieved or maximum dose is reached (provide at least three days in between dose increases to monitor for side effects and improvements in symptomology); 3) once an effective dose is identified for core ADHD symptoms, switch to a long-acting stimulant formulation to reduce the need for multiple daily doses; 4) if a sufficient response was not achieved, try a different short-acting stimulant formulation and proceed through the titration process again. Consistent with

previous TRAAAY guidelines, if a robust clinical response in aggression symptoms occurs with a long-acting stimulant medication, maintain treatment and continue to monitor progress. If the stringent definition of responder is not met and/or physical aggression symptoms continue to be unmanageable despite psychosocial treatments, consider switching to another long-acting psychostimulant and monitor. If the child still does not show a robust response after adequate trial of alternative psychostimulant, probe for symptoms of anxiety and social withdrawal, especially as evidenced at school. If present, consider augmentation with cognitive-behavioral therapy and/or SSRI. If response is not robust, consider suspending/tapering SSRI and adding antipsychotic (e.g., risperidone). If child shows a favorable response, continue treatment for approximately 6 months and consider tapering the antipsychotic while monitoring carefully for worsening. If treatment response is not favorable, withdraw the antipsychotic and consider other options in light of current symptoms.

DISCUSSION

The TOSCA study was one of the first large-scale investigations to examine antipsychotic augmentation of established evidence-based treatments for childhood aggression. Clinical guidelines regarding the use of concomitant medications are sorely needed, given the increasing use of polypharmacy in every-day clinical practice.⁴ There are several potential clinical insights to take away from the 9-week trial, the 12-week extension, the 52-week followup, secondary reports, and the re-analyses conducted in this paper. According to TRAAAY,⁵ psychosocial approaches and psychopharmacological monotherapy (e.g., stimulant for a child with ADHD) should be attempted before adding an atypical antipsychotic. The results of the TOSCA study support this principle, with a large effect for stimulant + PT in the first few weeks of treatment ($d=1.36$); however, there was no placebo to control for time or expectation. Increasing reduction in symptomology was seen for 6 weeks while stimulant + PT treatment was provided. Additionally, the improvements were maintained over time.

A conundrum that many clinicians face is deciding when to add an atypical antipsychotic to stimulant + PT. According to the re-analyses conducted, different definitions of “responder” at week 3 affected the number of children who received the second medication and had some impact on effect size. Based on the results, giving risperidone only to those who failed to meet the lenient responder definition (i.e., CGI-I of 1 or 2 plus 25% improvement) at week 3 resulted in fewer children receiving the drug ($n=83$) and a larger effect size than the D-15 (i.e., D-Total ≥ 15) and CGI-S (CGI-Severity score of 3 or better) definitions. However, using the stringent definition (CGI-I of 1 plus D-Total score ≥ 15) yielded an even larger effect size with more children, suggesting a greater benefit for more children. Therefore, use of the stringent definition seems the best option when considering the cost–benefit analysis of adding an atypical antipsychotic to a treatment regimen of the four considered. However, these definitions were only examined within the context of the TOSCA study, and clinicians should also consider whether physical aggression symptoms continue to be unmanageable despite psychosocial treatments. The primary analyses of the TOSCA study⁶ suggested that the optimal time to make the decision may be after 6 weeks of PT and stimulant. This conservative approach would limit the number of children needing a second medication and

prevent unnecessary polypharmacy (see Figure 1, reproduced with permission from the original primary analysis publication).

When warranted, the addition of an atypical antipsychotic to PT and stimulant leads to further moderate improvements in symptomology. Most adverse events, such as sexual side effects secondary to altered prolactin, weight gain, and gastrointestinal upset, associated with the addition of risperidone were limited across all three TOSCA reports, but they did occur. However, although weight gain was modest in the augmented treatment, we still saw it as problematic, as a majority of the participants were already overweight on entering the studies. Notably, extrapyramidal side effects were negligible. It is possible that this may be due to co-administration of the dopaminergic stimulant; however, more research is necessary to confirm this interaction. Both those who responded to stimulant + PT and those who responded to stimulant + PT + risperidone continued to demonstrate these improvements after three months. However, 12 months after the start of the study, 45% of participants still had impairment in one area (ADHD, DBD, or aggression). Although 55% had no impairment at 1-year follow-up, future research is needed to continue to identify more efficacious approaches for the 45% who did. It is worth noting that all study procedures and medicines were free through the 12-week extension, whereas families had to procure study medication on their own out to one-year follow-up. Hence, real-world considerations (e.g., family income; insurance coverage) can and do influence treatment outcome.

The limitations to the TOSCA papers can be found in other publications.^{6,8,9,12} Limitations specific to these re-analyses pertain to the way the data for responders in each definition were obtained. Participants identified as a non-responder by each additional definition (i.e., Lenient, D-15, and CGI-S) were a subset of the participants identified as non-responders by the stringent definition of responder. The generalization of our results to everyday real world clinical settings is limited by the following, in common with most randomized controlled trials: PT and both medications were free to participants, and families were reimbursed for their time and travel costs. Moreover, clinical status was regularly and rigorously assessed with highly validated measures. All of our clinical information is predicated on the use of the NCBRF as a treatment response measure and the COPE as a parent intervention. Given that the success of our trial hinged on continued involvement of our participating families, study personnel worked hard to nurture them through the extension study. In clinical practice, working this closely with families may not be practical due to a lack of resources. Additionally, the frequency of parent training meetings (i.e., one per week) is often not feasible in clinical practice given the overwhelming demand for clinician time. Therefore, it is possible that the full effect of parent training combined with stimulants may take longer than six weeks in real world practice. Finally, it is unclear what relative contribution each intervention (i.e., parent training, stimulant) made to the continuing improvement in symptoms from week 1 to week 6 in the basic group. It is possible that the improvements during these weeks could have been due to a longer latency being needed for a complete stimulant response or the effects of ongoing parent training. Additionally, given the lack of a non-treated comparison group, it is possible that measurement bias played a role in the observed improvements over time. Despite this, multiple studies have demonstrated the efficacy of stimulant medications³ and parent training¹⁸ on aggressive behavior, making it highly unlikely that improvements were solely due to measurement error.

Combined PT + stimulant treatment was highly effective in treating physical aggression associated with ADHD and ODD or CD and becomes more effective with time at least through 6 weeks. Given the substantial improvement from stimulant + PT treatment and absent major crises, practitioners should consider waiting at least a month after initiating this treatment before carefully weighing the possible benefits of adding an antipsychotic such as risperidone in order to reduce unnecessary treatment with multiple medications. Additionally, using the stringent definition of responder to identify those who failed to improve from stimulant + PT was the most effective way in this study to determine who might benefit from the addition of risperidone. When warranted, augmentation of treatment with risperidone leads to additional moderate improvements in functioning with tolerable side effects. Given these findings, the treatment algorithm detailed in Figure 2 may be helpful to clinicians working with youth displaying severe physical aggression, pending further validation. However, there is a continued need for the identification of more efficacious treatments for physical aggression and associated disruptive behavior disorders.

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Figure 1.

Nisonger Child Behavior Rating Form Disruptive Behavior Total score as a function of treatment condition and study visit. Note: Mean doses for risperidone are provided above the x axis. Solid line = parent training + stimulant + placebo; Dashed line = parent training + stimulant + risperidone. Reprinted with permission from Aman MG, Bukstein OG, Gadow KD, et al. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry*. 2014;53:47–60.

Figure 2.

Potential treatment algorithm for children with severe physical aggression. Note: Clinicians should weigh adverse reactions into their cost-benefit analysis. ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive-behavioral therapy; CD = conduct disorder; CGI-I = Clinical Global Impression–Improvement (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change); D-total = disruptive behavior total; NCBRF =

Nisonger Child Behavior Report Form; ODD = oppositional defiant disorder; SSRI = selective serotonin reuptake inhibitor.

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Table 1

Results of Reanalysis With Effect Sizes (Cohen's D) Outcome (Nisonger Child Behavior Rating Form Disruptive-Total [D-Total] Score)

Responder Definition	n	BL to Week 9 Mean (SD)	Week 3 to Week 9 Mean (SD)	Week 3 to Week 9 <i>p</i> value	Week 3 to Week 9 Effect Size (CI)
Stringent	136				.72 (.37 – 1.06)
Augmented	65	–5.31 (1.70)	–3.56 (2.04)		
Basic	71	–4.51 (2.13)	–1.58 (3.28)		
Lenient	83				.65 (.20 – 1.09)
Augmented	36	–4.99 (2.04)	–4.04 (2.17)		
Basic	47	–4.51 (2.05)	–2.27 (3.1)		
CGI-S	109				.59 (.20 – .97)
Augmented	55	–5.26 (1.81)	–3.59 (2.13)		
Basic	54	–4.51 (2.09)	–1.97 (3.27)		
D15	106				.64 (.24 – 1.02)
Augmented	52	–5.23 (1.84)	–3.91 (2.00)		
Basic	54	–4.46 (2.24)	–2.19 (3.22)		

Note: The varied Ns result from different numbers failing to meet the specific responder definition. Risperidone was provided to participants who failed to meet the following response criteria: Stringent = Clinical Global Impressions–Improvement (CGI-I) of 1 plus D-Total score 15; lenient = CGI-I of 1 or 2 plus 25% improvement on the D-Total; CGI-S = CGI-Severity score of 3 (mild) or better; or D15 = D-Total of 15 or less. BL = baseline.