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

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Objective: Although combination pharmacotherapy is common in child and adolescent psychiatry, there has been little research evaluating it. The value of adding risperidone to concurrent psychostimulant and parent training (PT) in behavior management for children with severe aggression was tested. **Method:** One hundred sixty-eight children 6 to 12 years old (mean age 8.89 ± 2.01 years) with severe physical aggression were randomized to a 9-week trial of PT, stimulant (STIM), and placebo (*Basic* treatment; n = 84) or PT, STIM, and risperidone (*Augmented* treatment; n = 84). All had diagnoses of attention-deficit/hyperactivity disorder and oppositional-defiant disorder (n = 124) or conduct disorder (n = 44). Children received psychostimulant (usually Osmotic Release Oral System methylphenidate) for 3 weeks, titrated for optimal effect, while parents received PT. If there was room for improvement at the end of week 3, placebo or risperidone was added. Assessments included parent ratings on the Nisonger Child Behavior Rating Form (Disruptive-Total subscale was the primary outcome) and Antisocial Behavior Scale; blinded clinicians rated change on the Clinical Global Impressions scale. **Results:** Compared with *Basic* treatment (PT + STIM [44.8 ± 14.6 mg/day] + placebo [1.88 mg/day ± 0.72]), *Augmented* treatment (PT + STIM [46.1 ± 16.8 mg/day] + risperidone [1.65 mg/day ± 0.75]) showed statistically significant improvement on the Nisonger Child Behavior Rating Form Disruptive-Total subscale (treatment-by-time interaction, $p = .0016$), the Nisonger Child Behavior Rating Form Social Competence subscale ($p = .0049$), and Antisocial Behavior Scale Reactive Aggression subscale ($p = .01$). Clinical Global Impressions scores were substantially improved for the 2 groups but did not discriminate between treatments (Clinical Global Impressions–Improvement score ≤2, 70% for *Basic* treatment versus 79% for *Augmented* treatment). Prolactin elevations and gastrointestinal upset occurred more with *Augmented* treatment; other adverse events differed modestly from *Basic* treatment; weight gain in the *Augmented* treatment group was minor. **Conclusions:** Risperidone provided moderate but variable improvement in aggressive and other seriously disruptive child behaviors when added to PT and optimized stimulant treatment. Clinical trial registration information—Treatment of Severe Childhood Aggression (The TOSCA Study), URL: *http://clinicaltrials.gov*, unique identifier: NCT00796302. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(1):47–60. **Key Words:** disruptive behavior disorders, parent training, physical aggression, psychostimulants, risperidone

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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 DBDs and aggression have been linked

to adult smoking, alcohol use, hard drug use, physical aggression, and risky sexual behavior[1]; frequent occurrences on police registers, repeated or serious crimes, and involvement in confrontational and destructive offenses[2]; 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]; and nonviolent offending and violent delinquency.[4] Thus, DBDs 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 increasing 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 children with ADHD and 61% of 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 increased from 14% (1996–1999) to 20% (2004–2007) of patient visits that included psychotropic medication (43% increase in combination therapy over 8 years).[6] When risperidone (RIS) 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 (ESs) for overt aggression (0.24–2.12, confidence interval 0.70–1.02). Furthermore, the presence of oppositional-defiant disorder (ODD) or conduct disorder (CD) led to significantly smaller ESs in managing overt aggression. This raises the possibility that DBDs may be linked to a decreased psychostimulant effect on aggression and poses the question of what to do when children show unsatisfactory psychostimulant response.

Risperidone has been shown consistently to decrease disruptive behavior in children. Findling *et al.*[10] reported less aggression after 10 weeks of RIS versus placebo (PBO) in 20 children with CD. Two large trials (N = 110 and 118) of RIS 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 decreases on the Conduct Problem subscale; an approximately 45% decrease accompanied RIS compared with an approximately 15% decrease with PBO.[11,12] Large follow-up studies (N = 107 and 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 decreases 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 RIS versus PBO, Armenteros *et al.*[15] studied 25 children with ADHD and overt aggression; only children with affective/impulsive aggression were enrolled. They added RIS or PBO 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 RIS or PBO augmentation. Although the study reported a statistically significant difference in response rate (≥30% improvement on the parent-rated aggression scale) favoring RIS, the authors' reanalysis of that finding was not statistically significant (Fisher exact test, $p = .22$; Yates χ^2,