

Prescribing Antipsychotics in Aggressive Children With ADHD

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Dr. Good has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

It's a vexing question: At what point do you consider prescribing antipsychotics for aggressive children? The potential side effects—weight gain, sedation, possible movement side effects, and metabolic abnormalities—encourage us to think long and hard about this, and there are few good evidence-based guidelines.

The recent Treatment of Severe Childhood Aggression (TOSCA) study provides us with clinically useful results (Barterian JA et al, *J Am Acad Child Adolesc Psychiatry* 2017;56(12):1026–1033).

Background of the TOSCA study

The TOSCA study builds on the 2003 Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY) guidelines. TRAAY combined evidence-based findings with expert consensus and was unique in that the guidelines focused on a symptom rather than a specific diagnosis (Pappadopulos E et al, *J Am Acad Adolesc*

Psychiatry 2003;42(2):145–161). The guidelines recognized that polypharmacy may be needed in children who exhibit recurrent and persistent harm to themselves, others, or their environment.

Previous research found both stimulants and parent training (PT) to be helpful for children with both ADHD and aggressive behavior. Sessions of PT, which is also referred to as parent management training (PMT), often use role-playing to give caregivers practical strategies for managing impulsive behaviors and reactive aggression.

TOSCA design

TOSCA focuses on children with severe ADHD, who also meet criteria for oppositional defiant disorder (ODD) or conduct disorder (CD). These children tend not to do as well with stimulants alone and often end up being prescribed antipsychotics. TOSCA was devised to help clinicians understand whether this is a helpful practice.

Recruitment for the multisite study began in 2008 and proceeded in 3 phases: a 9-week acute trial, a 12-week extension (responders only), and a 52-week follow-up study.

The findings of the acute trial phase were published in 2014 and included 168 children (ages 6–12 years) with ADHD and severe aggression (ODD, $n = 124$; CD, $n = 44$). Study participants received PT and titration of stimulant medication, primarily osmotic release oral system (OROS) methylphenidate.

Assessments included parent ratings: Nisonger Child Behavior Rating Form (NCBRF) and Antisocial Behavior Scale (ABS), as well as blinded clinician ratings on the Clinical Global Impression-Improvement Scale (CGI-I). Children who had not improved enough after week 3 were randomized to a 6-week trial of an additional agent, either placebo (basic treatment; $n = 84$) or risperidone (augmented treatment; $n = 84$). Risperidone was started at 0.5 mg at bedtime and titrated to a maximum daily dose of 3.5 mg (2.5 mg for patients < 25 kg).

TOSCA results

The results supported the efficacy of risperidone in the study population, with statistically significant improvement on the primary outcome measure, NCBRF Disruptive-Total subscale (D-Total; $p = 0.0016$), as well as other measures.

Following the 9-week acute trial was a 12-week extension with 2 booster PT sessions. Both groups maintained their improvement over 21 total weeks, although there was regression in some measures.

Clinical implications

The latest reanalysis, published in the December 2017 Journal of the American Academy of Child & Adolescent Psychiatry (See: <https://bit.ly/2vzTzGO>), provided specific

recommendations to help us decide when to start an antipsychotic. To determine the best time to augment with risperidone, the researchers reexamined response criteria, grading response to interventions from both general and more stringently defined perspectives.

The investigators recommend that, after PT is started and the stimulant drug is optimized, clinicians should wait at least 1 month before adding an antipsychotic. This is because the combined benefit of stimulant and PT continues to increase over a 6-week period. Clinicians can expect ongoing improvement beyond the first 3 weeks, and waiting a bit longer for the primary interventions to work would result in fewer patients requiring a second drug.

An additional encouraging finding is that responders to any of the interventions continued to do well over the next 3 months. At the end of a year, those who received risperidone continued to do better than those who did not—although half had stopped one or both of the drugs.

Treatment algorithm

The TOSCA paper concludes with a treatment algorithm for children with ADHD and severe physical aggression. PT and stimulant titration are first-line treatments, but if after 4–6 weeks there is room for symptom improvement, try a different stimulant. Next, if there is evidence of anxiety, treat with an SSRI and/or CBT prior to considering an antipsychotic. If the patient has ongoing aggression despite the stimulant and PT, an antipsychotic can be added—but a taper should be considered 6 months after starting it.

Bottom line: Clinical recommendations from TOSCA

Oscar Bukstein, MD, MPH, professor of psychiatry at Harvard Medical School and one of the principal investigators on the TOSCA study, states that the study's results provide important clinical guidance for providers treating children with persistent and severe physical aggression and coexisting ADHD.

Dr. Bukstein says that, although the results point to the efficacy of second-generation antipsychotics (SGA) for persistent, severe aggression and ADHD, many of these children will show a robust response to a standard or established combination of stimulant medication and PT. SGAs, he adds, should be reserved for those children who do not respond or fully respond to this standard combination. Further research is necessary to completely understand the long-term safety issues involved with SGA treatment and to test pharmacologic alternatives for SGAs for children who do not respond to standard treatment.

It should be noted that TOSCA excluded patients with other neurodevelopmental disabilities and mood disorders. Longer-term studies are also needed to determine the impact of treatment on psychosocial outcomes, such as rates of substance abuse or violent crime.

CCPR Verdict: For patients with severe disruptive symptoms, we should proceed carefully and avoid jumping to antipsychotics. But there are several challenges, including implementing parent training and, when indicated, CBT. The side effects of risperidone and the lack of additional data on other antipsychotics used in this situation are a concern; additionally, our patients often have mood and developmental challenges that were excluded in TOSCA and likely limit the benefit of this approach.

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