Not Just Another Antipsychotic-for-Conduct-Problems Trial

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If you follow developments in child and adolescent psychiatry, it is understandable if, when you glanced at this issue's contents, you asked, "Does the world really need another antipsychotic-beats-placebo trial for childhood aggression? Does Seattle really need another Starbucks?"

Yet, just as a seemingly superfluous coffee shop can fulfill a need, for instance, by opening on your block, many features of the study by Aman *et al.*[1] that compared risperidone (RISP) with placebo when they were added to methylphenidate in aggressive children with attention-deficit/hyperactivity disorder (ADHD) make it exceptionally useful indeed. So before appraising this important trial's significance for clinical practice and research, let us take a moment to consider the innovations through which it transcends its predecessors.

First, this trial's design helps to reconcile an incongruity between practice guidelines and evidence for the treatment of a large patient population. Volatile, impulsive children with brittle frustration tolerance who display persistent aggressive behavior are the dominant preadolescent group receiving mental health care.[2] These problems most often emerge on a substrate of weak impulse control, and ADHD is ubiquitous in these youngsters.[3] Accordingly, guidelines suggest that initial pharmacotherapy target ADHD using agents well established for that purpose.[4,5] This is sensible guidance. Stimulant monotherapy can alleviate many manifestations of ADHD and the conduct problems often associated with it, including chronic aggressive behavior. These medications are generally well tolerated and one's response to a stimulant regimen can be deduced in a matter of days. The effect sizes of stimulants for the broader spectrum of ADHD symptoms remain unmatched. If, after an adequate stimulant medication trial, aggressive behavior persists, adding another compound, such as a second-generation antipsychotic (SGA), may be indicated.[4,5] However, the evidence base for antipsychotic treatment of aggression is rooted chiefly in trials that did not use this stepped-care approach. Some trials let patients stay on pre-enrollment stimulant treatment, but this passive approach has drawbacks. There is no way to tell whether the regimen is helpful for ADHD symptoms or aggression, whether it could be improved on, or whether it has in fact worsened irritability and rage. Adherence to such "allowed" stimulant treatment is never mentioned. Therefore, with the few exceptions noted in the articles,[6,7] SGAs for aggression in children with ADHD remain essentially untested in their recommended use: as add-on therapy for those demonstrably underresponsive to first-line ADHD therapy. Aman *et al.* overcome this deficiency in our literature.

Second, it is great to see a trial in this area use inclusion criteria that contain a meaningful threshold of aggressiveness. Most often, some surrogate characteristic defines the patient sample (e.g., irritability, rating scales that include a broader range of nonaggressive behavior problems, diagnoses of conduct disorder). Third, affording all families psychosocial therapy has little precedent in SGA trials for aggressive youngsters, but I believe is important to do for numerous methodologic and ethical reasons. Fourth, the effort to distinguish treatment effect on proactive aggression versus reactive aggression furnishes worthwhile data.

Now on to what this study teaches us.

The trial's overall finding is that children randomized to have RISP added to methylphenidate, the latter openly titrated during the first 3 weeks, had greater decreases on parent-rated disruptive behaviors than those allocated to receive adjunctive placebo. The magnitude of effect was

moderate (effect size 0.52). At the trial's end, blinded evaluators judged 79% of the RISP-treated patients as "much" or "very much" improved compared with 70% of those on placebo; the number needed to treat for 1 patient to achieve this outcome attributable to RISP was 11, and the group difference was not statistically significant. Similarly, 72% in the RISP group were rated as no more than "mildly ill" after treatment, whereas 59% in the placebo group were—also not significant and the number needed to treat was approximately 8. Compared with other trials for severe aggressive behavior, this trial showed smaller benefit for RISP over placebo, which the authors discuss at length. Because satisfactory response in placebo-treated groups was uncommon in earlier trials, the effect size reported here is smaller here since so many children got better without antipsychotic exposure. The trajectory of behavioral ratings over time (Figure 2 in Aman *et al.*[1]) showed that the initial 3 weeks of stimulant monotherapy for everyone did much of the heavy lifting toward the ultimate response measured at week 9. In the placebo group, continuation on the stimulant and behavioral therapy regimen culminated in even further decreases in conduct problem ratings.

In the context of these results, the authors discuss whether stimulant-plus-RISP "co-therapy is worth the added expense, inconvenience, and potential risks that may accompany use of more than one drug." The enduring, widespread public and practitioner concerns about polytherapy's proliferation in children with severe behavioral disorders, SGA use in particular, and the minuscule evidence base for its value make the question an almost existential one for child and adolescent psychiatry and you should read their consideration of it. However, suppose we tweak the topic to ask more specifically, "Should clinicians adopt this trial's strategy of a 3-week stimulant monotherapy period and then start RISP if there is 'room for improvement'?" The ensuing discussion would show the depth of the gratitude we owe these investigators, because they contribute, at long last, real data to formulate detailed treatment guidelines affecting the care of many thousands of children.[8-10]

Indeed, these results seem to show that a longer period of well-monitored stimulant monotherapy accompanied by competent psychosocial treatment is a wiser course than starting adjunctive SGA therapy. Judging from the symptom trajectories in Figure 2, unless we find strong predictors at 21 days that show whose progress is likely to stall, or unless dangerous behavior distills the choices to start another drug or get hospitalized, introducing another compound much before, say, 5 to 6 weeks seems hasty.

Moreover, it is doubtful that 21 days is a suitable maximum period to establish an optimal stimulant regimen. Greater flexibility in dosing, agent selection, and overall duration might have culminated in an even greater clinical response during the monotherapy phase. As a veteran of trials involving stimulant-optimization and behavior therapy before randomization to adjunctive treatments for those whose aggression persists,[11-13] I know how difficult they are. I understand the choices Aman *et al.* made to bracket the open monotherapy phase to a manageable, relatively brief, and uniform period. However, the exigencies of an efficient clinical trial do not always match what does, or should, happen in clinical care. My colleagues and I opted for a variable-length stimulant monotherapy lead-in whose titration algorithm includes more dose options and assessment occasions to reconfirm response. Our total time from baseline to the final assessment that determines eligibility for the adjunctive treatment phase of the trials is typically 5 to 7 weeks, often longer, which also allows more time for the behavioral interventions to gain traction. In this context, we have consistently found that at least half the patients show remission of their aggressive behavior during this lead-in phase. In comparison, Aman *et al.* reported that only 8 of their 138 patients responded well enough in the 3-week monotherapy period to preclude adding the other compound (RISP or placebo). I also suspect that more time devoted to optimizing first-line treatment picks the low-hanging fruit more thoroughly so that placebo response rates decrease, improving statistical power. For instance, the incidence of remitted aggression in children randomized to add placebo to optimized stimulant in our first trial was only 15% versus 57% of those randomized to add divalproex sodium. Aman *et al.*, as noted, reported response rates in the add-on placebo condition of approximately 60% to 70%.

Another way to assess whether first-line ADHD treatment has really been titrated to optimal effect is to see how much ADHD improves. Curiously, Aman *et al.* do not discuss their ADHD symptom outcomes over the trial's course, but I hope they do in their subsequent reports.