**Why JAACAP Published an "Inconclusive" Trial: Optimize, Optimize, Optimize Psychostimulant Treatment**

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In this issue of the *Journal*, Blader et al.1 report the results of a double-blind randomized controlled trial (RCT) aimed at assessing the comparative efficacy and tolerability of adjunctive risperidone (RISP), valproex sodium (DVPX) or placebo for aggressive behaviors in children (aged 6-12) with Attention-Deficit/Hyperactivity Disorder (ADHD) and comorbid Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) as well as a prior history of psychostimulant treatment. Participants with aggressive symptoms persisting after an open-label optimization of psychostimulant medication entered the 8-week randomized phase. Weekly sessions of family-based behavioral treatment were offered both during the optimization and the randomized phases. Among the 151 participants who completed the optimization phase (175 were initially enrolled), an unexpected 63.6% met the study criteria for remission, i.e., three consecutive weeks with subthreshold scores on the Retrospective - Modified Overt Aggression Scale (R-MOAS). Therefore, only 45 participants were eligible for randomization and 40 (RISP: n = 17; DVPX: n = 14; placebo: n = 9) were included in the primary analysis. Both children in the RISP and DVPX arm showed significantly greater reductions in the R-MOAS scores compared to placebo, with higher effect size (ES) for RISP (-1.32) compared to DVPX (-0.91). Weight gain was significantly increased in the RISP compared to the placebo group (ES: 0.28). However, the study authors acknowledged that “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...”.

Why did *JAACAP* publish an inconclusive trial? Because, in our view, the lessons that can be learnt from this RCT (in particular, from its optimization phase) are highly relevant both for clinicians and trialists in the field.

Physical aggressiveness is one of the most common reasons for referral to child and adolescent mental health services. Clinicians are in general aware that, for the management of aggressiveness in children with ADHD, current guidelines (e.g.,2) recommend adjunctive pharmacological treatment only after an adequate but ineffective trial of psychostimulant. But what does “adequate” mean? The optimization phase in Blader et al. provides an evidence-based answer. They used the following algorithm: participants were started on 18 mg/d of methylphenidate (MPH) OROS with a titration of 18 mg increments until a maximum dose (72 mg/d) could be reached, even though clinicians could titrate up to 90 mg/d if indicated and well tolerated. In case of adverse effects probably related to the long duration of MPH-OROS, clinicians had the option to switch to a biphasic MPH preparation (MPH-BI), up to 60 mg/d. Mixed amphetamine salts (MAS-XR), up to 35 mg/d, was the second line option when MPH was not efficacious or not well tolerated. Overall, at the end of the optimization phase, 104 participants were treated with MPH-OROS, 17 MPH-BI and 42 MAS-XR. The appealing aspect of this algorithm is its ecological validity. Indeed, it is implementable in daily clinical practice, even though some would argue it is time consuming. Importantly, it is also in line with the evidence from the most comprehensive network meta-analysis3 of RCTs of ADHD medications across the lifespan, which concluded that, in children/adolescents, methylphenidate should be considered as first line because, even though it is (at the group level) slightly less efficacious than amphetamines, it has better tolerability and acceptability. The hierarchy in the choice of medication during the optimization phase also reflects the recommendations of evidence-based guidelines such as those from the UK National Institute for Health and Care Excellence (NICE),4 which suggest methylphenidate and amphetamine as first and second pharmacological choice, respectively, for children and young people with ADHD. The results of the optimization phase in Blader et al. are also consistent with what some researchers in the field consider one of the main lessons from the randomized phase of the well-known Multimodal Treatment of ADHD (MTA) study, i.e., the pivotal role of an accurate delivery and titration of stimulants.5 It is also notable that Towbin et al.6 observed a similar, though not as substantial, response to stimulant optimization in their randomized controlled trial focused on the treatment of chronic severe irritability. In that study, 11 out of 69 (15.9%) did not enter the randomized component of that trial because they no longer met study criteria for significant irritability after stimulant optimization. It is likely that the lower response rate during the optimization phase in Towbin et al.’s study is due to the higher baseline severity among study participants. A careful titration has also been reported by some authors as crucial for the sustained effects of methylphenidate beyond the short-term.7

Overall, there are at least three practical take-home messages from the optimization phase of the study by Blader et al. First, even mild increases in total daily dose of stimulant may make a difference to effectively control aggressiveness. Indeed, the authors did their best to increase the chance of recruitment in the randomized phase, including in the trial only participants with previous or ongoing psychostimulant treatment at a minimum total daily dose equivalent to 30 mg of immediate release MPH, but, nonetheless, still symptomatic. Interestingly, at the end of the optimization phase, the mean dose of psychostimulant in immediate-release MPH equivalence units was 41.6 mg. Second, patients who struggle with intolerable effects of methylphenidate may benefit from a switch to another preparation of methylphenidate and, failing this, to amphetamine. Third, a properly optimized trial of methylphenidate might be more effective than antipsychotics. In fact, 24% of the participants had received antipsychotic treatment for behavioral disturbance before the trial.

Therefore, the main lesson for clinicians/prescribers is: “Be an optimizer!”. While many clinicians would take this for granted, a study of ADHD prescribers’ attitude in UK and Belgium showed that around 22% of them use a non-systematic approach, least in line with evidence-based practice compared to the “optimizers”.8 Furthermore, if the plethora of compounds and formulations of ADHD medications available in some countries, especially in the USA, allows prescribers to tailor the psychostimulant treatment to the specific needs of the patients, it also may make it tempting to quickly switch rather than carefully titrating. It is important to note that the remissions in the optimization phase may have been accounted for by factors beyond the psychostimulant treatment, such as the fact of taking part in a trial and the effects of the family-based behavioral therapy. If, on the one hand, many of the families of children in the trial benefitted from previous behavior therapy, on the other hand one may argue that the intensity of the treatment in the trial (1 week) made the difference.

And what is the lesson from this study for trialists? Probably, that no trial is a waste and every trial should be published. Publishing inconclusive, negative or even failed trials may lead to useful insights for the field, but it is also an ethical obligation to study participants. Unfortunately, it has been reported that 30% of RCTs in pediatric patients never get published.9 To address this issue, in 1997 the US Congress passed the FDA Modernization Act, which mandates public access to information of trials for patients with serious/life threating conditions. Following this, in 2000 ClinicalTrials.gov, a publicly available registry of trials, was created, with the requirement for trialists to upload the results of their registered trials. However, arguably important messages/contents such as the one on optimization discussed in this Editorial can be hardly conveyed by just uploading data in a non-peer reviewed repository. Important initiatives have been proposed to facilitate the publication of unpublished studies, such as the Restoring Invisible and Abandoned Trial (RIAT),10 which proposes to make public all the confidential information/data about missing and abandoned trials in one year’s time if trial sponsors fail to publish it themselves.

The publication of the Blader et al. paper is in line with these initiatives and with the commitment of the *Journal* to transparency, already highlighted in a previous Editorial11 focused on the importance of publishing negative trials.

We are confident the Blader et al. study will contribute to make clinicians in the field more “optimizers” and trialists more “transparent”.

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