AAP GRAND ROUNDS™
www.aapgrandrounds.org
Vol. 24 No. 3 | Pages 29-40 | September 2010

Mission: To provide pediatricians with timely synopses and critiques of important new studies relevant to pediatric practice, reviewing methodology, significance, and practical impact, as part of ongoing CME activity.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

ADHD: Adding a Placebo to Reduce Stimulant Dose

Source: *Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? J Dev Behav Pediatr. 2010;31(5):369-375; doi:10.1097/DBP.0b013e3181e121ed*

PICO

Question: Among children with ADHD, can the dose of stimulant medication be reduced while maintaining effective treatment of symptoms by using a placebo?

Question type: Intervention

Study design: Prospective, open-label, placebo-controlled trial

Investigators from the Mission Children's Hospital in Asheville, NC and the University of North Carolina-Chapel Hill sought to determine the acceptability, side effects, and efficacy of adding a placebo to achieve a reduction of stimulant medication dose in children ages 6 to 12 years being treated for a primary diagnosis of attention deficit-hyperactivity disorder (ADHD). Excluded were individuals with an IQ less than 80, a diagnosis of a major neurological/medical condition (eg, epilepsy, cerebral palsy, autism), and those on other psychotropic medications.

After an initial double-blind dose finding to identify the optimal dose of extended-release mixed amphetamine salt for each participant, 99 of 138 eligible subjects were enrolled and randomized into three groups: the full dose/control group (FD) took their optimal dose for two months; the dose reduction only/comparison group (RD) took their optimal dose for one month and then reduced their dose by 50% during the second month; the dose reduction with placebo/experimental group (RD/P) took their optimal dose and a placebo capsule for one month, and then took 50% of the optimal dose with the placebo for an additional month. Both parents and children were explicitly informed that the placebo capsule had no active ingredients. Of note, the placebo was referred to both as a "placebo" and "dose extender" to maintain some positive expectancy.

Parent and teacher measures of symptoms were obtained at baseline and weekly using the Inattention/Overactivity with Aggression (IOWA) Conner's scales and Pittsburgh Side Effects Rating Scale. These scales are subjective and parents were not blind to the treatment condition. The investigators also utilized an objective measure, Conner's Continuous Performance Test (CPT), a computer-administered test of reaction time, omission and commission errors, and variability of response.

Seventy subjects completed the study, with no difference in dropout rates between groups. On the Parent IOWA rating scale, children in the RD group demonstrated an increase in symptom severity compared to children in the FD and RD/P groups. The RD/P group had symptom severity similar to the FD group over time, while the RD group deteriorated. The teacher IOWA demonstrated no differences in ADHD symptoms among the three groups at all time points. The change in CPT t-score from baseline to posttest did not differ significantly between the three groups in attentional performance. Ratings by parents indicated an increase in side effect severity among the RD group (after dose reduction) relative to the FD and RD/P groups. The RD/P group demonstrated a decrease in side effects over the eight weeks. The authors conclude that pairing placebos with stimulant medication elicits a placebo response that allows children with ADHD to be effectively treated on 50% of their optimal stimulant dose.

Commentary by

Lisa Nalven, MD, MA, FAAP, Kireker Center for Child Development-Valley Hospital, Ridgewood, NJ

Dr Nalven has disclosed that her husband is an employee of Eisai. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

There is public concern that children are being "overmedicated." Parental concern regarding the use of medication in children can result in suboptimal dosing or discontinuation of treatment. By identifying the behavioral and side effect profile at the optimal dose[1] and then implementing classical conditioning (pairing the placebo with an effective dose), these investigators demonstrated that a large dose reduction (50%) with continued placebo could be achieved while maintaining control of ADHD symptoms and reducing medication side effects.

The fact that the placebo was effective in an open label trial is interesting.[2,3] Would the same result be achieved in a blind placebo study or with no mention of a dose extender? This study is limited by the fact that it is unclear whether the influence of "expectancy" simply changed parental perceptions of child behavior or whether it actually impacted the child's behavior. The actual mechanism of the placebo effect remains unknown; is it behavioral or neurophysiologic?

The blind ratings by teachers did not demonstrate differences among the study groups. The authors indicate that teacher information was not consistently available. Given that one of the major targets of ADHD treatment is the impact on behavior in the school setting, future studies should seek to determine whether maintenance of symptom control (as opposed to alteration of parental perception) can be achieved with dose reduction paired with placebo. If such an effect can be demonstrated, the next step is to determine whether maintenance of symptom control can be achieved long-term.

Editors' Note

Kudos to the Homeric courage of these researchers who chose to sail between the Scylla of ADHD and Charybdis of placebos. Albeit a relatively small study, reducing the stimulant dose by half while sustaining parents' perception of symptom control despite awareness of the nature of the placebo boggles this editor's mind – particularly because the group whose dose was reduced without an accompanying placebo was perceived as deteriorating badly. If ever there was a study that raised more questions than it answers, this is it.

References

1. Jensen PS, et al. *J Dev Behav Pediatr*. 2001;22:60-73.
2. Sandler A. *MRDD Research Reviews*. 2005;11:164-170.
3. Sandler AD, et al. *Child Care Health Dev*. 2008;34:104-110.

Key words: ADHD, placebo, treatment

INSIDE

The AAP Policy on Disclosure of Financial Relationships and Resolution of Conflicts of Interest for AAP CME Activities is designed to ensure quality, objective, balanced, and scientifically rigorous AAP CME activities by identifying and resolving all potential conflicts of interest prior to the confirmation of service of those in a position to influence and/or control CME content. The AAP has taken steps to resolve any potential conflicts of interest.

All individuals in a position to influence and/or control the content of AAP CME activities are required to disclose to the AAP and subsequently to learners that the individual either has no relevant financial relationship or any financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in CME activities.

Downloaded from http://aapgrandrounds.aappublications.org/ by guest on January 15, 2021

ADHD: Adding a Placebo to Reduce Stimulant Dose

AAP Grand Rounds 2010;24;29
DOI: 10.1542/gr.24-3-29

Updated Information & Services	including high resolution figures, can be found at: http://aapgrandrounds.aappublications.org/content/24/3/29
References	This article cites 5 articles, 0 of which you can access for free at: http://aapgrandrounds.aappublications.org/content/24/3/29.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Developmental/Behavioral Pediatrics** http://classic.aapgrandrounds.aappublications.org/cgi/collection/development:behavioral_issues_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: https://shop.aap.org/licensing-permissions/
Reprints	Information about ordering reprints can be found online: http://classic.aapgrandrounds.aappublications.org/content/reprints

Downloaded from http://aapgrandrounds.aappublications.org/ by guest on January 15, 2021

AAP Grand Rounds
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

ADHD: Adding a Placebo to Reduce Stimulant Dose

AAP Grand Rounds 2010;24;29
DOI: 10.1542/gr.24-3-29

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://aapgrandrounds.aappublications.org/content/24/3/29

AAP Grand Rounds is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1999. AAP Grand Rounds is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2010 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1099-6605.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Downloaded from http://aapgrandrounds.aappublications.org/ by guest on January 15, 2021