Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study

James T. McCracken, MD, James J. McGough, MD, Sandra K. Loo, PhD, Jennifer Levitt, MD, Melissa Del'Homme, PhD, Jennifer Cowen, PhD, Alexandra Sturm, MA, Fiona Whelan, MA, Gerhard Hellemann, PhD, Catherine Sugar, PhD, Robert M. Bilder, PhD

Journal of the American Academy of Child & Adolescent Psychiatry
DOI: http://dx.doi.org/10.1016/j.jaac.2016.05.015

Abstract

Objective
Because models of attention-deficit/hyperactivity disorder (ADHD) therapeutics emphasize benefits of both enhanced dopaminergic and noradrenergic signaling, strategies to enhance D1 and alpha2A agonism may yield enhanced clinical and cognitive responses. The study tested the hypothesis that combined effects of a dopamine and noradrenergic agonist, d-methylphenidate extended-release (DMPH), with guanfacine (GUAN), an alpha2A receptor agonist, would be clinically superior to either monotherapy, and have equal tolerability.

Method
An 8-week, double-blind, three-arm comparative trial randomized 7- to 14-year-olds with DSM-IV ADHD to GUAN (1-3 mg/day), DMPH (5-20 mg/day), or the combination (COMB) with fixed-flexible dosing. Outcome measures were the ADHD Rating Scale IV (ADHD-RS-IV) and the Clinical Global Impression-Improvement (CGI-I) Scale. Adverse events and safety measures were obtained.

Results
207 participants were randomized and received drug. Analyses showed significant treatment group main effects for ADHD-RS-IV ADHD total (p = .0001) and inattentive symptoms (p = .0001). COMB demonstrated small but consistently greater reductions in ADHD-RS-IV Inattentive subscale scores versus monotherapies (DMPH: p = .05; f² = .02; and GUAN: p = .02; f² = .02), and was associated with a greater positive response rate by CGI-I (p = .01). No serious cardiovascular events occurred. Sedation, somnolence, lethargy, and fatigue were greater in both guanfacine groups. All treatments were well tolerated.

Conclusion
COMB showed consistent evidence of clinical benefits over monotherapies, possibly reflecting advantages of greater combined dopaminergic and alpha2A agonism. Adverse events were generally mild to moderate, and COMB treatment showed no differences in safety or tolerability.

Clinical trial registration information
Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder (Project1); http://clinicaltrials.gov/; NCT00429273.