Age-Dependent Effects of Methylphenidate on the Human Dopaminergic System in Young vs Adult Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial.


Abstract

IMPORTANCE: Although numerous children receive methylphenidate hydrochloride for the treatment of attention-deficit/hyperactivity disorder (ADHD), little is known about age-dependent and possibly lasting effects of methylphenidate on the human dopaminergic system.

OBJECTIVES: To determine whether the effects of methylphenidate on the dopaminergic system are modified by age and to test the hypothesis that methylphenidate treatment of young but not adult patients with ADHD induces lasting effects on the cerebral blood flow response to dopamine challenge, a noninvasive probe for dopamine function.

DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled trial (Effects of Psychotropic Drugs on Developing Brain-Methylphenidate) among ADHD referral centers in the greater Amsterdam area in the Netherlands between June 1, 2011, and June 15, 2015. Additional inclusion criteria were male sex, age 10 to 12 years or 23 to 40 years, and stimulant treatment-naive status.

INTERVENTIONS: Treatment with either methylphenidate or a matched placebo for 16 weeks.

MAIN OUTCOMES AND MEASURES: Change in the cerebral blood flow response to an acute challenge with methylphenidate, noninvasively assessed using pharmacological magnetic resonance imaging, between baseline and 1 week after treatment. Data were analyzed using intent-to-treat analyses.

RESULTS: Among 131 individuals screened for eligibility, 99 patients met DSM-IV criteria for ADHD, and 50 participants were randomized to receive methylphenidate and 49 to placebo. Sixteen weeks of methylphenidate treatment increased the cerebral blood flow response to methylphenidate within the thalamus (mean difference, 6.5; 95% CI, 0.4-12.6; \( P = .04 \)) of children aged 10 to 12 years old but not in adults or in the placebo group. In the striatum, the methylphenidate condition differed significantly from placebo in children but not in adults (mean difference, 7.7; 95% CI, 0.7-14.8; \( P = .03 \)).

CONCLUSIONS AND RELEVANCE: We confirm preclinical data and demonstrate age-dependent effects of methylphenidate treatment on human extracellular dopamine striatal-thalamic circuitry. Given its societal relevance, these data warrant replication in larger groups with longer follow-up.

TRIAL REGISTRATION: identifier: NL34509.000.10 and trialregister.nl identifier: NTR3103.