Treatment of Children with Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Multicenter, Double-Blind, Crossover Study of Extended-Release Dexamethasone and D,L-Methylphenidate and Placebo in a Laboratory Classroom Setting

By Raul Silva, MD, Rafael Muniz, MD, Kevin McCague, MA, Ann Cloudress, MD, Matthew Brams, MD, and Alice Mao, MD

ABSTRACT - The purpose of this study was to compare the efficacy and safety of extended-release dexamethasone (D-MPH-ER) to that of D,L-MPH-ER and placebo in children with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting. This multicenter, double-blind, crossover study randomized 82 children, 6-12 years of age, stabilized on a total daily dose to the nearest equivalent of 40-60 mg of D,L-MPH or 20 or 30 mg/day of D-MPH. Patients participated in a screening day and practice day, and were randomized to one of 10 sequences of all five treatments in five separate periods. Treatments included D-MPH-ER (20 mg/day), D-MPH-ER (30 mg/day), D,L-MPH-ER (36 mg/day), D,L-MPH-ER (54 mg/day), and placebo. Primary efficacy was measured by the change from predose on the Swanson, Kethin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale—Combined scores at 2-h postdose during the 12-h laboratory assessment (D-MPH-ER 20 mg/day vs. D,L-MPH-ER 36 mg/day). Adverse events were monitored throughout the study period. D-MPH-ER (20 mg/day) was significantly more effective than D,L-MPH-ER (36 mg/day) in...
the primary efficacy variable, change from baseline to 2-h postdose in SKAMP combined score. In general, d-MPH-ER had an earlier onset of action than d,l-MPH-ER, while d,l-MPH-ER had a stronger effect at 12-h postdose. No serious adverse events were reported. Treatment with either agent was associated with significant improvements in ADHD symptoms. d-MPH-ER and d,l-MPH-ER can be differentiated on what part of the day each is more effective. Psychopharmacology Bulletin. 2008;41(1):19–33.

**INTRODUCTION**

Attention-deficit/hyperactivity disorder (ADHD), a serious condition affecting 3–7% of school-age children, is characterized by persistent core symptoms of inattention, hyperactivity, and impulsivity. Symptoms of ADHD lead to impairments in learning, cognition, behavior, and social and family interactions. ADHD is associated with low self-esteem, precipitated by multiple factors including poor school performance, frequent criticism from family and teachers, and even rejection from peers.

Psychoactive stimulants have a long history of proven efficacy in the treatment of symptoms of ADHD (effect size of 0.91–0.95 for intermediate- and long-acting stimulants, respectively). Racemic methylphenidate hydrochloride (d,l-MPH) has proven safety and efficacy in the treatment of childhood ADHD.**Dexmethylphenidate hydrochloride (d-MPH)** is the pharmacologically active d-three enantiomer of racemic MPH (d,l-MPH); l-MPH does not appear to contribute to the clinical efficacy of d,L-MPH,** and demonstrates substantial differences in receptor binding from d-MPH.** D-MPH is approved in the United States for the treatment of adults and children 6 years and older with ADHD. Since it does not racemize after oral administration,** doses of d-MPH at half those of the racemic mixture have similar safety and efficacy profiles.**

Dexmethylphenidate was first developed as an immediate-release tablet requiring a twice-daily dosing regimen. Immediate-release preparations of MPH have been associated with reduced adherence to therapy, symptom-rebound, and the need for a second dose administered at midday.** Long-acting methylphenidate preparations of MPH are active over 8–12 h, eliminating the need for a midday dose at school.

The d,l-MPH-ER formulation releases 22% of the drug initially, with the remainder released through a controlled osmotic process that results in an initial peak at 1–2 h after drug administration, followed by a gradual increase over several hours, with a maximum concentration occurring at 6.8 h.** Once-daily d-MPH-ER uses the proprietary spheroidal oral drug absorption system (SODAS™) technology developed by Elan...
Corporation, where 50% of the dose is released immediately and the remaining 50% is released after 4 h, resulting in a maximum peak at about 1.5 h and a second peak at about 6.5 h. The onset and duration of the effect of D-MPH-ER has been explored in two double-blind, placebo-controlled, crossover studies in children 6–12 years old with ADHD. In those studies, D-MPH-ER was statistically superior to placebo for all efficacy outcome measures at all time points tested, from 0.5-h up to 12-h postdose (p < .001 for primary measure, and p < .001 to p = .046 for all secondary measures). This randomized, multicenter, double-blind, crossover study was designed to evaluate the efficacy and safety of D-MPH-ER (20 and 30 mg/day) to that of D,L-MPH-ER (36 and 54 mg/day), employing a placebo control, in children 6–12 years old with ADHD in a 12-h laboratory classroom setting.