

Key Words: attention-deficit/hyperactivity disorder, dexamethylphenidate, methylphenidate, double-blind, crossover

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

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ABSTRACT ~ The purpose of this study was to compare the efficacy and safety of extended-release dexamethylphenidate (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 1 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, Kotkin, 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

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the primary efficacy variable, change from predose 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.^{1–3} 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.⁴

Psychostimulants 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).⁵ Racemic methylphenidate hydrochloride (D,L-MPH) has proven safety and efficacy in the treatment of childhood ADHD.^{6–10} Dexmethylphenidate hydrochloride (D-MPH) is the pharmacologically active *D-threo* enantiomer of racemic MPH (D,L-MPH); L-MPH does not appear to contribute to the clinical efficacy of D,L-MPH,¹¹ and demonstrates substantial differences in receptor binding from D-MPH.¹² 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,¹¹ doses of D-MPH at half those of the racemic mixture have similar safety and efficacy profiles.^{13,14}

Dexmethylphenidate was first developed as an immediate-release tablet requiring a twice-daily dosing regimen. Immediate-release formulations of MPH have been associated with reduced adherence to therapy, symptom-rebound, and the need for a second dose administered at midday.¹⁵ 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.¹⁶ 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.¹⁷

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).^{18,19}

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.

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