

Drug Regimen Individualization for Attention-Deficit/Hyperactivity Disorder: Guidance for Methylphenidate and Dexmethylphenidate Formulations

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Abstract

In 2000, the first biphasic modified-release (MR) formulation of methylphenidate (MPH) was approved for the treatment of attention-deficit/hyperactivity disorder (ADHD). An immediate-release (IR) MPH pulse (22% of the dose) facilitates rapid onset of stimulant action, while the remaining MR portion of the dose provides for day-long duration of efficacy. A wide array of oral MR-MPH products has subsequently been approved that also allows for once daily dosing, though each product is characterized by distinctive exposure time courses. This review compares each member of the current MPH armamentarium to assist in the rational selection of a specific MPH regimen for the individualized treatment of patients with ADHD. The IR portion of biphasic MPH formulations now ranges from 15%, 20%, 22%, 25%, 30%, and 37% IR-MPH, as well as a 50% IR-MPH product whose distinctly pulsatile time courses closely resemble that of the pre-century "gold standard" twice-daily IR-MPH regimen. Further, transdermal, suspension, and orally-disintegrating tablet products are now available to overcome any solid dosage form swallowing difficulties. Most of these formulations are racemic, though in 2001 a chiral switch drug IR-dexmethylphenidate (dexMPH) was approved, followed by biphasic MR-dexMPH (50% IR) in 2005. New United States Food and Drug Administration partial area under the curve (pAUC) bioavailability metrics have improved discrimination between specific generic MR-MPH products. This has resulted in two Orange Book MR-MPH products being recoded from "AB" (i.e., meets necessary bioequivalence requirements) to "BX" (i.e., insufficient data to confirm bioequivalence). The metabolic drug interaction between MPH and alcohol, which increases MPH bioavailability, potentiates euphoric effects, and heightens abuse liability, is discussed. This review concludes with brief considerations of pharmacogenomic predictors of ADHD first-line drug selection, carboxylesterase allelic variants influencing inter-individual MPH metabolism, and novel MPH formulations in the regulatory pipeline.