Medication Persistence, Duration of Treatment, and Treatment-switching Patterns Among Canadian Patients Taking Once-daily Extended-release Methylphenidate Medications for Attention-Deficit/Hyperactivity Disorder: A Population-based Retrospective Cohort Study

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ABSTRACT

Purpose: We conducted a retrospective cohort study to compare medication use patterns of a long-acting extended-release methylphenidate (Osmotic Release Oral System [OROS®] methylphenidate, CONCERTA®) and Teva-methylphenidate (methylphenidate ER-C), a generic drug determined by the Canadian regulatory authority, Health Canada, to be bioequivalent to OROS® methylphenidate.

Methods: We established an OROS® methylphenidate–experienced and new-user population cohort to compare medication use patterns, including medication persistence, duration of therapy, and treatment-switching patterns. Multivariable log-binomial regression was used to adjust for confounders of the associations with persistence.

Findings: In the OROS® methylphenidate–experienced cohort (n = 21,940), OROS® methylphenidate was associated with a 70% higher rate of medication persistence at 12 months relative to methylphenidate ER-C (adjusted relative risk = 1.70; 95% CI, 1.64-1.77). In the new-user cohort (n = 20,410), OROS® methylphenidate had a 58% higher rate of medication persistence relative to methylphenidate ER-C (adjusted relative risk = 1.58; 95% CI, 1.51-1.65). Median duration of therapy was significantly longer in patients taking OROS® methylphenidate compared with those taking methylphenidate ER-C, and treatment-switching occurred significantly more frequently in patients taking methylphenidate ER-C compared with those taking OROS® methylphenidate.

Implications: Significant differences were observed in how the medications were used by patients in the real-world setting. Because the data sources were administrative databases, it was not possible to control for all potentially important confounding variables. Although differences in medication persistence may not directly reflect differences in treatment efficacy, the findings are important because these products are used interchangeably in a number of Canadian provinces. (*Clin Ther*. 2016;38:1789–1802)

Key words: generic, methylphenidate, persistence, therapeutic equivalence.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in the pediatric population, affecting 2% to 5% of children and commonly persisting into adulthood.[1] Pharmacologic treatment with stimulant medication is commonly used as first-line therapy for ADHD, and

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extended-release (ER) formulations of methylphenidate hydrochloride have become a mainstay of treatment in recent years. The branded ER formulation of methylphenidate* uses the Osmotic Release Oral System (OROS®) (Janssen Inc., Toronto, Ontario, Canada) to release methylphenidate as a once-daily formulation.[2] In January 2010, a generic formulation of ER methylphenidate, methylphenidate ER-C (initially named Novo-methylphenidate ER-C and later renamed Teva-methylphenidate ER-C) was approved by Health Canada. The product was considered bioequivalent to the trademark drug based on review of comparative bioavailability studies and despite several differences between the products' characteristics. Methylphenidate ER-C does not use an OROS® drug-release system; has an earlier peak concentration, shorter half-life, and faster drug elimination compared with OROS® methylphenidate, and does not seem to exhibit the multiphasic profile of OROS® methylphenidate.[3,4] After methylphenidate ER-C became available, it was listed as an interchangeable product to OROS® methylphenidate in several Canadian provinces, including Ontario (2010), Manitoba (2010), Nova Scotia (2012), New Brunswick (2012), and Newfoundland (2014).

Since the approval of methylphenidate ER-C, 2 Canadian studies have studied the use of methylphenidate ER-C in patients whose conditions had been stabilized with OROS® methylphenidate. Both studies identified significant differences in efficacy when patients were switched to methylphenidate ER-C.[5,6] The first study was conducted independently of the pharmaceutical manufacturer of OROS® methylphenidate and was a double-blind, randomized, crossover study of adults (n = 17) with ADHD initially stabilized with OROS® methylphenidate who were randomized to switch to methylphenidate ER-C or continue treatment with OROS® methylphenidate. Patients who switched to methylphenidate ER-C experienced a shorter duration of effect and efficacy failure when randomized to a switch to the methylphenidate ER-C product.[5] The second study was sponsored by the pharmaceutical manufacturer of OROS® methylphenidate (Janssen Inc.) and was a retrospective study of 162 pediatric patients whose conditions were also initially controlled with OROS® methylphenidate and switched to methylphenidate ER-C after methylphenidate ER-C was approved for interchangeable use in the proinvce.[6] The study found that 87% of patients who switched to methylphenidate ER-C experienced ADHD symptom destabilization compared with 26% in patients who continued use of OROS® methylphenidate through the study period.[6]

These clinical studies support the results of early pharmacokinetic-pharmacodynamic studies that identified an association of the OROS® methylphenidate time-concentration curve with clinical outcomes[7–9] and a comparative pharmacokinetic study of OROS® methylphenidate and methylphenidate ER-C.[3] Literature reviews of pharmacokinetic-pharmacodynamic studies have reported that the clinical efficacy of methylphenidate ER across the day generally follows the same pattern of the pharmacokinetic profile across the day, and thus differences in the pharmacokinetic course can translate into differences in clinical outcomes.[7–9]A comparative pharmacokinetic analysis found that although the Canadian regulatory pharmacokinetic measures of bioequivalence were met for methylphenidate ER-C compared with OROS® methylphenidate, the concentration-time profiles of the 2 drug products were different. OROS® methylphenidate exhibited a biphasic profile across the day with a rapid increase to 1.5 hours, which plateaued at approximately 4 hours followed by another increase to a peak of 6 hours. In contrast, the profile for methylphenidate ER-C revealed an increase without interruption to a peak at 5 hours. After reaching their peaks, methylphenidate ER-C concentration decreased faster than that of OROS® methylphenidate.[3] Taken together, the differences in therapeutic effectiveness reported in the clinical studies, may be explained by the differences in the pharmacokinetic time-concentration profiles of the 2 drugs.[5,6] In the United States, the US Food and Drug Administration (FDA) created a unique bioequivalence guideline for long-acting methylphenidate products in 2012, requiring the use of additional partial AUC metrics to ensure more similarity over the time-concentration pharmacokinetic profile of generic comparators to OROS® methylphenidate. The FDA guideline for long-acting methylphenidate bioequivalence underwent another revision in 2014, due to ongoing issues with therapeutic equivalence of the US generic comparators to OROS® methylphenidate.[10,11] Partial AUC metrics are not required for bioequivalency in Canada.

*Trademark: Concerta® (Janssen Inc, Toronto, Ontario, Canada).