# Differences in Adverse Event Reporting Rates of Therapeutic Failure Between Two Once-Daily Extended-Release Methylphenidate Medications in Canada: Analysis of Spontaneous Adverse Event Reporting Databases

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## ABSTRACT

**Purpose:** Our study evaluated adverse events of therapeutic failure (and specifically reduced duration of action) with the use of a branded product, Osmotic Release Oral System (OROS) methylphenidate, which is approved for the treatment of attention deficit/hyperactivity disorder, and a generic product (methylphenidate, methylphenidate ER-C), which was approved for marketing in Canada based on bioequivalence to OROS methylphenidate. This study was initiated following reports that some US-marketed generic methylphenidate ER products had substantially higher reporting rates of therapeutic failure than did the referenced brands.

**Methods:** Through methodology similar to that used by the US Food and Drug Administration to investigate the issue with the US-marketed generic, reporting rates were calculated from cases of therapeutic failure identified in the Canadian Vigilance Adverse Reaction Online database for a 1-year period beginning 8 months after each product launch. Corresponding population exposure was estimated from the number of tablets dispensed. An in-depth analysis of narratives of individual case safety reports (ICSRs) with the use of the generic product was conducted in duplicate by 2 physicians to assess causality and to characterize the potential safety risk and clinical pattern of therapeutic failure. Similar secondary analyses were conducted on the US-marketed products.

**Findings:** Reporting rates of therapeutic failure with the use of methylphenidate ER-C (generic) and OROS methylphenidate (brand name) were 411.5 and 37.5 cases per 100,000 patient-years, respectively (reporting rate ratio, 10.99; 95% CI, 5.93–22.21). In-depth analysis of narratives of 230 ICSRs of therapeutic failure with the Canadian-marketed generic determined that all ICSRs were either probably (60 [26%]) or possibly (170 [74%]) causally related to methylphenidate ER-C. Clinical symptoms suggestive of overdose were present in 31 reports of loss of efficacy (13.5%) and occurred primarily in the morning, and premature loss of efficacy (shorter duration of action) was described in 98 cases (42.6%) and occurred primarily in the afternoon. Impacts on social functioning, such as disruption in work or school performance or adverse social behaviors, were found in 51 cases (22.2%).

**Implications:** The ~10-fold higher reporting rate of therapeutic failure with the generic product relative to its reference product in the present Canadian study resembles findings with US-marketed generic products. While these results should be interpreted with caution due to the limitations of spontaneous adverse event reporting, which may confound comparisons across products, similar findings nonetheless led the US Food and Drug Administration to declare in 2014 that 2 methylphenidate ER generic products in the United States were neither bioequivalent nor interchangeable with OROS methylphenidate—their reference product. Our results indicate a potential safety issue with the Canadian-marketed generic and suggest

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a need for further investigation by Health Canada. (*Clin Ther*. ▮▮▮▮;▮:▮▮▮–▮▮▮) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** adverse event, bioequivalence, extended-release methylphenidate, generic, reporting rate, therapeutic failure.

## INTRODUCTION

Extended-release (ER) formulations of methylphenidate HCl have become a mainstay of attention deficit/hyperactivity disorder (ADHD) treatment.[1] Studies have shown a close relationship between the pharmacokinetic profile (shape of the concentration–time curve) of ER methylphenidate and its corresponding pharmacodynamic profile (time-course of clinical response); as the plasma concentrations of methylphenidate rise and fall across the day, a corresponding clinical response follows a similar time-course.[2–7]

The most commonly used ER formulation of methylphenidate in Canada is Osmotic Release Oral System (OROS) methylphenidate,* which has a multiphasic pharmacokinetic profile and provides 12 hours of efficacy with a once-daily formulation.[3] Unlike many drugs that are titrated to steady-state conditions over a period of days, the short half-life of methylphenidate means that the drug is normally almost completely cleared from the body before the next daily dose, without reaching steady state or accumulating, and the pharmacokinetic profile remains consistent from day to day.[8] Because the clinical response correlates closely with the concentration–time profile of methylphenidate, there have been problems associated with several approved generic formulations referencing OROS methylphenidate that have a different drug-delivery profile.

Health Canada approved the first Canadian-marketed generic ER formulation of methylphenidate, methylphenidate ER-C,† in January 2010, based on bioequivalence to OROS methylphenidate, as assessed by a comparison of the $AUC_{\tau}$ and $C_{max}$ of the products. In contrast to the United States and the European Union, where partial AUC metrics are required for demonstrating the bioequivalence of ER products, in Canada, none of the currently available generic products were approved based on partial AUC metrics.[9] While 2 other generic products have been approved in Canada, recent data from QuintilesIMS (Durham, North Carolina) indicate that methylphenidate ER-C received the majority of generic use in Canada.

In the United States, the US Food and Drug Administration (FDA) approved generic methylphenidate ER products produced by 2 manufacturers,‡ which were launched in 2013 after meeting US bioequivalence standards, including $AUC\tau$, $C_{max}$, and the partial AUC from 0 to 3 hours postdose. An authorized generic version of OROS methylphenidate has also been available in the United States since May 1, 2011; an *authorized generic* is the branded product that is marketed and distributed as a generic product. Consequently, the US-marketed authorized generic (OROS methylphenidate) may be considered as being the same as the Canadian branded OROS methylphenidate for comparison purposes, and may be used as a reference product.

Since the market approval of the first generic drug in Canada, the Canadian Centre for ADHD Awareness, Canada patient advocacy group has received reports of issues with generic methylphenidate ER formulations, including shortened or reduced clinical effects, and adverse events.[10] Although adverse events are more typically thought of as additional unwanted effects of a drug (e.g., a headache or rash), if a product fails to produce its expected intended clinical effect, or fails to produce its clinical effect for the intended duration, this is considered to be an adverse event by Health Canada, as there may be an adverse outcome in the patient, including an exacerbation of the condition for which the product is being used. Health Canada's guidance in Reporting Adverse Reactions to Marketed Health Products[11] provides the example of a patient whose condition is well-stabilized but deteriorates when the patient is switched to a different brand or receives a new prescription as an example of an *unusual failure in efficacy*, which is a reportable adverse event. Such issues have also been more formally studied and supported in several scientific publications.[12–15] A comparative bioavailability study found a multiphasic profile with OROS methylphenidate, which included a rapid increase in concentration after dosing to 1.5 hours, a plateau at

*Trade name: OROS® and Concerta® (Janssen Inc, Toronto, Ontario, Canada).

†Teva Canada Ltd, Toronto, Ontario, Canada.

‡Mallinckrodt Pharmaceuticals Inc (Hampton, New Jersey), Kudco/Kremers Urban Pharmaceuticals Inc (Princeton, New Jersey).