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ADHD MANAGEMENT IN PRACTICE: WHY THE CHOICE OF METHYLPHENIDATE FORMULATION MATTERS FOR RESTORATIVE FUNCTIONALITY

Psychiatry

Joel Lamoure — Rph, DD, FASCP, Regional Manager, Ambulatory; The Northwest Company, Former Canadian Section Head to UNESCO Chair In Bioethics.

Dr. Angelo Fallu — MD, Clinique Woodward.

Dr. Kenny Handelman — MD FRCPC, Child and Adult Psychiatrist, Centre for Integrative Mental Health, Assistant Clinical Professor, McMaster University.

Dr. Martin Katzman — Clinic Director, START Clinic for the Mood and Anxiety Disorders, Professor, Adler Graduate Professional School, Adjunct Professor, Department of Psychiatry, Northern Ontario School of Medicine, Adjunct Professor, Department of Psychology, Lakehead University.

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders. Stimulant medications remain a cornerstone of ADHD multimodal management. Methylphenidate extended release (ER) is available in osmotic and non-osmotic formulations. The osmotic delivery system used in the Osmotic-Controlled Release Oral Delivery System (OROS) methylphenidate ER (Concerta®) functions like a precision biomedical device, using osmotic pressure to provide a release profile that ensures symptom control throughout the day. Clinical guidelines and real-world data suggest that osmotic and non-osmotic delivery formulations are not interchangeable and achieving restorative functionality can be influenced by the choice of delivery system. No historically available generic non-OROS methylphenidate ER to date has been demonstrated to provide consistent results across the past 15 years. Thus, the osmotic delivery system is more than the medication; it is a technology that safely and predictably delivers medication to restore functionality for patients with ADHD. Only now, with Taro-Methylphenidate ER, has an osmotic delivery system technology been available in a subsequent entry methylphenidate ER product.

KEYWORDS

methylphenidate, ADHD, osmotic delivery system, extended-release, restorative functionality

INTRODUCTION

ADHD Landscape in Canada

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders and is often diagnosed in childhood. ADHD presents as persistent inattention, hyperactivity, and impulsivity that lead to significant functional impairments (CADDRA, 2020). In Canada, CADDRA (Canadian ADHD Resource Alliance) estimates 5.4% of Canadians have ADHD, with rates among children estimated to be 0.5% in preschoolers, up to 8.5% in children and adolescents and rates in adults reported up to 7.3% (Espinet et al., 2022). In a review of published Canadian papers in which all provinces were represented, the CADDRA authors further identified that estimates varied by gender, ranging from 3.7% to 13% in males and from 1.5% to 7% in females. Interestingly, this gender/sex discrepancy decreases with age. (Espinet et al., 2022)

Increasing numbers of adults are being diagnosed with ADHD in Canada. Based on a national insurance claims database, there was a 24.5% increase in the number of unique claimants over 18 years of age prescribed ADHD medication between 2021 and 2022 compared to a 15.3% increase in the previous 5 years, 2017-2021. (Manulife, 2023). Further, there is a noted shift in the number of women being diagnosed with ADHD as adults , which may be explained by the under or missed diagnosis of females in childhood (Attoe et al., 2023; Martin, 2024), though ongoing research is warranted to better explore the variation of ADHD symptoms, diagnosis and overall prevalence by gender (Attoe et al., 2023; Martin, 2024; Platania et al., 2025).

Implications of undiagnosed and /or untreated ADHD are significant. A recent review identified impacts on both mental wellbeing and social interactions with observed higher risks of substance abuse, accidents and lower education level and income (French et al., 2023). One study that explored the risks of motor vehicle accidents (MVA) for those with ADHD found that as ADHD symptoms increased, the risks of crashes and near misses also significantly increased (Aduen, 2018). Undiagnosed/untreated ADHD can affect not only the individual but can have wide reaching impacts on families, schools and communities (Dalsgaard et al., 2015; Dalsgaard, Østergaard et al., 2015; Faraone, 2015; O'Nions et al., 2025).

Pharmacotherapy remains a cornerstone of ADHD multimodal management of medication plus therapy/strategies, especially in moderate-to-severe presentations due to the established efficacy in improving core symptoms and a goal to restorative functional outcomes.

Medication Selection

The goal of optimizing pharmacotherapy is to provide the right medication to the right patient, at the right dose and for the right condition. This paper will explore the hallmarks of medication and medication delivery systems, as not just the active pharmaceutical ingredient (API) should be considered, but its means of delivery in vivo as well.

Among extended release (ER) stimulant treatments, the Osmotic [Controlled] Release Oral [Delivery] System (OROS) formulation of methylphenidate (MPH)—marketed under the trade name Concerta®—has emerged as a unique and effective agent capable of achieving what clinicians and caregivers seek most: restorative functionality. This paper outlines how achieving this degree of restorative functionality provides stability that hinges on selecting the right pharmacological tool—and why OROS methylphenidate remains central to the Canadian ADHD story.

The Canadian ADHD Treatment Paradigm: CADDRA's Position

The CADDRA Guidelines (CADDRA, 2020) emphasize a comprehensive, biopsychosocial approach. When it comes to pharmacological treatment, the guidelines prioritize evidence-based long-acting psychostimulant medications as first-line options, specifically:

- Amphetamine-based ER stimulants
- Methylphenidate-based ER stimulants

However, not all MPH ER formulations are created equally. The CADDRA Guidelines Committee has explicitly stated that current generic formulations substituted for the original OROS MPH ER tablet (Concerta®) should be considered different drugs-thus not automatically interchangeable-due to significant variation in delivery mechanisms and pharmacokinetics (CADDRA, 2020).

Efficacy, Tolerability and Impact on Function

Numerous clinical trials and real-world studies have confirmed the efficacy of MPH in reducing ADHD symptoms and improving overall functioning. For example, Fallu et al. (2016) report substantial improvements in patient satisfaction, concentration, and side effect

profile with OROS MPH ER. Steele et al. (2006) found that once-daily OROS MPH ER yielded higher remission rates and better symptom control compared to immediate-release (IR) MPH, especially for inattention and oppositional behaviors.

Improvements in social, academic, and emotional functioning are clinically meaningful for patients. By providing consistent symptom coverage throughout the day, MPH can help children maintain focus during school, reduce impulsive outbursts, and improve peer relationships—all key metrics of patient functionality (Steele et al., 2006). Traditional IR formulations of MPH require multiple daily doses, often during school hours, leading to stigma, inconsistent adherence, and logistical challenges around controlled substance administration (Steele et al., 2006). These barriers frequently result in suboptimal dosing and reduced treatment efficacy.

In contrast, sustained-release formulations aim to maintain therapeutic plasma concentrations over time, avoiding the peaks and troughs that can occur with IR dosing. Most of the sustained release formulations are biphasic in medication delivery, with the exception of the OROS triphasic delivery system.

One of the foundational studies that shaped how we think about ADHD medication was the "sipping study" led by Dr. Swanson (Swanson et al, 1999), which helped to develop the ascending profile of MPH released by the OROS MPH ER tablet. This research compared different delivery profiles of MPH: short-acting doses that create a quick spike and drop in blood levels, a sustained-release version that maintains a flat, steady concentration, and an ascending profile like what we now see with OROS MPH ER (Concerta®). What the study found was striking—not all forms of delivery had the same clinical impact, even when the total amount of medication was the same. The ascending profile, which gradually increases MPH levels over time, resulted in significantly better symptom control. The key takeaway wasn't just that the medicine reached the brain, but how it got there. The rate of delivery profoundly influenced the therapeutic effect, suggesting that optimizing the timing and pattern of absorption can be just as important as the dosage itself. The subsequent entry generic MPH ERs do not deliver the medicine in the same way that OROS does, and this can change the clinical response.

Further studies have also found advantages to the OROS delivery system. With OROS MPH ER, we know that patients stay on treatment longer than generic IR forms of MPH (Kemner et al., 2006).

In a study which compared OROS MPH ER to mixed amphetamine salts (MAS) extended release in driving performance in adolescent drivers with ADHD, the researchers found that OROS MPH ER led to significant improvements in driving performance compared to placebo and MAS extended release (Cox et al., 2006).

In a study which reviewed OROS MPH ER compared to generic IR MPH, OROS MPH ER led to significantly fewer accidents or injuries, significantly fewer emergency room visits, and general practitioner visits per patient on average over 1 year (Lage et al., 2004).

As a controlled medication, there are concerns about the risk of misuse, or abuse of MPH. Researchers have shown that the OROS MPH ER formulation is much less likely to be abused compared to the immediate release formulation. The generic extended-release formulations have no such research completed (Parasrampuria, 2007; Spencer, 2006).

Commentary: Dr. Angelo Fallu

Finding the right treatment for a patient with ADHD can be complicated. The molecule chosen must be a good fit for the patient and it can be a challenge to find the right medication for the patient in terms of efficacy and side effect profile. When we do find the right fit with a treatment, we're happy to be in that optimal spot.

Non-osmotic MPH ER is MPH, but it is not Concerta®. I consider it another MPH derivate. For a patient that is well-stabilized on Concerta® in terms of efficacy and side effect profile, based on the evidence, you should not necessarily expect the same type of reaction to generic MPH ER if it uses a non-osmotic delivery system. This was seen in our randomized, double-blind, cross-over study where patients were not tolerating, not responding or both to the non-osmotic MPH ER. (Fallu et al. 2016)

Clinically, it's reasonable to expect that a switch from Concerta® to a non-OROS MPH ER could be as dramatic as being switched from any medication to a new one. It's possible the new medication will not work as well, or the patient could experience side effects.

In everyday practice, clinicians have little control over which MPH ER product patients receive; the pharmacist chooses the generic substitution. Often, patients aren't informed of the switch. Pharmacists may simply say they're providing a less expensive "copy" of Concerta. Many patients then return reporting reduced efficacy, or new side effects.

When comparing Concerta to other MPH ER formulations, despite the area under the curves being similar, it is "not the end of the story" and some clinical improvements would be expected in some patients. Clinically, when using a non-osmotic delivery system, you have no assurance that the effect or the delivery or the peak of action will be the same as Concerta.

The Technology Behind OROS: A True Biomedical Device

OROS is not just a conventional tablet—it is a drug delivery system, essentially functioning as a precision biomedical device. The OROS tablet features:

- A tri-layer core consisting of two medication and excipient layers (external and internal layers)
- A semi-permeable osmotically active push layer, acting as a membrane that allows water influx
- A laser-drilled orifice that delivers a controlled release

In the intestinal system, the drug overcoat, which consists of 22% of the drug dose, quickly dissolves, providing an initial dose within one hour, aligning with the start of daily functioning. Water from the intestinal tract permeates through the membrane into the osmotic layer. As the osmotically-active polymer excipients expand, MPH is released through the laser-drilled orifice. The osmotic layer regulates the balance of the internal layers, representing 78% of the medication and this allows for a delayed and effective drug delivery system, irrespective of pH. This MPH release rate from the internal layers increases with time over a period of 6-7 hours, corresponding to the mid-point of the patients' day and prevents acute, daily tachyphylaxis of MPH. (Swanson et al., 1999.) Through the balance of the intestinal transit, more water expands the push layer, producing the third of the triphasic layers over 12 hours. This triphasic delivery system thus provides steady medication delivery through a normal work or school day flow.

This sophisticated delivery system contrasts with current non-osmotic delivery systems used in generics, which often release drug through passive diffusion and cannot replicate the same pharmacokinetic profile (Park-Wyllie et al., 2017; Narayan et al., 2025).

The OROS trademarked pill delivery formulation qualifies as a biomedical device because it incorporates mechanical and engineered design principles to achieve precise, time-controlled drug delivery independent of physiological conditions such as pH, food intake, and motility. Unlike traditional oral medications that rely on passive disintegration and absorption, the OROS system uses a semi-permeable membrane, osmotic pressure gradients, and a laser-drilled orifice to control the release of the active pharmaceutical ingredient (API), embodying the characteristics of a biomedical device. OROS is a registered trademark of the ALZA Corporation for this osmotic delivery system. Taro-Methylphenidate ER (Sun Pharma) is the only other MPH preparation that uses an osmotic delivery system and has a triphasic delivery of MPH that mirrors that of Concerta®. This is supported by dissolution data from a comparison of the two products. Like Concerta®, the Taro-manufactured product uses an osmotic delivery system.

From a regulatory standpoint, biomedical devices are defined not solely by their material composition, but by their mode of action—whether they function via mechanical, physical, or chemical means. The osmotic delivery system exemplifies this: water from the gastrointestinal tract diffuses through the semi-permeable membrane, dissolving an osmotic agent inside the pill. This generates pressure that pushes the drug formulation through a precision orifice at a controlled rate (Theeuwes, 1975; Santus & Baker, 1995). The release rate can be finely tuned by adjusting the composition of the osmotic core and the thickness of the membrane—features that demonstrate deliberate

device engineering.

Though it contains pharmaceutical compounds, the OROS system's device-like delivery and independent mechanism mean it meets criteria defined by the FDA for combination products—those composed of both a drug and a device (FDA, 2020). It does not depend solely on human physiology for activation or release, reinforcing its status as a biomedical device component.

By integrating pharmaceutical science with mechanical engineering, the OROS pill operates as more than a conventional drug: it functions as a controlled-release system with device-like precision and reliability, situating it clearly within the domain of biomedical devices.

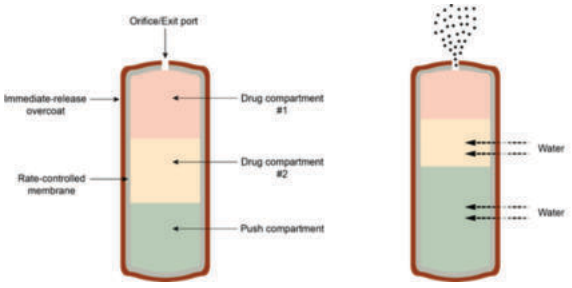

Figure 1- Cross Section of osmotic delivery system tablet

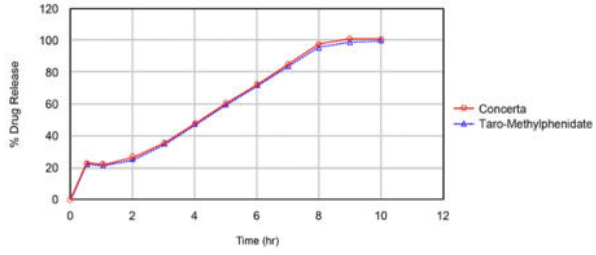

Figure 2 - Dissolution curve of Concerta® vs. Taro-MPH ER

Real-World Evidence: Osmotic vs. Non-Osmotic Delivery System
In the context of ADHD, symptom suppression is not the sole goal. Rather, treatment must aim to restore the individual's ability to function effectively-cognitively, socially, and emotionally-across the day. "Restorative Functionality" can be construed as unique to osmotic delivery systems, and this term means:

- Regaining executive function necessary for task completion
- Re-establishing social skills and peer interactions
- Achieving academic and workplace success

Only a medication with a consistent, full-day therapeutic window, minimal rebound, and stable plasma levels can reliably support this goal. Poor symptom control-whether due to fluctuating plasma levels, early wear-off, or inconsistent bioavailability-can have serious implications. Several studies highlight the clinically meaningful differences between osmotic and non-osmotic delivery ER products.

Park-Wyllie et al. (2017) reported that patients using non-OROS ER MPH formulations often experienced premature loss of efficacy, especially in the afternoon, impairing school and social functioning. In 22.2% of reports, this contributed to behavioral disruption and academic decline. By contrast, OROS MPH ER has demonstrated sustained efficacy and lower rates of adverse events or therapeutic failure. It also improves adherence by eliminating the need for mid-day dosing and reduces the risk of missed doses, loss of privacy, and treatment-related embarrassment (Steele et al., 2006; Lally et al., 2016). Functionality, the ability to engage in expected developmental, academic, occupational, and social activities—is a core goal of ADHD treatment. An osmotic release system supports this goal by providing consistent symptom control aligned with the daily rhythm of demands placed on children and adults with ADHD. Moreover, patients and caregivers have reported higher satisfaction with OROS MPH ER in multiple studies (Fallu et al., 2016; Fife et al., 2018). At study endpoints, participants almost uniformly opted to remain on OROS MPH ER over non-osmotic generic formulations, underscoring real-world preference and perceived benefit.

In a single-centre, retrospective observational study involving 162 pediatric patients prescribed Concerta®, 87% of those switched to a non-OROS generic experienced destabilization in either symptom control or functionality ($p<0.001$). Nearly half (43%) reported reduced duration of action (Van Stralen, 2013), which presents a challenge for patients doing homework or late afternoon activities such as driving or hobbies. Supporting case evidence may also be seen in a clinical case series of 14 youths with ADHD; patients who were non-responsive to non-OROS ER formulations showed significant improvement when switched back to OROS MPH ER. The mean T-score on the Conners-3 Inattention Scale dropped by 23 points ($p<0.0001$), restoring function to below the clinical threshold (Lally et al., 2016).

In a randomized, double-blind, cross-over, phase IV trial, twenty adult ADHD patients previously stable on OROS MPH ER (Concerta®) for at least 3 months, were treated with OROS MPH ER (Concerta®) or a non-OROS generic for 3 weeks and then crossed over to the other treatment for an additional 3 weeks. Patients treated with Concerta were more satisfied with efficacy and side effects vs. non-OROS generic (p-0.0433 and p=0.0321 respectively). The most common adverse event reported with the non-OROS generic was ADHD exacerbation (59% with non-OROS generic vs 13% with Concerta). (Fallu et al., 2016)

A retrospective cohort study by Park-Wyllie et al. (2016), analyzed real-world use in Canada from private and provincial drug plan databases (Ontario and Quebec). In a cohort of 41,900 patients taking OROS MPH ER (Concerta®) or non-OROS generic ER, duration of therapy was significantly longer in patients taking OROS ($p<0.0001$ vs. non-OROS MPH ER). Additionally, significantly more patients taking non-OROS MPH ER were switched to a different medication (38% of non-OROS treated patients vs. 11% of OROS treated patients, $p<0.0001$).

A pharmacovigilance study by Park-Wyllie et al. (2017), analyzing spontaneous adverse event reports in Canada found:

- A nearly 10-fold increase in therapeutic failure reports for non-OROS MPH compared to OROS (411.5 vs. 37.5 cases/100,000 patient-years)
- 42.6% of failures were due to shorter duration of effect
- 22.2% of reports described adverse social or functional outcomes such as poor school/work performance

These Canadian studies highlight the potential for clinical implications when patients are dispensed non-OROS formulations under the guise of interchangeability.

Commentary: Dr. Kenny Handelman
Doctors who treat ADHD in children and adolescents know the importance of finding a medication which works well for their patient and is well tolerated. There is often significant hesitance for parents and patients to make the decision to try medication, and if the medicine provided is not reliably working, or causes too many side effects, patients and parents may refuse ADHD medication. This could put them at higher risk of long-term negative outcomes – such as higher risks of accidents or injuries, depression, anxiety, driving accidents, and more (Biederman 2009).

It is imperative that medication products that doctors prescribe for youth are reliable and consistent for our patients. We want sustained therapeutic effectiveness with rapid onset of action, and we want a medicine which will provide a consistent 12-hour duration of effect for full-day coverage of ADHD symptoms in the morning, afternoon, and early evening with one dose. We want to know that the medicine delivers medication that is consistently delivered without peak and trough kinetics, which are associated with unreliable forms of medication delivery.

Methylphenidate is a controlled medication, and there are concerns about the risk of misuse, diversion or abuse of it. Researchers have shown that the OROS MPH ER formulation is much less likely to be abused compared to the immediate release formulation. The non-osmotic ER formulations have no such evidence (Parasrampuria 2007; Spencer 2006). Lowering the risk of abuse of a MPH medicine formulation is not only an important public health issue, it is also critically important for the young patients and their families that we treat.

OROS MPH ER has extensive research and experience that helps us have the confidence that this medicine will help kids and teens with

ADHD consistently and reliably and minimize the risk of side effects or lack of efficacy related to non-osmotic MPH extended-release products. The non-osmotic delivery system formulations often lead to more side effects in the morning and an earlier crash in symptom control, with more individuals experiencing a rebound medication wear-off at the end of the day. With the osmotic delivery system (OROS) MPH ER, rebound virtually does not exist.

FDA and CADDRA's Recommendation: Proceed with Caution with Non-OROS

These findings mirror earlier U.S. FDA actions that led to the reclassification of non-OROS MPH ER generics, meaning they are still approved and can be prescribed, but they are no longer recommended as automatically substitutable, due to being not therapeutically equivalent (FDA, 2014). The change reflects concerns that these products may not produce the same therapeutic effects as the brand-name drug. (FDA, 2016 Update)

Edition 4.1 of the CADDRA Guidelines explicitly states that substitution with non-OROS generics is not automatic and interchangeability factors weighed cautiously. Clinicians should specify an osmotic delivery system formulation when therapeutic consistency is paramount (CADDRA, 2020).

Commentary: Dr. Martin Katzman

It has been estimated that 5.4% of Canadians have ADHD (Canadian ADHD Resource Alliance), with rates among children estimated to be 0.5% in preschoolers, up to 8.5% in children and adolescents with prevalence rates in adults reported up to 7.3% (Espinet et al, 2022). In these people it is imperative to understand the importance of stability and consistency of catecholamine levels and activity in patients with ADHD; not being able to maintain the concentration throughout the day keeps you in a too variable situation where mood, impulsivity, anxiety, motivation, energy and executive function are all variable throughout the day. Use of a product which maintains stable concentration throughout the day contributes to stable and better outcomes. OROS technology-based MPH ER maintains stable and effective concentration, and it is important to remind the patient of the importance of maintaining this stable blood concentration, informing them of how this variation might manifest in them. A good question is: "Are there times of the day where you feel less effective, with less energy, motivation or the ability to focus and think?"

In order to ensure these stable levels throughout the day, it is imperative to be on the right delivery system, and the osmotic delivery system ensures that stable level throughout the day. And so, it is important to remind the patient at the pharmacy to:

- Make sure that the prescription you get from your prescriber is for an osmotic delivery system MPH ER
- Make sure the pharmacist provides you with an osmotic delivery system MPH ER

CONCLUSION

The goal of ADHD pharmacotherapy is not just inherent symptom suppression, but a return to normative functioning—restorative functionality. Achieving this requires:

- A long-acting, stable pharmacokinetic profile, with a quick ascending curve
- Avoidance of peaks and troughs through the day
- Minimization of dose titration and adverse events
- Support of real-world daily activities like school and work

The osmotic delivery system OROS MPH ER (Concerta®) offers all of these, and no historically available generic non-osmotic MPH ER to date in Canada has been demonstrated to provide consistent results across the past 15 years reliably. (CADDRA,2020) Thus, the osmotic drug delivery system is more than the medication; it is a technology that safely and predictably delivers medication to restore functionality for patients with ADHD. Only now with Taro-Methylphenidate ER has osmotic delivery system technology been available in a subsequent entry MPH ER product.

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