doi.org/10.58931/cpct.2025.XXXX

ABOUT THE AUTHOR



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Affiliations: None declared.

Choosing a Therapy for ADHD

Isaac Szpindel, MD

When choosing a therapy for a person with ADHD it is important to consider the whole patient including the entirety of the patient's environment and the resources available to them. As detailed in the section above, long-acting stimulant formulations are the recommended 1st line therapeutic choice according to CADDRA.[1] Once-daily dosing which has become possible through advances in medication delivery systems of the active ingredient provide the added benefit of improved adherence.

The initial choice of pharmacotherapy is dictated by individual needs and environmental factors such as availability or experience with medications taken by other family members, exposure to environments or individuals at risk of abuse, and milieus, occupations or locations where medications are restricted and or unavailable. Comorbidity may direct medication choice as may polypharmacotherapeutic considerations. It should be noted that even within the same family, affected individuals may respond differently to the same or similar medications both within and across classes. As stimulant-naïve patients are at greater risk of side-effects and intolerance, starting low and going slow is a prudent choice. This will reduce side-effect risk and running-over response when reassessing at several week intervals or more as appropriate after stepwise dose titration to optimal response. As methylphenidate formulations are strong dopaminergic and weak noradrenergic neurotransmitter reuptake inhibitors, they may represent a milder starting point for the stimulant-naïve. Comorbidity considerations may similarly suggest amphetamine formulations due to their additional action through vesicular neurotransmitter release for both dopamine and norepinephrine in addition to their action as reuptake inhibitors. As ADHD should be treated to remission rather than simply to response one should consider this as an iterative process in which initial choice is built upon, revised or added to similarly according to response and side-effect.

Due to well established effect sizes, rapid times to response, improvements in response and

reductions in side effects with reduced risk of misuse and abuse, long-acting psychostimulants are typically my first medication choice on patient environment and comorbidity. Commonly this will be an all-day-long-acting, extended-release (ER) methylphenidate or amphetamine. In patients with ADHD I prefer smooth release rather than phasic release and triphasic over biphasic release where such medications are utilized. Smooth long-acting releases are achieved chemically in the amphetamine medication lysdexamphetamine dimesylate and mechanically in the methylphenidate osmotic delivery formulations. This is due to flatter release profiles which may reduce likeability and craving[2] and the combination of all-day-long-acting duration, relative pH immunity and reduced potential for abuse and misuse. pH-altering conditions and medications can be common in adults and may impact release of pH-based delivery system medications.

In Canada where bioequivalent medication substitution is available and in some places, mandated, one should differentiate between similar medications such as bioequivalents and what I consider to be identical bioduplicate medications. While bioequivalent drugs use the same active underlying molecule, the overall dose, delivery mechanisms and systems and accompanying excipients can vary. Dose delivery timing may also vary, including smoothness of delivery and time to peak dose and fall-off. ADHD bioequivalents may not closely simulate the curves of their parent drugs. It is my experience as suggested by the literature that substitution with these products may be associated with loss of effect and/or greater side effects.[3,4,5,6,7] Abuse and misuse potential also increases in formulations that can be crushed and administered by alternate routes. Lysdexamphetamine and polyresin methylphenidate formulations are less prone to such risks, and as such are preferred. Given these factors, the current and growing methylphenidate ER bioequivalent landscape in Canada must be considered. At the time of this writing, it should be noted that one of the available methylphenidate ER bioequivalents is what I consider to be a true bioduplicate that uses the identical base chemical, identical osmotic delivery system, and identical polyresin matrix with identical excipients. Due to the aforementioned vulnerabilities and the current bioequivalent landscape specific to Methylphenidate Extended Release (ER) formulations in Canada I address this topic specifically.

My experience with these medications, consistent with that of clinicians across Canada, the decisions of various provincial regulators, and the 2020 CADDRA Guidelines was that initial generic extended-release methylphenidate bioequivalents at that time that did not employ the osmotic delivery system were different drugs that behaved sufficiently differently that they should not be automatically interchangeable.[1] There is a mounting body of evidence for these claims including the following 3 examples:

Fallu et al. 2016[3]
- Randomized, double-blind, cross-over, phase IV trial,
- 20 adult ADHD patients OROS MPH ER (Concerta®) for at least 3 months and stable
- Patients given OROS MPH ER (Concerta®) or a non-OROS generic for 3 weeks then crossed over treatment for a subsequent 3 weeks.
- Concerta-treated patients treated reported increased satisfaction for efficacy (p=0.0433) and side effects (p=0.0321) vs. non-OROS generic
- Most common adverse event was ADHD exacerbation (59% vs 13%, non-OROS generic vs. Concerta).

Park-Wyllie et al. 2016[6]
- Retrospective cohort of patients receiving OROS MPH ER (Concerta®) or non-OROS MPH ER, (n=41,900)
- Cohort data from Ontario and Quebec private and provincial drug plan databases
- Length of therapy was significantly increased in OROS-treated patients (p<0.0001 vs. non-OROS MPH ER).
- 38% of non-OROS treated patients vs. 11% of OROS treated patients were switched to a different therapy, p<0.0001).

Park-Wyllie et al. 2017[4]
- Canadian pharmacovigilance study reviewed spontaneous adverse event reports
- Non-OROS MPH ER reports had an ~10-fold greater occurrence of therapeutic failure vs. 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 were of adverse social or functional outcomes (e.g. poor school/work performance)

In Canada, bioequivalent substitution is often mandated by provincial and private insurance coverage. Currently, there are 3 generic versions of the long-acting methylphenidate ER brand (Concerta®) available in Canada. The recent release of Taro-Methylphenidate ER in Canada represents in my opinion, an available generic option that is what I consider to be bioduplicate in that it uses an identical drug component, identical osmotic delivery system and identical excipients.

Again, once a treatment is chosen, as described previously, dose titration for treatment of ADHD to remission should follow the adage "start low, go slow" independent of medication choice. This allows for effective monitoring of response and any side effects. Blood pressure and heart rate should be monitored following any medication increase or change and at appropriate intervals as indicated on a long-term basis to rule out outlying rare instances of excessive increase. Treatment should be optimized to remission and patients followed along the lifespan as different needs arise, different environments are encountered and as the body and brain mature. Co-morbid physical and psychiatric conditions should be addressed and treated appropriately and prioritized according to severity, need, and associated risk. Overall, ~90% of patients will respond to a stimulant medication from either the methylphenidate or amphetamine class for treatment of their ADHD. Where indicated by partial or incomplete response, stimulant therapy may be combined with non-stimulant therapy as appropriate and tolerated.

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Financial Disclosures

I.S.: Honoraria: Sun Pharmaceuticals

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