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Review of Long-Acting Stimulant and Nonstimulant ADHD Pharmacotherapy in Canada

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Foreword

Acknowledgment

Disclosure Information

Review of Long-Acting Stimulant and Nonstimulant ADHD Pharmacotherapy in Canada

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Abstract

Objective: To review differences among long-acting stimulant and nonstimulant medications available in Canada for the management of attention-deficit/hyperactivity disorder (ADHD) and to describe strategies for implementing treatment with these medications.

Method: A literature review of relevant English-language manuscripts on long-acting pharmacotherapy was conducted. Additional information was gathered from product monographs, material presented at recent scientific meetings, and practice guidelines.

Results: Long-acting medications are recommended as first-line pharmacotherapy for management of ADHD in children, adolescents, and adults and include methylphenidate- and amphetamine-based stimulants and the nonstimulant atomoxetine. Long-acting formulations aim to improve convenience and avoid the pitfalls associated with in-school dosing and may help to improve adherence. With the exception of the prodrug lisdexamfetamine dimesylate, long-acting stimulant preparations employ mechanical delivery systems to prolong release of the stimulant. In some cases, the technology used to confer a prolonged effect may serve to reduce the risk of abuse and provide smoother, less disrupted coverage.

Conclusions: Long-acting medications have significantly impacted the management of ADHD. Despite the preponderance of long-acting medications, short-acting stimulants hold a place in the therapeutic armamentarium, particularly as adjunctive/augmentative therapy. Overall, the availability of a wide spectrum of medications has increased our capacity to optimize individual treatment of ADHD.

Keywords: attention-deficit/hyperactivity disorder, long-acting, amphetamine, nonstimulant, methylphenidate

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Introduction

The worldwide prevalence of attention-deficit/hyperactivity disorder (ADHD) is ~5%, with considerable variability across geographic areas and diagnostic criteria (Polanczyk et al., 2007). In Quebec, the 6-month prevalence of ADHD among 6- to 14-year-olds was estimated to be 5.0% and 8.9% by parent and teacher reports, respectively (Breton et al., 1999). The overall prevalence of ADHD among children aged 4 to 16 years was 9.0% in boys and 3.3% in girls, in the Ontario Child Health Study (Szatmari et al., 1989).

The impact of ADHD symptoms is seen across multiple functional domains and varies throughout a patient's lifespan. Children with ADHD frequently exhibit impaired peer relationships, decreased academic performance, and increased rates of injuries and accidents (Hoza, 2007; Reiff et al., 2003). Adolescents with ADHD have higher rates of academic failure and are more likely to drop out of school than their peers (Barkley, 2002). As reviewed by Barkley, reports of young adults with ADHD show they have greater social difficulties, earlier sexual activity, more teenage pregnancies, and higher rates of sexually transmitted diseases (Barkley, 2002). Compared with controls, adults with ADHD complete less schooling, report higher rates of driving violations, obtain lower job status, experience more frequent job losses and unemployment, are less likely to be in a stable relationship, and more likely to be divorced (Biederman et al., 2006).

Treatment of ADHD can be broadly classified as either pharmacologic or psychosocial. Efficacious psychosocial therapies include behavioral parent training and behavioral classroom management (Pelham, Jr. et al., 2008; Knight et al., 2008). Such therapies, which will not be further reviewed in this article, can be used alone or as an adjunct to pharmacotherapy (Knight et al., 2008).

Pharmacotherapies can be categorized by active ingredient (stimulants and nonstimulants) or anticipated duration of effect (long-, intermediate-, and short-acting). Practice guidelines by the Canadian ADHD Resource Alliance (CADDRA) state that once-daily, long-acting preparations should be first-line pharmacotherapy for children, adolescents, and adults with uncomplicated ADHD (CADDRA, 2008). Other preparations are considered second-line or adjunctive therapies. This paper will review long-acting stimulant and nonstimulant medications available in Canada. Differences among formulations, pharmacokinetics, and mechanisms of actions will be explored, and practical strategies for implementing treatment will be included. Discussion will largely be limited to treatment of children and adolescents, with brief mention of relevant recommendations for adults. In addition to reviewing efficacy and duration of effect data, the effects of treatment on less commonly studied measures (eg, emotional expression, quality of life [QoL], and patient/parent satisfaction) will be explored. Finally, issues of abuse liability and safety will be discussed.

Methods

A literature review of relevant English-language manuscripts on long-acting pharmacotherapy for ADHD was conducted using MEDLINE (1950 to May 2010). Additional information was gathered from product monographs, abstracts and posters presented at recent scientific meetings, and appropriate practice guidelines. Where noted, anecdotal evidence from the authors' extensive clinical experience was included.

Long-Acting ADHD Treatments

Approved short-acting amphetamine- and methylphenidate (MPH)-based stimulants, although effective, often require repeat dosing throughout the day. In addition to issues of convenience, taking medications in school may result in lack of medical privacy and a sense of embarrassment (Swanson, 2003; Connor et al., 2004; Steer, 2005). The stigma of taking medicine in school may also impact adherence. Knowledge that a student is taking a stimulant medication may lead to increased peer pressure to divert medication or to outright theft (Connor et al., 2004; Dupont et al., 2007). As Connor and Steingard (2004) highlight, the decrease or "trough" in coverage between medication doses may result in escalation of symptoms. Although gaps in coverage can also occur with long-acting formulations, their frequency may be increased when multiple daily doses are required.

Long-acting treatments for ADHD offer several advantages over short-acting counterparts. By eliminating the need for same-day repeated dosing, long-acting formulations aim to improve convenience and avoid the stigma and embarrassment with in-school dosing

(Buitelaar et al., 2009; Steer, 2005). Most long-acting stimulant formulations use various technical strategies for delayed, sustained release of active agents with inherently short-acting pharmacokinetic properties. Thus, it may be important to understand similarities and differences in intra- and interindividual pharmacokinetic variability since, for example, low intraindividual variation may reduce the likelihood of patients falling into subtherapeutic drug levels or reaching levels at which the risk of adverse events (AEs) increases (Ermer et al., 2010). Long-acting formulations are also intended to provide continuous symptom control beyond the classroom, into less-structured after-school activities, which can be particularly important for a child's personal and social development (Buitelaar et al., 2009). The risk of rebound symptoms, those that deteriorate beyond baseline behavior and are sometimes observed when beneficial effects of short-acting stimulants wear off, may also be reduced by long-acting stimulants (Cantwell, 1996; Carlson et al., 2003).

Compared with formulations requiring multiple daily dosing, long-acting stimulants may be associated with improved adherence (Buitelaar et al., 2009). A recent comprehensive literature review of studies examining adherence with prescribed ADHD treatments found nonadherence rates ranging from 13.2% - 64% (Adler et al., 2010). Although data are limited and largely restricted to studies of MPH formulations, adherence appears to increase with long-acting formulations (vs short-acting formulations) (Adler et al., 2010; Sanchez et al., 2005). A frequent concern with stimulant therapy is the risk of abuse, misuse, and diversion. Data suggest that nonmedical use is more common with short-acting formulations of both MPH and amphetamine, although the relationship with availability based on prescriptions has not been studied (Bright, 2008; Wilens et al., 2008b; Wilens et al., 2006).

MPH-Based Stimulants

A summary of the long-acting MPH formulations available in Canada is presented in **Table 1.** The effects of MPH are likely mediated by inhibition of catecholamine (ie, dopamine, norepinephrine) reuptake from the synapse (Arnold, 2000; Markowitz et al., 2003). Although 4 enantiomers of the MPH molecule

exist, only the 2 threo isomers (ie, d- and l-MPH) are included in currently marketed formulations (Markowitz et al., 2003). Data suggesting that behavioral effects of MPH are mostly attributable to the d-MPH enantiomer has led to development of single-isomer (d-MPH) formulations, which are currently available in some countries outside of Canada (Markowitz et al., 2003; Quinn et al., 2004). Although no overall by-weight dose recommendations are available for MPH formulations (CADDRA, 2008), MPH is usually administered at average daily doses of ~1 mg/kg in randomized controlled clinical trials (Steele et al., 2006; Pelham et al., 2001). In a recent dosing analysis of adolescents, ADHD symptom severity but not patient age, height, or weight was predictive of optimal stimulant dose (Newcorn et al., 2010). When prescribing, clinicians should also consider the approximate hourly dose of stimulant delivered. Since stimulant efficacy appears to mirror blood levels, such calculations may help explain clinical differences observed with various dosing regimens (Swanson et al., 2003; Greenhill et al., 2003).

MPH-Sustained Release (SR)

MPH-SR (eg, Ritalin SR®, Novartis Pharmaceuticals Canada Inc.) was the first approved MPH extended-release formulation (Markowitz et al., 2003). The formulation relies on a wax-based matrix to provide a slow, prolonged single pulse of MPH (Markowitz et al., 2003; Prince, 2006). MPH-SR tablets must be swallowed whole and cannot be crushed or chewed (Ritalin SR Product Monograph, 2007). As the wax matrix technology is dependent on stomach acidity, absorption may vary among patients (Prince, 2006).

MPH-SR was designed to provide the same duration of effect as twice-daily immediate-release (IR) MPH 10-mg and has an 8-hour duration of effect (Ritalin SR Product Monograph, 2007; Pelham, 1987). Studies conducted by Pelham and colleagues (1987), however, suggested that the clinical effects of MPH-SR show considerable variability. Compared with IR-MPH, MPH-SR has a slower onset of action, sometimes requiring 3 hours after ingestion to demonstrate an effect (vs 1 hour for IR) as assessed by continuous performance tasks. As assessed by teacher ratings of behavior, the effects of MPH-SR appeared to wane 4-5 hours after ingestion, suggesting that it may be

Table 1. Formulation Characteristics of Long-Acting ADHD Pharmacotherapy Available in Canada

Medication	Formulation	Dosages available	Sprinkle	Monograph duration of action	Clinical experience duration of action[j]
MPH-SR[a]	Tablets	20-mg	No	8 hours	4-6 hours
OROS-MPH[b]	Tablets	18, 27, 36, 54-mg	No	12 hours	12-12.5 hours
Generic MPH-ER[c]	Tablets	18, 27, 36, 54-mg	No	12 hours[d]	Unknown
MLR-MPH[e]	Capsules	10, 15, 20, 30, 40, 50, 60, 80-mg	Yes	12 hours	8-10 hours
d-Amphetamine-SR[f]	Spansules	10, 15-mg	Yes	10-12 hours	6-8 hours
MAS-XR[g]	Capsules	5, 10, 15, 20, 25, 30-mg	Yes	12 hours	12 hours
LDX[h]	Capsules	20, 30, 40, 50, 60-mg	No (can be dissolved in water)	13 hours	12-14 hours
Atomoxetine[i]	Capsules	10, 18, 25, 40, 60, 80, 100-mg	No	Up to 24 hours	Up to 24 hours

ADHD	attention-deficit hyperactivity disorder
ER	extended-release
LDX	lisdexamfetamine dimesylate
MAS-XR	extended-release mixed amphetamine salts
MLR	multilayer-release
MPH	methylphenidate
OROS	osmotic-release oral system
SR	sustained-release.

[a] (Ritalin SR Product Monograph, 2007)

[b] (Concerta Product Monograph, 2010)

[c] (Novo-Methylphenidate ER-C, 2009)

[d] Not demonstrated in clinical trials

[e] (Biphentin Product Monograph, 2009; Weiss et al., 2007)

[f] (Dexedrine Spansules Product Monograph, 2009; CADDRA, 2008)

[g] (Adderall XR Product Monograph, 2009; Wigal et al., 2005)

[h] (Vyvanse Product Monograph, 2010; Wigal et al., 2009)

[i] (Strattera Product Monograph, 2009; Kelsey et al., 2004)

[j] Based on the clinical experience of the authors.

inappropriate for once-daily dosing in children requiring full-day symptom reduction. Pelham et al concluded that once-daily MPH-SR was generally less effective for the treatment of ADHD than twice-daily IR-MPH. Based on this, MPH-SR is best considered a short- to intermediate-acting formulation and is viewed as a second-line agent (CADDRA, 2008). In the authors' experience, MPH-SR may be most appropriate for multiple daily dosing in cases in which short-acting MPH wears off "too early" (eg, before an opportunity to administer the next dose).

Osmotic-Release Oral System (OROS®) MPH

OROS-MPH (Concerta®, Janssen-Ortho Inc.) tablets employ a modified-release technology with a drug overcoat that supplies ~22% of medication as IR-MPH, and the remaining 78% within the tablet and driven out through an exit port via a controlled osmotic process (Connor et al., 2004; Markowitz et al., 2003; Prince, 2006). Although the product monograph indicates a maximum dose for both children and adolescents of 54-mg/d (Concerta Product Monograph, 2010), CADDRA recommendations raise these limits to 72 and 81-mg/d, respectively (CADDRA, 2008).

OROS-MPH tablets must be taken whole and cannot be chewed, split, or crushed, rendering the formulation inappropriate for use by patients who cannot swallow pills (Concerta Product Monograph, 2010). The rigid, nonabsorbable tablet structure could potentially cause obstructive symptoms in patients with preexisting gastrointestinal strictures (Concerta Product Monograph, 2010; Markowitz et al., 2003). The release of MPH from OROS tablets is dependent on gastrointestinal transit time, suggesting cautious use when treating patients with altered intestinal motility (Weisler, 2007).

The rate of release of MPH from OROS-MPH tablets increases until reaching a maximum, ~6-7 hours after administration (Concerta Product Monograph, 2010). This "ascending curve" was intended to mimic thrice-daily IR-MPH and minimize "acute tachyphylaxis" (Swanson et al., 2003). Although OROS-MPH can be taken with or without food, the fed state is associated with slight delays in time to maximal concentration (T_{max}) and 10%-30% increases in extent of absorption (ie, maximum plasma concentration

[C_{max}] and area under the time-concentration curve [AUC]) (Modi et al., 2000). As assessed by the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and other laboratory classroom assessments, OROS-MPH has a duration of effect of ~12 hours (Prince, 2006; Pelham et al., 2001). OROS-MPH demonstrates efficacy within 1-2 hours postdose (Pelham et al., 2001; Concerta Product Monograph, 2010). In a recent double-blind, randomized, placebo-controlled, crossover analog classroom study conducted in children aged 9-12 years with ADHD, OROS-MPH (up to 54-mg/d) was associated with significant benefits over placebo as assessed by Permanent Product Measure of Performance (PERMP) Math Test beginning 1 hour after dosing (Starr et al., 2009). Effects persisted through 12.5 hours postdose, the last assessment time.

The ascending delivery profile makes OROS-MPH well-suited for patients with greater impairment in the afternoon, but less so for patients most impaired in the morning. In cases where additional symptom control is needed, clinicians have several options, including increasing the overall dose (if tolerated), administering the medication earlier, or supplementing the OROS-MPH with IR-MPH.

Generic MPH Hydrochloride Extended Release

A "generic equivalent" of OROS-MPH (Novo-Methylphenidate ER-C®, Novopharm Limited), designed deliberately to mimic OROS-MPH both in dose and in appearance, was recently approved by Health Canada (Novo-Methylphenidate ER-C, 2009). This means that a prescription for Concerta could be substituted for generic without the patient or prescriber being aware of the change.

Information regarding this formulation is extremely limited. It does not use the OROS delivery system (CADDRA, 2008). Although not specifically designed for this (Novo-Methylphenidate ER-C, 2009), the formulation (unlike that of OROS-MPH) allows tablets to be divided, crushed, and powdered (CADDRA, 2008). Whether this may influence abuse potential of this formulation is not known.

Per current standards regarding the development and approval of generics, comparative bioavailability

studies involving small numbers of healthy adults were performed to compare the new formulation with OROS-MPH. Drug exposure (C_{max} and AUC) of the generic formulation had a T_{max} approximately 3-4 hours earlier than OROS-MPH (Novo-Methylphenidate ER-C, 2009; CADDRA, 2010). This relatively early T_{max} is more consistent with that observed following multilayer-release (MLR-)MPH versus OROS-MPH administration.

There are no published studies evaluating the efficacy of this formulation. Therefore, its clinical properties remain largely unknown. Changing the delivery system of a drug can also change its pharmacological properties. Thus, as highlighted by CADDRA, "Bioequivalence does not mean clinical efficacy equivalence" (CADDRA, 2010). Although this formulation was designed to "match" OROS-MPH, the absence of a published mechanism of drug release, onset, duration of action, or efficacy data makes any labeling of this formulation as equivalent to OROS-MPH largely clinically irrelevant. Given the many unanswered questions, Canadian organizations have expressed concerns regarding the potential risks that may be associated with automatic pharmacy substitution of OROS-MPH with this generic form (Centre for ADHD/ADD Advocacy Canada, 2010; CADDRA, 2010).

MLR-MPH

Beaded formulations consisting of both immediate- and delayed-release medication are commonly used to prolong the duration of effect of stimulant formulations. In Canada, MLR-MPH (Biphentin®, Purdue Pharma) (Biphentin Product Monograph, 2009) is the only long-acting beaded formulation of MPH available for ADHD. Unlike other beaded formulations that contain distinct IR and delayed-release beads, each bead in an MLR-MPH capsule contains a composite of IR and delayed-release components. This composition allows for the fractionation of doses, if needed based on clinical judgment. The formulation is designed to provide an initial release (40% of total MPH), followed by a delayed, prolonged phase of release (60% of total MPH) (Schachar et al., 2008; Quinn et al., 2007). As a beaded formulation, the capsules should not be crushed or chewed but may be sprinkled on food for patients who have difficulty swallowing capsules (Biphentin Product

Monograph, 2009). Whether MLR-MPH absorption is dependent on gastric acidity is unknown.

A randomized, 2-way crossover study evaluated the comparative single-dose pharmacokinetics of MLR-MPH (20-mg) and OROS-MPH (18-mg) in healthy young adults (Reiz et al., 2008). This study found a higher proportion of the administered dose of MPH was delivered in the first 4 hours with MLR-MPH versus OROS-MPH. Conversely, when comparing equivalent doses of OROS-MPH and MLR-MPH, investigators found that less MPH is delivered later in the day (ie, 8-12 hours postdose) with MLR-MPH. Thus, supplemental IR-MPH may be required to extend effects at the end of the day.

In a double-blind, controlled trial, stabilized once-daily doses of MLR-MPH resulted in significant improvements (vs baseline) through 12 hours postdose as assessed by parental ratings (Weiss et al., 2007). Once-daily MLR-MPH was similar in clinical effect and time course to twice daily IR-MPH. Cognitive and behavioral measures have demonstrated that the onset of effect of MLR-MPH is comparable to that observed for IR-MPH (ie, as early as 1 hour postdose) (Schachar et al., 2008). Although OROS-MPH was initially developed to "match" the delivery profile of IR-MPH administered 3 times daily, subsequent long-acting drugs such as MLR-MPH were developed with a focus on duration of action, rather than exactly matching a pharmacokinetic profile per se. Clinical experience has shown that some patients receiving MLR-MPH will require supplemental doses of IR-MPH (CADDRA, 2008) since duration of action may be 8-10 hours. The characteristics of MLR-MPH make it particularly suited for patients requiring even release of drug during the day or relatively more effect early in the day, those unable to swallow pills, those requiring higher doses of medication (in a single pill), and those who would benefit from the fine incremental dose titration possible with 8 available dosages.

Amphetamine-Based Stimulants

A summary of the long-acting amphetamine formulations available in Canada is presented in **Table 1**. Amphetamine has 1 chiral center and can exist as levoamphetamine (l-amphetamine) and dextroamphetamine (d-amphetamine) enantiomers

(Wilens et al., 2000). Amphetamine may have presynaptic effects on both dopamine and norepinephrine, influencing aspects of neurotransmitter release, storage, and uptake (Wilens, 2006; Arnold, 2000; Wilens et al., 2000). In this way, amphetamine differs from MPH, which blocks reuptake of dopamine and norepinephrine but does not promote release.

d-Amphetamine-SR

An extended-release formulation of d-amphetamine, d-amphetamine-SR (Dexedrine® Spansules®, Paladin Labs Inc.), contains IR and delayed-release beads in a 1:1 ratio (Prince, 2006). In small trials, this formulation demonstrated efficacy up to 12 hours postdose as assessed by the Conners' Parent Rating Scale (James et al., 2001) and 9 hours postdose on continuous performance tasks (Pelham et al., 1990). Although efficacy versus placebo has been demonstrated at 1 hour postdose, d-amphetamine-SR appears substantially less effective than the IR formulation in early morning assessments (James et al., 2001).

In the authors' clinical experience, the duration of action of d-amphetamine-SR is frequently shorter than 12 hours. Additionally, no published trials are available that assess duration of effect in a standardized laboratory classroom study, the gold standard measure for duration. The authors have found that d-amphetamine-SR generally requires twice-daily dosing to provide symptom reduction into the evening. Such findings are consistent with recommendations by CADDRA, which considers the medication an intermediate-acting, second-line/adjunctive agent that may last for 6-8 hours (CADDRA, 2008).

Mixed Amphetamine Salts Extended Release

The extended-release formulation of mixed amphetamine salts (MAS-XR; Adderall XR®, Shire Canada Inc.) is intended to mimic the effect of 2 doses of the IR-MAS (not available in Canada) dosed at 4- to 6-hour intervals (Biederman et al., 2002; Weisler et al., 2006). Each capsule contains IR and delayed-release MAS beads in a 1:1 ratio (Biederman et al., 2002; Weisler et al., 2006). MAS beads are composed of d- and l-amphetamine in a 3:1 ratio and contain equal parts d-amphetamine sulfate, d-amphetamine saccharate,

d,l-amphetamine aspartate monohydrate, and d,l-amphetamine sulfate (McCracken et al., 2003).

MAS-XR capsules can be opened and the beads sprinkled on food (ie, applesauce) but they should not be chewed or crushed (Adderall XR Product Monograph, 2009). The medication can be administered with or without food, and although administration with food does not impact the extent of absorption, it does prolong T_{max} by approximately 2.5 hours, which is consistent with the impact of food on gastric emptying (Tulloch et al., 2002). The release of amphetamine from MAS-XR delayed-release beads is dependent on gastric pH (Sallee et al., 2004). Coadministration of MAS-XR with proton pump inhibitors appears capable of influencing the release of amphetamine and should be avoided (Haffey et al., 2009; Adderall XR Product Monograph, 2009).

Among children with ADHD, MAS-XR has demonstrated a 12-hour duration in numerous trials. In an analog classroom setting, MAS-XR was associated with sustained improvements through 12 hours postdose on a majority of SKAMP and PERMP variables (vs placebo) (McCracken et al., 2003). Similar results have been reproduced in subsequent trials (Wigal et al., 2005; Biederman et al., 2007). In 2 studies, parental ratings of global improvement have demonstrated efficacy of MAS-XR into the late afternoon (the last time point assessed) (Biederman et al., 2002) and 12 hours postdose (Ambrosini et al., 2006). McCracken et al (2003) demonstrated that following administration of MAS-XR 20 or 30-mg, onset of effect is generally within 1.5 hours.

Lisdexamfetamine Dimesylate

The long-acting stimulants described above rely on mechanical strategies for extended delivery of active agent. Lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire Canada Inc.) is unique because it relies on prodrug technology to provide an extended duration of effect and is not intended to mimic multiple daily dosing. LDX is a therapeutically inactive molecule. Following oral ingestion, LDX is converted to l-lysine and d-amphetamine, the active molecule responsible for the drug's therapeutic effect. Hydrolysis of LDX into active d-amphetamine primarily occurs in the blood (Pennick, 2010). A recent comparison of pharmacokinetic

variability of long-acting stimulants suggests that the unique prodrug formulation of LDX may contribute to improved consistency in interindividual pharmacokinetic parameters (Ermer et al., 2010).

In Canada, LDX is currently indicated for the treatment of ADHD in children (aged 6 to 12 years), adolescents (aged 13 to 17 years), and adults (Vyvanse Product Monograph, 2010). Clinical trials in adolescents (Findling et al., 2011) and adults (Adler et al., 2008) have demonstrated similar efficacy and safety to that seen in children. New CADDRA recommendations include LDX dosing information for children, adolescents, and adults (CADDRA, 2010). When switching from another stimulant to LDX, doses should be titrated to optimal from a reasonable baseline (ie, equivalence with other stimulant formulations cannot be assumed). LDX capsules may be opened and the contents dissolved in water. This may allow for dose fractionation in special circumstances based on clinician's judgment. As LDX delivery is not mechanical, release of the active ingredient does not rely on gastrointestinal factors such as transit time or gastric pH (Haffey et al., 2009; Shojaei et al., 2007; Krishnan et al., 2008; Mattingly, 2010).

The duration of effect of LDX in children with ADHD has been evaluated in 2 laboratory school studies. In the first study, a double-blind, placebo-controlled crossover trial involving 52 children with ADHD, treatment with LDX was associated with significant improvements (vs placebo) in mean SKAMP and PERMP scores from 2-12 hours postdose (Biederman et al., 2007). The second study was conducted to further characterize the time course of effect of LDX treatment and demonstrated that LDX was associated with significant improvements over placebo in SKAMP and PERMP scores from 1.5-13 hours postdose (Wigal et al., 2009).

Safety of Stimulants

Short- and long-acting stimulants, either MPH- or amphetamine-based, generally share the same common side effects, which often result in some discomfort and, for individual patients, may lead to discontinuation (CADDRA, 2008). Common somatic side effects include anorexia, abdominal pain, headache, insomnia, and weight loss/decreased appetite (Greydanus et al., 2009). Generally, decreased appetite, insomnia, headache, and upper abdominal pain occurred with the

highest incidence (≥10%) for approved long-acting stimulants while weight loss is typically lower (<10%)(Ritalin SR Product Monograph, 2007; Concerta Product Monograph, 2010; Biphentin Product Monograph, 2009; Adderall XR Product Monograph, 2009; Weiss et al., 2009). Stimulants may also exacerbate tic disorders in individual patients, although this has not been evident in statistical studies (Gadow et al., 1995; Greydanus et al., 2009). Psychiatric side effects of stimulants may include being "too quiet or [exhibiting] a loss of sparkle," dysphoria, irritability, worsening of behavior distinct from baseline ADHD symptoms upon drug withdrawal (rebound), insomnia, and delayed sleep onset (Wigal, 2009; Carlson et al., 2003; Greenhill et al., 2002; Greydanus et al., 2009).

In the authors' experience, most side effects decrease over the first few weeks. Patients and parents should be made aware of this and of strategies that may ameliorate potential side effects. While not empirically tested, the following have proven useful in the authors' clinical practice and are also included in CADDRA guidelines (2008). Deficient food intake due to decreased appetite can be improved by increasing intake during times when medication effects are minimal, in the morning before dosing (eg, a substantial breakfast) and in the evening when the medication has worn off (eg, a substantial dinner and/or an equally substantial late snack) to maintain 24-hour calorie intake. As needed, high calorie, balanced nutritional supplements may be considered, especially to supplement calorie intake during school hours. Adverse effects on sleep can be managed by giving daily medication as early as possible and encouraging good sleep hygiene (eg, regular bedtime routine, environment conducive to sleep, quiet time before bed). If these prove inadequate, mild sleep-aids such as melatonin supplements can be considered (see [Weiss et al., 2010b] for more detailed discussion). Long-acting stimulants generally produce less rebound than short-acting formulations. However, if necessary, small supplemental dosages of short-acting formulations during medication wear-off may be helpful. Less common effects (ie, dysphoria or tics) may improve with a decrease in dose or a change in the type of medication.

Stimulants tend to increase blood pressure and/or pulse (see all cited drug monographs); they should not be used

in patients with symptomatic cardiac disease without cardiac consultation, uncontrolled hypertension, advanced arteriosclerosis, or hyperthyroidism (CADDRA, 2008; Health Canada, 2010). The incidence of sudden death between ADHD populations and the general population are similar. However, CADDRA guidelines recommend that "the small (but unproven) potential contribution of ADHD drugs to the rare incidence of sudden death in children and adolescents must be weighed against the clinical benefit of the medication"(CADDRA, 2008). Prior to beginning therapy with stimulants, the authors suggest that patients be screened for chest pain, dyspnea on exertion, fainting, or family history of early cardiac death and, if positive, an electrocardiogram should be performed. Stimulants have also been shown to affect growth, resulting in reductions in expected height and weight in a dose-related manner (Faraone et al., 2008). Such reductions do not appear to differ by stimulant type (ie, amphetamine or MPH). Swanson et al (2007) demonstrated that patients taking stimulants continuously are at greater risk for reduction in growth rates than those taking stimulants intermittently. In this analysis of the Multimodal Treatment of ADHD (MTA) study, Swanson and colleagues estimated that at 36 months of treatment, medicated children with ADHD were approximately 4.2 cm shorter and 3.5 kg lighter than nonmedicated children with ADHD (Swanson et al., 2007). A recent follow-up MTA analysis of long-term growth effects in subjects up to 20 years old using stimulants continuously, suggests final height attainment is decreased by approximately 1.9 cm (Wigal et al., 2010). Overall, given these concerns, assessment of height, weight, body mass index, and vital signs should occur at every follow-up visit.

Nonstimulants

The only nonstimulant medication currently approved in Canada for ADHD is atomoxetine (Strattera®, Eli Lilly Canada Inc.). A summary of atomoxetine is presented in **Table 1**. The capsule must be swallowed and cannot be crushed or sprinkled (Strattera Product Monograph, 2009). Patients are titrated every 7 to 14 days up to a maximum dose of 1.4-mg/kg/d or 100-mg/d whichever is less. Atomoxetine is believed to exert therapeutic effects by inhibiting presynaptic

norepinephrine reuptake (Connor et al., 2004; Strattera Product Monograph, 2009; Kelsey et al., 2004). Atomoxetine can be taken with or without food. As per CADDRA guidelines, atomoxetine is a first-line therapy for the treatment of ADHD across all age groups (CADDRA, 2008). Although generally regarded as less effective for ADHD symptoms than stimulants, atomoxetine is a practical option for patients who do not respond optimally to or do not tolerate stimulants, have medical contraindications to stimulants (eg, severe insomnia), are at risk of stimulant abuse, or have certain comorbid disorders that may be exacerbated by stimulants (eg, tics, anxiety) (Olfson, 2004; Pliszka et al., 2006; Daughton et al., 2009). Atomoxetine is used off-label in combination with stimulants (Adler et al., 2006), especially in patients with primary impairment in the late evening.

Taken once daily, atomoxetine improved ADHD symptoms into the evening and, by some measures, up to 24 hours (ie, before the next morning's dose) (Kelsey et al., 2004). It should be noted that this study used higher maximal doses (up to 1.8-mg/kg/d or 120-mg/d) than currently recommended (**Table 2**). Atomoxetine was slightly more effective when given in the morning versus in the evening (Block et al., 2009) or in split-dosing regimens (Akinnusi et al., 2010). However, evening or split dosing regimens may be useful at the beginning of treatment to minimize stomach upset and dizziness, and to promote sleep (Block et al., 2009). Unlike the effects observed with stimulant therapy, the clinical benefits of atomoxetine may take 1 month to become apparent, and optimal effect may not be obtained for several months (Newcorn et al., 2009; Weiss et al., 2009).

Common side effects associated with atomoxetine include decreased appetite, dizziness, dyspepsia, fatigue and/or lethargy, irritability, nausea, somnolence, and vomiting (Strattera Product Monograph, 2009). As with long-acting stimulants, common side effects of atomoxetine may decrease over time. Good clinical practice recommendations such as the one mentioned earlier to address decreased appetite, taking medication with food to minimize dyspepsia, nausea and vomiting (Daughton et al., 2009), and evening or split dosing (morning and evening) to minimize the impact of fatigue, lethargy, and somnolence maybe helpful. In the authors' experience, some patients receiving

atomoxetine exhibit marked psychiatric reactions including changes in personality. Parents should be told to discontinue therapy immediately and contact their physician if such changes are noted. Among adolescents and adults, the tolerability profile may be somewhat different and includes a variety of sexual side effects (Strattera Product Monograph, 2009).

Abuse Liability

Patients with ADHD are at increased risk versus the general population of developing substance use disorders (Wolraich et al., 2005; Spencer et al., 2007; Biederman et al., 2006). Most evidence suggests that appropriate treatment of ADHD with stimulants does not increase the risk for subsequent substance use disorders in adulthood (Biederman et al., 2008; Wilens et al., 2003; Wilens et al., 2008a). Although the precise role of stimulant therapy in reducing the risk of substance abuse into adolescence is unclear, clinicians can offer reassurance that appropriate stimulant medication use is not considered a risk factor for later substance dependence or abuse, while ADHD is (Wilens et al., 2008a; Wilens et al., 2003; Biederman et al., 1999). The use of stimulants, however, is associated with concerns regarding misuse and diversion. A review by Wilens et al (2008b) presented consistent evidence of stimulant misuse by adolescents and young adults with or without ADHD. In addition to recreational use, students report stimulant misuse to extend study time and improve academic performance (Wilens et al., 2008b; Tuttle et al., 2010). Since each year >50% of college students prescribed stimulants are asked to divert their medications (McCabe et al., 2006), educating patients on dangers associated with giving medication to others is important.

Long-acting formulations may confer a lower risk of abuse, misuse, and diversion compared with short-acting formulations as nonmedical use appears more common with short-acting formulations (Bright, 2008; Wilens et al., 2008b; Wilens et al., 2006). The connection between formulation and the risk of abuse, misuse, and diversion has not been fully elucidated. Also, the relationship of such behaviors with increasing clinical reliance on long-acting versus short-acting formulations has not been studied. The speed at which short-acting medications reach C_{max} and are then cleared from

the brain may contribute to the abuse potential of these formulations because both rapid rise and fall in concentration have been linked to abuse liability (Farré et al., 1991; Schuster, 2006; Volkow et al., 2003).

Clinical studies in populations using or abusing drugs appear to support a relationship between the stimulant's pharmacokinetics and its abuse potential. Among adults with a history of recreational stimulant use, single oral doses of IR-MPH (60-mg) were associated with higher subjective drug effects than single doses of OROS-MPH (108-mg) (Parasrampuria et al., 2007). Both formulations were associated with greater effects and liking scores than placebo. Administered orally, 50- and 100-mg of LDX were associated with significantly reduced abuse-related liking effects compared with 40-mg doses of IR d-amphetamine (equivalent amphetamine base content to LDX 100-mg) (Jasinski et al., 2009). At higher doses of LDX (ie, 150-mg), abuse-related liking scores were similar to those observed with 40-mg of IR d-amphetamine. Intranasal administration of LDX is unlikely to confer any greater abuse liability than oral administration as both routes are associated with a similar rates and extent of d-amphetamine exposure (Ermer et al, 2011). Comparative trials of the abuse liability of long-acting stimulants are needed to enable direct comparisons. The concept has been promoted that long-acting stimulants cannot be abused; this is not true. Such a view fails to account for the possibility of extracting the stimulant or combining it with other drugs of abuse. As anticipated, studies of atomoxetine suggest that it is unlikely to be abused. Among current stimulant abusers, doses of atomoxetine of up to 180-mg were not associated with significantly greater liking scores versus either placebo or desipramine (Jasinski et al., 2008).

Efficacy Measures

With the exception of the new generic "equivalent" of OROS-MPH, the approved long-acting treatments for ADHD have demonstrated efficacy in improving ADHD symptoms as assessed by behavior ratings. New research has attempted to evaluate the impact of treatment on additional measures, including functional outcomes, QoL, emotional expression, and executive function. This represents a shift from looking at short-term, protocol-driven efficacy outcomes, to

naturalistic measures that go beyond core symptoms and assess effectiveness based on overall well-being. What follows is by no means a comprehensive review of the efficacy profiles of the long-acting ADHD treatments; instead, it is intended to introduce some newer measures that are being used to evaluate efficacy. Understanding the effects of treatment using a broad range of measures may help identify subtle differences among available pharmacotherapies and help individualize treatment recommendations to meet patients' needs.

Driving Performance

ADHD has been associated with increased risk of traffic accidents and violations. Treatment with OROS-MPH or MAS-XR resulted in significant improvements in driving performance (Cox et al., 2006; Cox et al., 2008; Kay et al., 2009). In a study comparing the effects on driving of OROS-MPH with IR-MPH administered 3 times daily, OROS-MPH was superior to IR-MPH in the late evening and into the night (Cox et al., 2004). In a pilot study by Barkley et al, improvement in subjective self-ratings were noted for atomoxetine versus placebo but no objective improvement in driving performance or ratings were seen (Barkley et al., 2007). In small study by Kay and colleagues (2009), no benefits were observed following 3 weeks of treatment with atomoxetine. Clinicians should assess whether patients are being effectively treated during the parts of the day they are most likely to drive. This is particularly important since the effects of rebound on driving are unclear for patients in whom driving is impaired even while medicated. Additionally, for such patients whose driving may put themselves or others at risk based on their physician's judgment, notification of appropriate licensing authority by physicians is required in Canada.

Satisfaction

Beyond benefits conferred by convenience, Stein (2004) suggested that long-acting treatments may offer other, yet unidentified, advantages that result in greater patient/parent satisfaction than multiple daily dosing of IR stimulants. Even among long-acting formulations, there appear to be differences in levels of parental satisfaction. Data from a large survey of parents of children with ADHD being treated with LDX suggest high levels of parental satisfaction associated with LDX, including

among those participants whose children were treated with a prior long-acting amphetamine (MAS-XR) although the reasons for the change in pharmacotherapy were not discussed (Antonucci et al., 2010).

QoL

With increased recognition that ADHD affects varied aspects of a patient's life and the development of validated instruments to assess generic and ADHD-specific QoL, researchers have begun to examine the impact of treatment on QoL. Studies have also investigated the relationship between QoL and rater-reported symptoms. Klassen et al (2004) did not find an association between teacher-rated ADHD symptoms and parent-rated QoL. Weiss et al (2010a) reported that improvement in QoL with MAS-XR occurred simultaneously with improvement in symptom severity among adults, a finding that was also noted in the ADHD Observational Research in Europe (ADORE) study among children (D. Coghill, personal communication). Self-ratings of QoL may not correlate with parent-ratings because children with ADHD tend not to identify QoL impairments, perhaps because of positive illusory bias (Danckaerts et al., 2010). Another factor complicating evaluation of QoL is the considerable overlap between symptoms of ADHD and items on individual QoL rating scales, suggesting a need for better demarcation between ADHD symptomatology, functional impairment, and QoL.

As noted in a review by Danckaerts et al (2010), a dearth of information exists exploring the impact stimulant formulations have on QoL. In a laboratory school study, MAS-XR treatment was associated with improvements in health-related QoL (Wigal et al., 2005). In a prospective analysis of a community population of children and adolescents treated with stimulants or atomoxetine, similar levels of improvement in QoL were observed in both groups (Bastiaens, 2008). The effect of atomoxetine treatment on QoL has generally been associated with substantial improvements in psychosocial ratings of QoL (Danckaerts et al., 2010; Perwien et al., 2006). As highlighted by Danckaerts and colleagues (2010), no published study has examined the effects of psychosocial treatments using QOL measures in patients with ADHD.

Emotional Expression/Regulation

In addition to core symptoms of inattention and hyperactivity/impulsivity, disturbances in emotional regulation are thought to be a key manifestation of ADHD. Although differing theories exist regarding the interplay between executive function and behavioral inhibition (Barkley, 1997; Brown, 2006), it is clear that patients with ADHD can exhibit signs of emotional dysregulation, including temper outbursts, rages, mood lability, and dysphoria (American Psychiatric Association, 2000). Data from the US National Health Information Survey show that 23% of children with ADHD exhibit high levels of "emotional problems" (Strine et al., 2006).

In addition to emotional dysregulation associated with ADHD, it has been suggested that stimulants themselves can blunt or restrict emotional expression, causing children to become "zombie-like" (Greenhill et al., 2002; Kratochvil et al., 2007). In the authors' experience, children may be described as less "silly," "playful," or "talkative." Several studies have characterized the effect of ADHD treatments on emotional expression using the Expression and Emotion Scale for Children (EESC). In an open-label trial involving more than 300 children with ADHD, LDX was not associated with overall worsening of emotional expression as measured by EESC scores (Findling et al., 2009). In fact, small, but statistically significant improvements in the overall and subscale scores of the EESC were observed. The EESC was also used in a randomized, double-blind, placebo-controlled study of atomoxetine in which atomoxetine treatment did not negatively affect emotional expression in children as evidenced by small, but significant, improvements (vs baseline) in EESC scores while analysis of categorical change (worsening) did not differ between atomoxetine and placebo groups (Kratochvil et al., 2007). However, the clinical relevance of such statistical improvements is unclear and while reassuring that "blunting" is unusual in optimally dosed populations, they do not rule out that individual patients may exhibit such an adverse effect.

Executive Function

ADHD is associated with developmental impairment of executive functions (Brown, 2008), a heterogeneous group of cognitive functions broadly defined by Willcutt et al as "cognitive inputs facilitating decision making by maintaining information about possible choices in working memory and integrating this knowledge with information about the current context to identify the optimal action for the situation" (Willcutt et al., 2005). Recent studies have examined the impact of treatment on executive function. In an open-label trial of LDX, treatment was associated with improvements in the overall and index scores of the Behavior Rating Inventory of Executive Function (BRIEF), a validated parent-rated measure of executive function (Findling et al., 2009). LDX treatment resulted in mean T scores below 65, the cutoff commonly associated with potential clinical significance. In a 1-year open-label study, atomoxetine treatment led to improvements in BRIEF scores (Dickson et al., 2007). Among children with ADHD and a partial response to atomoxetine, the addition of OROS-MPH was associated with improvements in 8 of 9 BRIEF subscales (except for emotional control) and reductions to scores below 60 for all subscales (Wilens et al., 2009). Although the BRIEF is a reliable and validated instrument (Gioia et al., 2000), it is a behavioral parent-report measure that overlaps considerably with diagnostic criteria for ADHD; it correlates only modestly with neuropsychological measures and is not a substitute for such testing (Toplak et al., 2009).

Short-Acting Stimulants

Although the majority of this paper has discussed long-acting pharmacotherapies for ADHD, clinicians are reminded that there remain clinical settings where the use of short-acting agents may be appropriate. Some patients may desire to target therapy to specific times of day, for example a student who desires to be medicated for specific classes or activities (eg, tutoring, driving) (CADDRA, 2008). Short-acting agents can also be used to extend the duration of effect beyond that of long-acting formulations, to induce an earlier onset of action, or to cover periods in which medication coverage does not meet situational demands. For example, some patients report a midday "dip" in efficacy when using MLR-MPH. As patients (and parents) become increasingly aware of associations between certain time-of-day-related tasks and greater impairment (eg, exams, early morning routine, homework), short-acting medication can be employed to augment long-acting medication (Daughton et al., 2009). Short-acting agents

may be appropriate for the initiation of therapy in children weighing less than 16 kg or those particularly vulnerable to side effects (Pliszka et al., 2006). Although no pharmacotherapies are approved for children younger than 6 years, if clinical need and judgment dictate, it is helpful to start these children with "microdoses" (eg, 2.5-mg of MPH IR/d) of medication and titrate slowly based on clinical effect and tolerability. Such regimens may be easier with short-acting medications. Finally, cost becomes a concern for uninsured patients/parents whose income cannot support the cost of newer, extended-release medications. In Canada, provincial coverage for long-acting medications varies greatly and to our knowledge, no province has provided coverage for long-acting medications as a group.

Adults

Although ADHD symptoms can vary with age and environment (ie, the challenges at work are distinct from those in school), they can interfere with the functioning of adults at home and at work. In many cases, adults face a longer (18 hours) and arguably more demanding day, in relation to executive functions and cognitive tasks (Adler et al., 2002). Safe and effective treatments with long durations of effect are a key need for this population. The "gold standard" for assessing duration of effect, the laboratory classroom setting, has been adapted for use in adults as the simulated adult workplace environment (AWE) (Wigal et al., 2006). As yet, only one study has been published using the AWE in adults with ADHD: LDX demonstrated efficacy vs placebo from 2 to 14 hours after dosing as measured by PERMP math tests (Wigal et al., 2010). CADDRA recommendations advise use of a long-acting stimulant or atomoxetine as first-line pharmacotherapy for adults with ADHD (CADDRA, 2008). A summary of the CADDRA recommendations for ADHD treatment is presented in **Table 2.** In practice, patients requiring more than 12 to 14 hours of coverage can often be managed with one of 2 strategies: augmentation of long-acting medication with short-acting agents or "overlapping" the coverage of long-acting stimulants (eg, administration of an extended-release stimulant twice during the day).

Comparing Long-Acting Medications

Current CADDRA guidelines do not support the use of One long-acting therapy over another (CADDRA, 2008). Instead, optimization of treatment regimens requires that therapy be individualized to specific patient needs. While most patients are successfully treated with "recommended" doses of medication, others may require higher or lower dosages (Powell et al., 2010). For long-acting stimulant formulations, duration of action reported in the product monographs is established in controlled trials in comparison with the placebo condition. However, in the typical clinical setting, physicians, parents, and patients evaluate responses to treatment in comparison with the patient's untreated state or baseline, which may be more clinically relevant. Therefore, regarding these comparisons, the reported duration of action may not correspond with what is experienced by individual patients. Clinical experience on the part of the physician and individual patient may be a much better assessment of duration of action. To address this potential disparity, the authors have included consensus estimates of duration of action based on their clinical experience with the available long-acting formulations (**Table 1**). Also, individual patients may exhibit differential response to MPH, amphetamine, or atomoxetine (Newcorn et al., 2008; Arnold, 2000). Patients may, furthermore, respond variably to different release mechanisms, pharmacokinetic profiles, and psychosocial interventions. Arnold (2000) demonstrated that most patients will respond to both MPH and amphetamine. However, ~25% will respond preferentially to amphetamine, whereas ~20% will respond preferentially to MPH; less than 13% will respond to neither stimulant. Newcorn et al (2008) found that among patients not responding to OROS-MPH, about 40% responded to atomoxetine. Similarly, ~40% of patients not responding to atomoxetine responded to OROS-MPH. Patients who respond inadequately to 1 medication should be tried on another, with choices dependent on reasons underlying lack of response. Direct comparisons among long-acting therapies are generally lacking and those that have been conducted, frequently have methodological limitations that impede interpretation and generalizability

Table 2. CADDRA Recommendations for the Treatment of Uncomplicated ADHD[a,b]

	Maximum Daily Dose[c]		
	Children	**Adolescents**	**Adults**
First-Line Agents			
MAS-XR	30-mg	50-mg	50-mg
MLR-MPH	60-mg	80-mg	80-mg
OROS-MPH	72-mg	81-mg	108-mg
Atomoxetine	Lesser of 1.4 mg/kg or 100-mg	Lesser of 1.4 mg/kg or 100-mg	Lesser of 1.4 mg/kg or 100-mg
LDX[d]	70-mg	70-mg	70-mg
Second-Line or Adjunctive Agents			
d-Amphetamine	30-mg	30-mg	50-mg
d-Amphetamine-SR	30-mg	30-mg	50-mg
IR-MPH	60-mg	60-mg	100-mg
MPH-SR	60-mg	80-mg	100-mg

ADHD	attention-deficit hyperactivity disorder
CADDRA	Canadian ADHD Resource Alliance
IR	immediate-release
LDX	lisdexamfetamine dimesylate
MAS-XR	extended-release mixed amphetamine salts
MLR	multilayer-release
MPH	methylphenidate
OROS	osmotic-release oral system
SR	sustained-release.

[a] (CADDRA, 2008; CADDRA, 2010)

[b] The role of the generic MPH ER (ie, Novo-Methylphenidate ER-C) in clinical practice remains unclear.

[c] In several instances, CADDRA guidelines include a maximum dose, which is greater than the maximum approved dose per product monograph.

[d] Does not appear in 2008 CADDRA guidelines. Dosing recommendations obtained from http://www.caddra.ca/cms4/pdfs/medication%20chart%202010.pdf.

(eg, inadequate duration, restrictive inclusion/exclusion criteria).

In the absence of head-to-head trials, meta-analyses have examined differences among formulations. In a meta-analysis examining 23 trials, amphetamine-based stimulants demonstrated moderately greater effect sizes than did MPH-based stimulants (Faraone et al., 2009). Both short- and long-acting stimulants were associated with greater effect sizes than were nonstimulants (including atomoxetine, bupropion, and modafinil) (Faraone et al., 2006). Also, no class differences were observed between the long- and short-acting stimulants. Such analyses, however, do not consider the incidence, severity, or nature of AEs or that stimulants appeared to have variable safety/tolerability profiles (Arnold, 2000). Although efficacy differences have not generally been observed in controlled, protocol-driven settings, data from an effectiveness trial that attempted to mimic "everyday practice" with fewer restrictions on treatment delivery and monitoring of adherence suggest that long-acting formulations may offer an advantage (Steele et al., 2006). While the effect sizes of stimulants

are consistently more robust than nonstimulants on core symptoms of ADHD, the authors' experience is that their dramatic onset and offset of action may actually lead some patients, particularly adolescents, to report that it makes them "feel like 2 people." Whether this contributes to low rates of persistence observed with stimulant therapy is unclear (Bussing et al., 2005; Miller et al., 2004).

Summary

This paper provides the Canadian clinician with a review of long-acting pharmacotherapies for ADHD. For most patients with ADHD, long-acting medications should be considered first-line therapy. Differences in drug delivery systems employed in extended-delivery formulations can impact effectiveness and such differences may be exploited to tailor a treatment regimen to the needs of individual patients. Differences include variations in the pharmacokinetic profile of the active ingredient over the course of the day, the ability to split, dissolve, or sprinkle medications, and potential variations in abuse liability. Although long-acting preparations are intended for once daily administration and providing "all-day" coverage, in clinical practice this may not be sufficient for some patients (eg, their active days extend beyond the effective duration of all long-acting preparations). The emergence of long-acting medications has superseded the use of short-acting medications wherever possible, but has not eliminated their usefulness.

Further research is needed to clarify definitions of treatment response and to explore the impact of ADHD treatments on a wider spectrum of outcomes, including psychiatric side effects, functioning, adaptive skills, QoL, and long-term development. These are overlapping, but distinct outcomes that can provide a greater understanding of patients' overall treatment experience. Ultimately, it is vital to remember that clinicians treat individuals and that no medication "fits all." Recent research on long-acting medications has provided new and better treatment options-in some cases, enabling treatment of patients who could not be successfully manage in the past.

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