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Attention-Deficit Hyperactivity Disorder
Recent Advances in Paediatric Pharmacotherapy

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Abstract

Throughout this decade, there has been significant research into pharmacotherapies for attention-deficit hyperactivity disorder (ADHD). This article considers the efficacy and safety of five of the more novel long-acting pharmacological treatments recently approved by the FDA for marketing in the US for paediatric ADHD, along with an α_2-adrenoceptor agonist in preparation. Reviewed treatments include the non-stimulant atomoxetine, three novel extended-release (XR) stimulant preparations: dexmethylphenidate,

lisdexamfetamine dimesylate and the methylphenidate transdermal system (TDS), and the recently approved XR α_2-adrenoceptor agonist, guanfacine.

Dexmethylphenidate XR is a stimulant treatment in a single isomer form, and has an efficacy and tolerability similar to two doses of immediate-release (IR) dexmethylphenidate when taken 4 hours apart, but is dosed at half of the usual *d,l*-methylphenidate dose. Dexmethylphenidate XR utilizes a beaded bimodal release, with 50% initially released and another 50% released 4 hours later to provide benefit lasting up to 10–12 hours.

Lisdexamfetamine was the first stimulant treatment approved as a prodrug, whereby the single isomer *d*-amfetamine remains pharmacologically inactive until activated by cleaving the lysine. Its efficacy and tolerability are generally consistent with that of XR mixed amfetamine salts, with this activation method and more consistent absorption generally resulting in up to an 11- to 13-hour benefit.

The methylphenidate TDS patch utilizes skin absorption to provide predictable and uniform delivery of methylphenidate when worn for 9 hours/day. The efficacy and tolerability of the methylphenidate TDS patch is generally consistent with that of osmotic-controlled release oral system (OROS®) methylphenidate, providing benefit for about 11–12 hours. Because of their formulation, lisdexamfetamine and methylphenidate each have an onset of effect at about 2 hours after administration. An adjustable wear time for the methylphenidate TDS patch accommodates related adverse effects, but its disadvantages are frequent skin irritation and the need to remember to take the patch off.

Atomoxetine is the first non-stimulant treatment approved by the FDA and employs weight-based dosing up to 1.4 mg/kg/day. Benefit is generally observed within 2–8 weeks of initiation and is considered to have a lesser therapeutic effect than that of stimulants. A recent parallel-group controlled study found that atomoxetine (up to 1.8 mg/kg/day) and OROS® methylphenidate both improved ADHD symptoms, although subjects receiving OROS® methylphenidate had a significantly better response. Interestingly, treatment-naive children had a similar beneficial response to atomoxetine as those receiving OROS® methylphenidate. Subsequent crossover treatment revealed a subgroup of youths who did not respond well to OROS® methylphenidate but did respond to atomoxetine. Also identified was a larger than expected subgroup who did not respond well to either active treatment, confirming the need to continue the pursuit of novel treatments.

As of September of 2009, guanfacine in XR form is the first α_2-adrenoceptor agonist to gain approval to treat ADHD, approved for the treatment of 6- to 17-year olds. A second α_2-adrenoceptor agonist, clonidine, is in development as a potential XR treatment for paediatric ADHD. IR clonidine has a fast onset and short half-life, with its use historically limited by somnolence. Although early formulations did not improve inattention well, recent evidence suggests that clonidine XR may have potential use as monotherapy or in extending benefit when taken with a stimulant. Guanfacine has a more specific neuronal action and a longer action than that of clonidine. The approved dosing of guanfacine XR 1 to 4 mg daily generally provides symptom benefit lasting 8–14 hours, and up to 24 hours in some children and adolescents receiving a higher dose.

Such recent developments and ongoing study of additional potential pharmacological interventions may lead to additional future treatment options for children with ADHD.

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous syndrome of persistent, inappropriate levels of inattention and/or hyperactivity and impulsivity that result in pervasive impairments across multiple life domains (home, school, peers, extracurricular activities).[1] Evidence-based guidelines recommend that school-aged children and adolescents with ADHD receive comprehensive individualized treatment, which generally includes pharmacological treatment.[2-5] Several recently introduced novel long-acting pharmacological treatments and a growing list of others in development require further evaluation of their efficacy and safety to better understand where they will be placed in current treatment algorithms.

In this article, we review the efficacy and safety data of several of the more novel long-acting preparations, including the first non-stimulant noradrenergic reuptake-inhibitor, atomoxetine,[6] and three of the more novel extended-release (XR) stimulant preparations. Dexmethylphenidate XR[7] is a stimulant treatment in a single isomer form; lisdexamfetamine dimesylate[8] was the first stimulant-treatment in a prodrug form, whereby it remains pharmacologically inactive until the lysine is cleaved; and the methylphenidate transdermal system (TDS) was the first stimulant treatment in the form of a worn patch. Other XR stimulant treatments that have been available for some time are not reviewed in this article, including other methylphenidate XR formulations (e.g. sustained release via wax matrix tablets,[9] capsulated biphasic bead release[10,11] and osmotic-controlled release oral system [OROS®][12]), amphetamine XR[13] and dextroamfetamine XR.[14] Also in this article, we review two α_2-adrenoceptor agonists, clonidine[15] and guanfacine.[16] Guanfacine is now approved and is the first α_2-adrenoceptor agonist treatment for paediatric ADHD, whereas clonidine, at the time of writing, is not approved by the FDA for this indication in the US.

There are many data that support stimulant medications, such as methylphenidate and amfetamine, as effective treatments of paediatric ADHD, with their effect sizes computed versus placebo and typically ranging from 0.70 to 1.4 for immediate-release (IR) and XR preparations alike.[17-24] However, their efficacy and safety when used for longer than 3–5 years is less certain.[25-33] While ADHD can persist into adulthood,[34-38] the focus of this article is limited to a review of these novel long-acting pharmacotherapies when used in school-aged children and adolescents with ADHD.

1. Dexmethylphenidate Extended Release

Methylphenidate is a 50 : 50 mixture of two isomers, dextro (*d*)-threo-methylphenidate and levo (*l*)-threo-methylphenidate. When taken orally, methylphenidate undergoes enteric and hepatic enantioselective de-esterification to ritalinic acid, resulting in a limited bioavailability of approximately 22–50% for *d*-methylphenidate and 1% for *l*-methylphenidate.[39,40] Dexmethylphenidate (Focalin®[41]) is the single *d*-isomer that was shown to be more potent than (*d,l*)-methylphenidate in reducing motor activity in rats and humans. Dexmethylphenidate was FDA approved in the US in 2001 for use in children aged ≥6 years with ADHD.[41-43] Its XR formulation was similarly approved in 2005 and is available in four beaded-capsule strengths: 5, 10, 15 and 20 mg.[7]

A bimodal-pulsed beaded absorption is utilized, in which 50% of the medication is immediately released, with the remaining 50% released 4 hours later, after its overcoat is eroded by water. The initial peak concentrations (C_{max}) of dexmethylphenidate XR are reached in 1.5 hours (range 1–4 hours), with a second peak reached in 6.5 hours (range: 4.5–7 hours). The designed early onset and prolonged absorption provide less fluctuation than that associated with two doses of dexmethylphenidate taken 4 hours apart. Because medication release is pH-dependent, parents should be advised to avoid concomitant use of antacids or acid suppressants that could potentially alter release.[7,42,43]

The recommended initial treatment with dexmethylphenidate XR is a 5 mg capsule each morning. Dosing may be increased by 5 mg/week until optimal benefit is achieved, up to the

maximum FDA-approved dose of 20 mg/day. Patients previously treated with methylphenidate should begin treatment by taking half of their usual methylphenidate dose, whereas those previously treated with dexmethylphenidate should begin treatment with an equivalent dose of dexmethylphenidate XR.[7] A pharmacokinetic trial supported the option of opening the capsule to sprinkle the contained beads on a teaspoon of apple sauce.[44] Children, especially younger ones who have not developed their ability to swallow capsules, should immediately take this teaspoonful without crushing, chewing, dividing or storing beads for later use. No published pharmacokinetic study examined food effects on dexmethylphenidate XR in paediatric patients; however, food did not significantly change the bioavailability when healthy children took dexmethylphenidate, although there was delay in absorption and C_{max} was reached within 1–1.5 hours.[7,45,46]

1.1 Efficacy Data

Regulatory approval was based on one double-blind study of 103 children and adolescents (aged 6–17 years) treated with dexmethylphenidate XR or placebo for 7 weeks.[47] Flexible daily dosing (5–30 mg/day) for 5 weeks established maximum clinical benefit, after which the optimal dosage was maintained for 2 weeks. Based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and ADHD Index subscales of the Conners' ADHD Scale (CADS) for Teachers [mean total baseline scores: 33.4 dexmethylphenidate XR and 35.2 placebo],[48] mean change-scores from baseline to study end showed that dexmethylphenidate XR (−16.3) was superior to placebo (−5.7) in reducing core ADHD symptoms, with most subjects responding well on a dosage of 20–30 mg/day. The resulting effect size was 0.79, and clinician-determined response rates, defined as having 'much' or 'very much' improvement over baseline, were 67.3% for dexmethylphenidate XR and 13.3% for placebo.

Several classroom-laboratory studies have been conducted with children aged 6–12 years. In one study,[49] participants were taking methylphenidate 20–40 mg/day prior to study enrolment. Patients (n = 54) were treated in a blinded crossover manner with dexmethylphenidate XR 20 mg/day and placebo for 5 days each. After 1 day of washout, the youths took their last morning dose at the start of a 12-hour classroom-laboratory assessment. In a second study,[50] participants were treated with methylphenidate 20–40 mg/day or dexmethylphenidate 20–30 mg/day prior to study enrolment. Patients (n = 68) were similarly treated in the same blinded crossover manner of dexmethylphenidate XR 20 mg/day and placebo, but for 6 days each before completing the 12-hour classroom assessment. Primary efficacy in both studies was based on the Swanson, Kotkin, Angler, M-Flynn, and Pelham (SKAMP) rating scale of classroom manifestations of ADHD.[51,52] The 13-item SKAMP provides a combined score plus two validated subscales: the Deportment Scale (DS), reflecting behavioural symptoms, and the Attention Scale (AS). Each item is rated from 0 (normal) to 6–7 (maximum impairment), with lower scores representing greater improvement.

In the first study,[49] primary efficacy was based on SKAMP combined change-scores from pre-dose to 1 hour after administration. In the second study,[50] primary efficacy was based on averaged SKAMP combined scores, from 30 minutes until 12 hours post-dose. In both studies, dexmethylphenidate XR 20 mg/day proved superior to placebo at all assessment times on the SKAMP combined and subscale scores, as well as on a mathematics assessment. Subsequently, a similarly designed study treated 86 children (aged 6–12 years) with the same crossover treatments for 6 days each, prior to completing an 8-hour classroom-laboratory assessment.[53] This study confirmed that dexmethylphenidate XR provided an early morning benefit. Based on SKAMP combined change-scores from pre-dose to 30 minutes post-dose, dexmethylphenidate XR 20 mg (−1.0) proved superior to placebo (3.3), and was superior at all other assessment times. CADS-Parent Scale change scores averaged across assessments were −16.4 for dexmethylphenidate XR 20 mg and −4.6 for placebo, suggesting that parents also

viewed dexmethylphenidate XR 20 mg/day as more effective than placebo.

Two comparative classroom studies similarly demonstrated this early morning benefit.[54,55] The efficacy of dexmethylphenidate XR 20 mg/day was compared with placebo or OROS® methylphenidate (Concerta®[12]) 36 mg/day, and dexmethylphenidate XR 30 mg/day was compared to placebo or OROS® methylphenidate 54 mg/day. OROS® methylphenidate varies in its delivery system, as 22% of methylphenidate is immediately released with the remaining gradually released through osmosis. The patients in these studies were taking methylphenidate 40–60 mg/day or dexmethylphenidate 20–30 mg/day before study enrolment. The patients (n = 82, aged 6–12 years) were then treated with five of ten treatment sequences for 6 days prior to completing a 12-hour classroom-laboratory assessment.[54] Based on SKAMP combined change-scores from pre-dose to 2 hours post-dose, dexmethylphenidate XR 20 mg/day was superior to placebo and OROS® methylphenidate 36 mg/day, and dexmethylphenidate XR 30 mg/day was superior to placebo and OROS® methylphenidate 54 mg/day. Importantly, both active treatments and dosages were superior to placebo on SKAMP total and subscale scores at all assessed times. Each active treatment had superiority over the other, but at separate times. Dexmethylphenidate XR was superior during the morning hours, whereas OROS® methylphenidate demonstrated superiority in the late afternoon (10–12 hours post-dose), and a similar benefit was found during the earlier afternoon hours.

A similarly designed classroom comparison (n = 84) of 6- to 12-year-olds[54] supported this same pattern of superiority of dexmethylphenidate XR 30 minutes after administration. Secondary analyses suggested that dexmethylphenidate XR may provide an earlier effect for behavioural than for inattention symptoms. Based on SKAMP-DS scores (e.g. behavioural symptoms), dexmethylphenidate XR was superior to placebo and OROS® methylphenidate at 30 minutes after administration, and this lasted up to 4 hours. Unlike results of earlier studies, SKAMP-AS scores (e.g. inattention) did not reflect this same superiority until 1 hour after administration. However, this later superiority usually lasted longer, often up to 6 hours post-dose.

It is difficult to compare the results from the comparisons of dexmethylphenidate XR with OROS® methylphenidate in these two studies,[54,55] because these two treatments are formulated with different systems to deliver their medication. Perhaps a more equivalent comparison might have been to investigate the efficacy of dexmethylphenidate XR with biphasic XR methylphenidate (e.g. Ritalin LA®) since both of these treatments initially release 50% of their beaded medication. Nonetheless, dexmethylphenidate XR has evidence of a greater effect than placebo within 30 minutes that generally lasts about 10 hours, or 11–12 hours when a higher-than-approved dose is taken. Unfortunately, no published peer-reviewed data have documented continued benefit beyond the acute 7-week treatment.

1.2 Tolerability Data

There was initial speculation that dexmethylphenidate might prove to be better tolerated than methylphenidate. However, controlled studies have not demonstrated this. The short treatment of 5–7 days inherent in the classroom-designed studies may not be long enough to detect some adverse effects that might develop later or worsen with continued treatment (e.g. weight or cardiovascular change). The majority of the classroom studies excluded treatment-naive individuals, making it difficult to compare data with those of other FDA-approved stimulant treatments.

Investigators of the 7-week acute-treatment study[47] and the laboratory-classroom studies each concluded that dexmethylphenidate XR had an adverse-effect profile similar to that of methylphenidate.[49,50,53-55] Adverse effects commonly reported during the 7-week open-label study portion included gastrointestinal upset (38% dexmethylphenidate XR; 19% placebo), decreased appetite (30%; 9%), headache, (25%; 11%) and anxiety (6%; 0%). Although not as common, insomnia, feeling jittery and decreased appetite were each experienced to a severity that caused several patients to withdraw from the

study. Based on investigator opinion, no clinically important laboratory, ECG or other related safety changes or events occurred.

1.3 Clinical Application

Dexmethylphenidate XR has demonstrated superior efficacy to placebo and appears similar in efficacy to methylphenidate. Its advantage is a longer lasting effect at a lower dose than methylphenidate. Benefit in reducing ADHD symptoms is typically observed within 30 minutes and lasts up to 10 hours at the FDA maximum recommended dose (20 mg/day).[7] Dexmethylphenidate XR may be well suited for children and adolescents who require an early morning effect that extends throughout the school day. Some older children and adolescents involved in afterschool or evening activities may require an afternoon IR dose to extend symptom control. Dexmethylphenidate XR is not FDA approved for children aged <6 years.[7] Although approved for use in adolescents, this approval was based on data from only 17 adolescents,[48] and subsequent published peer-reviewed studies to date have not included adolescents.[49,50,53-55] Also, data that document continued benefit and safety when used for >7 weeks are lacking.

2. Methylphenidate Transdermal System

Methylphenidate TDS is a novel methylphenidate formulation that was approved in the US in 2006 for use in 6- to 12-year-olds as a patch that is applied to the child's hip.[56] Before application, a thin polyester backing is peeled off, exposing the methylphenidate, which is evenly mixed within a silicon-acrylic adhesive. Methylphenidate TDS patches are identified by the total dose delivered when worn for 9 hours/day (10, 15, 20 and 30 mg) that are manufactured in four patch sizes (12.5, 18.75, 25 and 37.5 cm^2), which come individually packaged in 10- and 30-count boxes. Treatment is typically initiated by having the child wear a 10 mg patch (12.5 cm^2) for 9 consecutive hours per day. Daily dosing may be increased by 5–10 mg/week as tolerated and clinically indicated, up to the maximum approved dose of 30 mg/day (37.5 cm^2). Wear time may be shortened to alleviate late-day adverse effects, although published data do not indicate by how much time. If not removed at or before 9 hours after application, absorption will persist for several additional hours, which could potentially induce or worsen adverse effects.[56]

The gradual skin absorption eludes the first pass effects of metabolic de-esterification in the liver and allows greater access to systemic circulation. The resulting bioavailability of methylphenidate TDS is 13% for *l*-methylphenidate and 55% for *d*-methylphenidate, which is similar to that of oral methylphenidate. Regardless of formulation, the *d*-isomer remains predominantly responsible for the therapeutic efficacy and adverse effects of methylphenidate TDS.[57] Lesser efficacy may occur if the methylphenidate TDS patch is not worn on the hip. When worn for 16 hours/day by 6- to 12-year-olds, there was a 31% higher bioavailability when applied to the hip versus the scapular area, even though both sites resulted in similar skin irritation.[58] Although worn for more hours than approved, this finding supports the importance of educating parents and patients of a differential effect when applied to areas other than the recommended hip area.

The average time until a noticeable onset of effect is 2 hours (range: 1–4 hours), which is slower and more gradual than IR or bimodal-release methylphenidate,[59] with its concentrations similar to those of OROS® methylphenidate.[60] Since methylphenidate TDS should be applied 2 hours before time of a desired effect, parents should be typically instructed to apply methylphenidate TDS on their child on their awakening or shortly after. In a few cases, children might require methylphenidate IR taken before school to improve morning benefit. An ongoing absorption promotes gradually rising plasma concentrations over the time worn, cumulating to an average time to C_{max} (t_{max}) at 7–9 hours after patch application, or at time of patch removal. When removed, plasma concentrations and symptom benefits persist for a short time and then diminish over 2–3 hours, with data supporting that this effect occurs across doses and varied wear-times.[61,62]

2.1 Efficacy Data

In an early dose-ranging study, 36 youths (aged 6–13 years) were treated with methylphenidate TDS or placebo for 8 days each in a summer camp setting.[63] Although methylphenidate TDS proved superior to placebo, it triggered frequent reports of adverse effects, including decreased appetite (61%) and insomnia (47%). After an earlier submitted marketing application was declined due to poor tolerability of the 12-hour worn patch, the 9-hour worn patch was tested in 27 children (aged 6–13 years) who wore methylphenidate TDS and placebo for 6 weeks each and were then assessed in a classroom-laboratory setting.[64] In both study segments, methylphenidate TDS was superior to placebo, with the 9-hour worn patch causing fewer adverse effects than the 12-hour worn patch.

The approval of the 9-hour methylphenidate TDS was based on data from two subsequent controlled studies[60,65] plus long-term data[66] from children who wore the 12-hour patch. In general, data indicates that methylphenidate TDS has a superior efficacy to placebo in short-term use (up to 6 weeks), with resulting response rates of ≥70% across studies, measures and raters. In the first of these studies,[65] 93 children (aged 6–12 years) were treated with open-label methylphenidate TDS (10–30 mg/day) for 5 weeks, followed by a blinded crossover of 1-week treatment segments (methylphenidate TDS, placebo). Treatments were assessed at pre-dose and eight times post-dose during a 12-hour classroom-laboratory assessment. Based on SKAMP-DS averaged scores on treatment day 7, methylphenidate TDS (3.2) was superior to placebo (8.0), with a resulting effect size of 0.93. A uniform effect was suggested, as a similar level of superiority was maintained across all assessments after 2 hours, although no hourly scores were reported to confirm this. Based on the clinician-rated Clinical Global Impression-Improvement Scale (CGI-I),[67] response was defined as having 'much' or 'very much' improvement over baseline, with rates of 80% for methylphenidate TDS and 12% for placebo.[65]

Although classroom laboratories are an excellent setting for pharmacokinetic studies and brief clinical outcomes, their brief duration may not allow for identification of important clinical or tolerability effects over time. Thus, a controlled study evenly randomized 270 children of similar age to methylphenidate TDS (10–30 mg/day), OROS® methylphenidate (18–54 mg/day) or placebo for 6 weeks.[60] TDS and OROS® methylphenidate were both superior to placebo, based on ADHD Rating Scale-IV (ADHD-RS-IV)[68] end-of-treatment score reductions of 66% for methylphenidate TDS (24-point decrease), 50% for OROS® methylphenidate (22-point decrease) and 23% for placebo (10-point decrease). Response rates were 72% for methylphenidate TDS, 66% for OROS® methylphenidate and 24% for placebo. Although methylphenidate TDS and the OROS® reference group appeared descriptively similar in relation to placebo, these active treatments were not statistically compared because of limited power inherent in the study design.

Based on data from one controlled study plus several small pharmacokinetic studies,[57,59] the patch may have an efficacy similar to that of IR methylphenidate.[57,59] In the one study,[59] 90 children (aged 6–17 years) were treated with a 12-hour patch for 5 weeks and then randomized to blinded crossover of 1-week treatment segments of methylphenidate TDS, placebo patch or methylphenidate IR (taken twice daily). Based on the CADS-Parent Scale total scores,[69] methylphenidate TDS and methylphenidate IR were both statistically superior to placebo, with neither active treatment superior to the other. Resulting response rates were 73% for methylphenidate TDS and 81% for methylphenidate IR.[59]

Although data from these acute-treatment studies provide evidence of a superior efficacy to placebo, there are no published data in a peer-reviewed journal that document methylphenidate TDS having a continued benefit beyond acute treatment. After completing an earlier study, the children who wore methylphenidate TDS for 12 hours/day were followed for continued treatment. Unfortunately, the only published long-term data concern their growth trends, and this report did not mention the effectiveness or tolerability profile of the patch, despite the fact that these youths were permitted to wear, for up to

3 years, larger sized patches (50 cm^2) than currently approved.[66] The manufacturer recently announced the completion of data from children who wore methylphenidate TDS for 9 hours/day for up to 12 months (n = 326), but these data have not been published at the time of writing.[70]

2.2 Tolerability Data

There was initial concern about the tolerability of methylphenidate TDS, since the 12-hour worn patch induced higher than usual rates of adverse effects. However, current data indicate that this is not the case for the 9-hour patch.[56] With the exception of frequent skin irritation at the patch site, methylphenidate TDS was generally well tolerated and not associated with any clinically important cardiovascular changes or other safety concerns when used for 6 weeks.[60] The most commonly reported adverse effects for methylphenidate TDS, OROS® methylphenidate and placebo during this 6-week controlled study are presented in table I. FDA-labelled warnings for children treated with methylphenidate TDS and those treated with lisdexamfetamine and atomoxetine are presented in table II.[56]

Interestingly, the previously mentioned classroom study published by McGough et al.,[65] reported that there were no substantial differences between methylphenidate TDS and placebo on any safety measure or reported tolerability event. This lack of reported adverse effects may have occurred as the study youths had already completed 5 weeks of open-label methylphenidate TDS treatment prior to randomization, in combination with the short 1-week controlled treatment evaluated during one classroom-laboratory session. As noted, most study participants who wore methylphenidate TDS experienced mild skin irritation at the patch site, although this generally improved or cleared within 24–48 hours of patch removal. There were some participants whose skin irritation was more bothersome and several withdrew from the study for this reason.[60,65] As a result, the manufacturer collaborated with dermatologists and other clinical experts to publish suggestions of how to minimize skin irritation and these are summarized in table III.[62,72]

In separate analyses, growth trends were described for 127 children (aged 6–12 years) who wore methylphenidate TDS for 12 hours/day for up to 3 years.[66] Overall mean annual growth deficits were: 0.7 cm (height), 1.3 kg (weight) and 0.5 units (body mass index). More specifically, the children typically lagged behind their expected

Table I. Adverse effects and physiological changes associated with the methylphenidate transdermal system (MPH-TDS), osmotic-controlled release oral system methylphenidate (OROS®-MPH), or placebo (PL) in a 6-week study of 6- to 12-year-olds with attention-deficit hyperactivity disorder (n = 270)[60]

Parameter	MPH-TDS (n = 98)	OROS®-MPH (n = 91)	PL (n = 85)
Adverse effects (%)			
Anorexia (decreased appetite)	26	19	5
Difficulty sleeping	13	8	5
Stomach upset/pain	12	8	2
Vomiting	10	10	5
Weight loss	9	8	0
Mood changes	6	3	1
Physiological changes			
Mean increase in heart rate (relative to PL)	4 bpm	None	NA
Mean increase in blood pressure (relative to PL)	1/2 mmHg	2/3 mmHg	NA
Change in laboratory test results[a]	None	None	None
Change in ECG measurement[a]	None	None	None

a Statistically significant change from baseline, which has been deemed as clinically important.

bpm = beats per minute; **NA** = not applicable.

Table II. US FDA-associated warnings for atomoxetine (ATM),[6] methylphenidate transdermal system (MTS-TDS)[9] and lisdexamfetamine dimesylate (LDX)[8]

Associated warning	ATM	MPH-TDS	LDX	FDA-recommended action(s)
Growth delays compared with expected trajectories	Yes	Yes	Yes	Monitor height, weight and BMI before and during treatment Interrupt or stop treatment with significant delay or concern
Potential drug tolerance/abuse	No	Yes	Yes	Dispense sparingly, and monitor for misuse or abuse
Increased risk of suicidal events	Yes	No	No	Assess for adverse change in moods and behaviours Assess patient's safety as needed Advise caregivers of need for close supervision
Increased psychiatric risk (e.g. psychosis, mania, aggression, hostility, depression or bipolar disorder)	Yes	Yes	Yes	Assess for co-morbidity prior to treatment and periodically thereafter Discontinue treatment with emergent or worsening of serious psychiatric symptoms
Increased risk of tics	No	Yes	Yes	Monitor for new onset or worsening of tics Discontinue treatment if they develop or worsen
Allergic skin reaction	NA	Yes	NA	Discontinue use of MTS-TDS if oedema, papules or vesicles do not improve in 48 hours, or if widespread, with referral to dermatology, as needed
Potential cardiovascular concerns (slight increase in pulse and blood pressure is usual; cardiac events and sudden deaths occurred in several youths with structural cardiac abnormalities)	Yes	Yes	Yes	Obtain detailed patient/family history, including physical exam Use caution with history of hypertension, tachycardia or cardiac disease Monitor pulse and blood pressure, and assess for related symptoms periodically during treatment
Potential for severe liver injury (3 post-marketing probable cases)[71]	Yes	No	No	Discontinue treatment with initial suspect, physical symptoms, or confirmation from laboratory testing
May lower seizure threshold (especially with prior EEG abnormalities)	Yes	Yes	Yes	Obtain medical history prior to treatment Discontinue if patient has a seizure
Drug interaction with strong CYP2D6 inhibitors	Yes	No	No	Obtain concomitant medication history Consider slower dose titration if taking potent CYP2D6 inhibitor (e.g. fluoxetine, paroxetine, quinidine)

BMI = body mass index; **CYP2D6** = cytochrome P450 2D6 isoenzyme; **EEG** = electroencephalogram; **NA** = not applicable.

growth-for-weight, but less so for height during their first year on methylphenidate TDS treatment. After this time, they gained weight at a more appropriate rate. By the time they were steadily treated for 2–3 years, most children had caught up and were growing and gaining weight at or above their expected trajectory rate. Mean length of time on methylphenidate TDS and taking a higher dose were both associated with a lag in weight, but not in height. Generally, the shortest youths continued to grow as expected, the tallest ones grew slower and the heaviest ones gained less weight.

These data are consistent with those found for other stimulant treatments, including IR methylphenidate up to 8 years, atomoxetine up to 5 years and lisdexamfetamine over 1 year.[31,73-77] Interestingly, this trend differed from data on OROS® methylphenidate and XR mixed amfetamine salts, which caused more delay in gaining height rather than weight.[78-81] As few studies have followed treated youths past 3–5 years, it remains unknown whether growth is maintained in subsequent years.[2,26-31,80]

2.3 Clinical Application

Methylphenidate TDS should not be worn by children with sensitive or problematic skin. It is also not recommended for those who are not likely to leave the patch on or alone, or if their caretakers are likely to persistently forget or refuse to take off the patch. Methylphenidate TDS is not FDA approved to wear for longer

Table III. Recommended patient education for methylphenidate transdermal system (TDS)[62,72]

Patch application
2 hours prior to desired onset, apply methylphenidate TDS patch to a dry, clean area of the hip
Hold patch steadily on skin for at least 30 seconds to make good contact
If the patch falls off, place a new patch on a different area of the hip
Alternate sides of hip used, and areas of each hip used
Do not apply patch to irritated areas or on other body areas
Avoid use of soaps, moisturizers and ointments just prior to patch application
Do not cut patch, as this may increase irritation or induce rapid absorption
Patch removal
Remove patch after worn for 9 hours to avoid further absorption
After removal, fold patch in half with the two sticky sides together
Dispose of used patch in lidded container, out of reach of children and pets
Mild, expected skin irritation at patch site normally improves or clears
May use petroleum jelly or mineral/olive oil to gently remove adhesive residue
Moisturize after shower or bath, but not near time of patch application
Use hydrocortisone cream, as needed, for skin irritation
Contact prescriber if significant skin swelling or blistering occurs
Wearing and storing
May wear patch while bathing, showering and swimming
Avoid direct sources of heat (e.g. heating pad, sauna/whirlpool, electric blanket)
Store patches away from high temperatures (e.g. vehicles, purses, windows)

than 9 hours/day, or for children aged <6 years or adolescents.[6]

As methylphenidate TDS has demonstrated a predictable efficacy with 4- and 6-hour wear times,[58,59] its flexible wear time may provide advantage to children who occasionally sleep in until later times and may not require the full duration of action. Similar to dexmethylphenidate XR, the primary limitation of methylphenidate TDS is the lack of data documenting continued effect and safety when used for >6 weeks.

3. The Amfetamine Prodrug Lisdexamfetamine Dimesylate

Lisdexamfetamine dimesylate was the first FDA-approved stimulant-treatment prodrug, being approved in the US in 2007 for use in 6- to 12-year-olds with ADHD.[8] Lisdexamfetamine is hypothesized to have a limited abuse potential because of its formulation. During the manufacturing process, *d*-amfetamine is inactivated by attaching the amino acid L-lysine onto it. After ingestion, enzymatic hydrolysis transforms lisdexamfetamine into L-lysine and *d*-amfetamine. It is believed that this hydrolysis process may be responsible for the longer duration of lisdexamfetamine.[8,82] The t_{max} ranges from 3.7 to 6 hours, compared with that of XR mixed amfetamine salts (range: 3–12 hours).[8,83] Although food does not affect activation, recent high-fat ingestion decreases absorption by about 1 hour.[8,84]

Lisdexamfetamine is available in six capsule strengths (from 20 to 70 mg). One 20–30 mg capsule each morning is recommended for initial treatment. Dosing may be increased by 10–20 mg/week as tolerated and clinically indicated, up to the maximum FDA-approved dose of 70 mg/day.[8]

3.1 Efficacy Data

The approval of lisdexamfetamine was based on data from two controlled trials in 6- to 12-year-olds.[85,86] In the first study,[85] 52 children were treated with open-label XR mixed amfetamine salts for 3 weeks, and then randomly assigned to 1-week crossover treatment segments of lisdexamfetamine, placebo and XR mixed amfetamine salts, with each child assessed during a 12-hour classroom-laboratory session on treatment day 7. Lisdexamfetamine was superior to placebo based on SKAMP-DS averaged scores at end-of-treatment (0.8 lisdexamfetamine; 0.8 XR mixed amfetamine salts; 1.7 placebo). Lisdexamfetamine was first assessed to be superior at post-dose hour 2 (vs XR mixed amfetamine salts at hour 3), with both active treatments remaining superior at all subsequent assessments, including at hour 12. Response rates were 74% for lisdexamfetamine, 72% for XR mixed amfetamine salts and 18% for placebo, which are similar to rates reported in comparative studies of methylphenidate TDS and oral methylphenidate.[60,65,20-24] A greater number of children responded better (with 'very much' improvement) to lisdexamfetamine (32%)

than to XR mixed amfetamine salts (16%); however, this cannot be compared with other treatments, as CGI-I response of 'much' and 'very much' improvement have not been separately reported by most other studies.

In the second study,[86] 290 children (aged 6–12 years) were evenly randomized and treated with placebo or one of three lisdexamfetamine daily doses (30–70 mg/day) for 4 weeks.[86] ADHD-RS-IV change scores demonstrated that lisdexamfetamine was superior to placebo, with average score reductions of 50–59% (vs 15% for placebo), with a dose-based effect size of 1.2–1.6. Resulting response rates were ≥71% for lisdexamfetamine and 18% for placebo.

Results from a recent classroom study have provided new evidence of an earlier and longer effect. The 113 enrolled children (aged 6–12 years) were initially treated for 4 weeks with open-label lisdexamfetamine 30–70 mg/day, followed by blinded crossover of lisdexamfetamine and placebo treatments for 2 weeks each.[87] Averaged SKAMP-DS and standardized mathematics test scores indicated that lisdexamfetamine was superior to placebo in reducing hyperactivity and general inattention during post-dose hours 1.5–13, with the 70 mg dose group experiencing the greatest symptom improvement. Response rates at 1.5 hours post-dose were 19.5% for placebo and 82% for lisdexamfetamine. In secondary analysis, the effect of lisdexamfetamine was numerically less at hours 11–12, but not statistically less than pre-treatment. Thus, clinicians should keep in mind that some patients may complain of a diminishing effect by 11–12 hours after administration. Also of note, lisdexamfetamine was not superior to placebo on selected items of SKAMP-AS (neat/accurate work completion), suggesting that benefit may occur later for some aspects of inattention.[86]

The patients who participated in these studies were subsequently offered participation in a 12-month open-label treatment study (n = 272).[88] By week 4, 90% of participants had responded to lisdexamfetamine with at least 'much' improvement over the pre-treatment ADHD-RS-IV total score. Unfortunately, this report did not include how many children maintained benefit without dose escalation.

3.2 Tolerability and Safety Profile

The tolerability and safety profile of lisdexamfetamine was based on data from 342 children who participated in the two controlled studies that led to its approval in the US,[85,86] with the most frequently experienced adverse effects reported during the 4-week, controlled-treatment study of lisdexamfetamine presented in table IV.[85] Its

Table IV. Adverse effects and physiological changes associated with lisdexamfetamine dimesylate (LDX) and placebo (PL) in a 4-week study of 6- to 12-year-olds with attention-deficit hyperactivity disorder (n = 290)[86]

Parameter	LDX (n = 176)	PL (n = 54)
Adverse effect (%)		
Anorexia (decreased appetite)	39	4
Difficulty sleeping	19	3
Stomach upset/pain	12	6
Vomiting	15	7
Weight loss	9	0
Mood Changes	10	0
Physiological changes		
Mean increase in heart rate (relative to PL)	4–5 bpm	NA
Mean increase in blood pressure (relative to PL)	None	NA
Change in laboratory test results (relative to baseline)[a]	None	None
Change in ECG measurements (relative to baseline)[a]	None	None

a Statistically significant change from baseline, which has been deemed as clinically important.

bpm = beats per minute; **NA** = not applicable.

short-term and 12-month tolerability was presumed similar to that of XR mixed amfetamine salts and stimulant treatment in general.[85-87] Most related adverse effects were experienced within the first treatment weeks and were generally mild to moderate in severity, with no clinically important cardiovascular or other safety problems identified by the study investigators.

3.3 Clinical Application

As lisdexamfetamine maintains *d*-amfetamine inactive until time of metabolism, it is theorized to discourage the misuse and abuse that has been commonly associated with other stimulants.[82] Additionally, lisdexamfetamine may benefit children who require a less varied absorption pattern than that of XR mixed amfetamine salts, with data supporting that lisdexamfetamine has a superior effect over placebo that lasts up to 13 hours.[87] On the other hand, the duration of effect of lisdexamfetamine may be too long for some younger children. Also, it is possible that some children may not respond as well to lisdexamfetamine as to XR mixed amfetamine salts. The *d*- and *l*-isomers of mixed amfetamine salts have shown distinct neuronal actions as markers of both clinical efficacy and toxicity. The use of *d*- and *l*-isomers together, as in XR mixed amfetamine salts, resulted in increased and prolonged dopamine release compared with *d*- or *l*-amfetamine alone. Whereas *d*-amfetamine improved hyperactivity and impulsivity more that *l*-AMP, the latter more selectively improved sustained attention; however, *l*-amfetamine induced more global neuronal changes than *d*-amfetamine, extending into the anterior and posterior brain regions.[88-91] Since lisdexamfetamine does not contain *l*-amfetamine, it is possible that lisdexamfetamine may offer less potential for adverse change in the motor and somatosensory cortices (e.g. nervousness, repetitive or compulsive behaviours).

There are no available data on the efficacy, tolerability or safety of lisdexamfetamine in preschool-aged children or in adolescents.[8] Unlike methylphenidate TDS and dexmethylphenidate XR, there is documented evidence of the continued effectiveness and acceptable safety profile for use of lisdexamfetamine for up to 12 months' duration in 6- to 12-year-olds.

4. The Noradrenergic Reuptake Inhibitor Atomoxetine

Atomoxetine[8] is a selective reuptake inhibitor of pre-synaptic noradrenergic neurons that was approved in the US by the FDA in 2002 to treat ADHD in children (aged ≥6 years). Atomoxetine recently gained approval in 2007 for treatment maintenance of up to 3 years' duration.[6] Atomoxetine is manufactured in seven different strength capsules from 10 to 100 mg, and dosed by weight with a recommended initial dosage of 0.5 mg/kg/day. The medication may be taken as a single morning dose, or in divided doses that may be taken each morning and again late each afternoon. Dosing may be increased as tolerated and clinically indicated, to the FDA-approved target dose of 1.2 mg/kg/day, over 2–8 weeks to evaluate its effect and tolerability. If response remains insufficient after 2–4 weeks, dosing may be further increased to a maximum dose of 1.4 mg/kg/day, but is not to exceed 100 mg/day. Although not approved for use, the label acknowledges dosing of up to 1.8 mg/kg/day, which was successfully used in a study related to maintaining treatment over time.[6]

The average t_{max} of atomoxetine is 1–2 hours, with a mean half-life of 5 hours.[92] Different from stimulants, atomoxetine is eliminated by an oxidative metabolism within the cytochrome P450 (CYP)-2D6 enzymatic pathway, with a slower titration recommended when taken with a CYP2D6 inhibitor, such as fluoxetine, paroxetine or quinidine.[6,93] In the few patients who lack this enzymatic activity, 2-fold higher plasma concentrations and a longer average half-life (24 hours) of atomoxetine may be seen. However, it is possible that these enzyme-deficient patients may not require a lower or slower dosing. Interestingly, a pooled data analysis of double-blind studies with CYP2D6-deficient (n = 87) and non-deficient (n = 1239) children and adolescents suggested that clinicians do not need to obtain genotyping as part of routine care. Compared with the non-deficient patients in this analysis, the

enzyme-deficient patients who responded well to atomoxetine had similar safety profiles, although their average dose was 0.1 mg/kg/day lower, and they had faster heart rates by about 4 beats/minute.[94] Atomoxetine is also different from stimulants in that reinforcing effects did not occur when atomoxetine was self-administered in studies assessing abuse potential.[95,96] Additionally, withdrawal symptoms did not occur when atomoxetine treatment was suddenly stopped without dose tapering.[97,98] As such, atomoxetine was not classified by the FDA as a schedule II controlled substance, which allows refills on prescriptions called in to pharmacies.[6]

4.1 Efficacy Data

The paediatric approval of atomoxetine in the US in 2002 was based on data from four placebo-controlled studies.[99-101] Data from the two initial studies were combined for a total of 291 children (aged 7–13 years) who were treated with atomoxetine or placebo twice daily at doses up to 2 mg/kg/day for 10 weeks.[99] Based on ADHD-RS-IV total score reductions, atomoxetine was superior to placebo, with a resulting effect size of 0.72. In two subsequent controlled studies, children and adolescents up to 18 years of age were treated with atomoxetine or placebo at dosages of up to 1.8 mg/kg/day (n = 171) and subsequently up to 1.5 mg/kg/day (n = 197).[100,101] In both studies, atomoxetine was superior to placebo, with the later study resulting in an effect size of ≥0.70. The efficacy of atomoxetine was confirmed in a later meta-analysis of nine controlled trials (atomoxetine: n = 1150; placebo: n = 678) in which atomoxetine was determined to be superior to placebo across varied studies, rating scales and raters.[102] In this analysis, the children with more severe symptoms were the most likely to respond, whereas males with combined-type ADHD and oppositional defiant disorder (ODD) had a smaller predicted chance of responding well to atomoxetine.

4.2 Treatment Comparisons

Although several early studies of atomoxetine resulted in a large effect size, atomoxetine has been generally associated with a medium effect size. In a meta-analysis conducted by Faraone et al.[20] of 33 controlled studies, six atomoxetine studies resulted in an effect size of 0.62, compared with IR stimulants (0.91) and XR stimulants (0.95). Several recent studies have directly compared atomoxetine with stimulant treatments. Kemner et al.[103] reported on a controlled comparison in which 1323 children were treated with OROS® methylphenidate (n = 850) or atomoxetine (n = 473) for 3 weeks. Although both treatments substantially reduced ADHD-IV-RS total scores over baseline, OROS® methylphenidate remained statistically superior to atomoxetine. In another study, 215 children (aged 6–12 years) were evenly randomized to atomoxetine (up to 1.2 mg/kg/day) or XR mixed amfetamine salts (up to 30 mg/day) for 3 weeks, as assessed in a classroom-laboratory session.[104] At the end of this study, almost 75% of the children receiving XR mixed amfetamine salts, but only 36% of those taking atomoxetine, were rated as showing 'much' improvement. Although data from both these studies support previous findings that atomoxetine generally provides a lower response rate than stimulant treatment, the 3-week treatment duration may not be long enough and the lower maximum atomoxetine dose used may be an inadequate dose to fully encompass all of the potential atomoxetine responders.

In an international treatment comparison, 330 youths from Mexico, China and Korea were treated with IR methylphenidate (0.2–0.6 mg/kg/day) or atomoxetine (up to 1.8 mg/kg/day) for 8 weeks.[105] Atomoxetine was statistically similar to IR methylphenidate, resulting in response rates of 77% for atomoxetine) and 81% for IR methylphenidate. Another recent study that used the 1.8 mg/kg/day maximum dosing found atomoxetine and OROS® methylphenidate to have differential treatment effects. In this study,[106] 516 subjects (aged 6–16 years) were treated with atomoxetine (up to 1.8 mg/kg/day), OROS® methylphenidate (up to 54 mg/day) or placebo for 6 weeks. OROS® methylphenidate and atomoxetine were both superior to placebo, and OROS® methylphenidate was superior to atomoxetine in reducing ADHD symptoms. After the participants assigned to OROS® methylphenidate were later treated with atomoxetine and placebo for

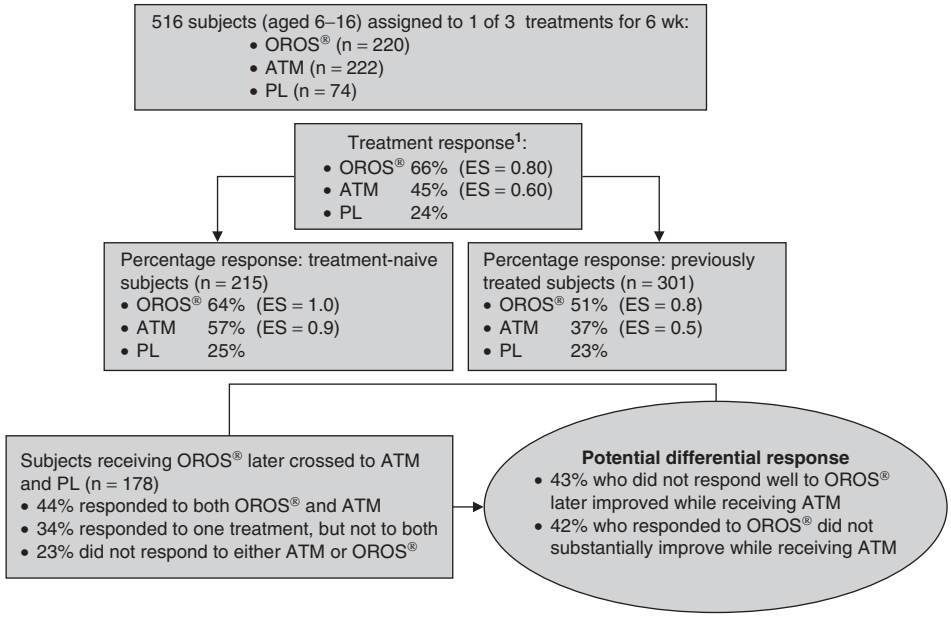

Fig. 1. Response rates and effect sizes (ES; based on Cohen's statistical d) in a 6-week controlled study of atomoxetine (ATM), osmotic-controlled release oral-system methylphenidate (OROS®-MPH) and placebo (PL) treatments.[106] **1** Treatment response is based on the Clinical Global Impression Scale, in which symptom severity was rated as 'borderline ill' or 'not at all ill', as expressed in a percentage.

6 weeks each, some who did not initially respond well to OROS® methylphenidate substantially improved with atomoxetine, as represented in figure 1. Furthermore, a larger than expected subgroup was found who did not respond well to atomoxetine or OROS® methylphenidate, confirming the need to continue the pursuit of novel treatments. As the number of participants in this crossover treatment study was relatively small, controlled replication of these results is needed. Children and adolescents for whom prior ADHD treatments had failed were excluded from study participation, but consideration might be given to their inclusion in future studies, as they may help to identify who might equally or preferentially respond to ADHD treatments.

4.3 Relapse Prevention

There are data indicating that atomoxetine may prevent future relapse of symptoms. After 416 children responded to 12 weeks of open-label atomoxetine treatment, they were treated with atomoxetine (n = 292) or placebo (n = 124) for 34 weeks. After these 34 weeks, the remaining 163 active participants were re-randomized to atomoxetine (n = 81) or placebo treatment (n = 82) for 24 weeks.[107] By study end, the percentage of subjects who at any time experienced ≥90% symptom return (from baseline) was 28% for atomoxetine recipients versus 48% for placebo recipients. Additionally, children treated with atomoxetine in long-term follow-up generally continued at the same level of response for up to 60 months without the need for dose escalation.[108-110]

4.4 Tolerability and Safety Data

Compared with children receiving placebo (n = 434) in four controlled studies, those who took atomoxetine twice daily (n = 715) reported common adverse effects as follows: upset stomach (atomoxetine 10%; placebo 5%), vomiting (11%; 6%), fatigue (8%; 3%), decreased appetite (16%; 4%), abdominal pain (18%; 10%), sleepiness (11%; 4%) and irritability (6%; 3%).[6,99-101] Data from the parallel-group comparison study

indicated that those receiving atomoxetine once daily (vs twice daily) experienced more nausea (13% vs 7%), and while those taking atomoxetine more often reported sleepiness, those treated with OROS® methylphenidate more often reported trouble sleeping. Children taking either active treatment (atomoxetine or OROS® methylphenidate) more frequently complained of a diminished appetite (atomoxetine 14%; OROS® methylphenidate 17%). Both active treatments resulted in an increased pulse rate compared with placebo, with those receiving atomoxetine often having a statistically faster mean pulse rate (increase of 4 beats/minute vs placebo) versus OROS® methylphenidate (increase of 3 beats/minute). Thus, clinicians should monitor vital signs of all patients on ADHD treatment.[6] Recently published data indicated that no new tolerability or safety concerns emerged for adolescents who were treated with atomoxetine for up to 8 years.[31]

A meta-analysis of 16 studies reported age-group differences in the tolerability profile of atomoxetine.[110] Compared with placebo, younger children (aged 6–7 years) were more likely to experience more impairing sedative effects or abdominal pain or upset when treated with atomoxetine. Older children (aged 8–12 years) complained of feeling sleepy or tired, but were more often described as irritable. In both age groups, those taking atomoxetine were more likely than those taking placebo to complain of a diminished appetite, and had a faster pulse rate and increased blood pressure.

As identified in table II, atomoxetine is associated with a warning of a potential rare development or worsening of suicidality during treatment, which is based on a meta-analysis of 14 controlled studies.[111,112] This analysis calculated the risk of experiencing a suicidal-related event while taking atomoxetine to be 0.4% (n = 5/1357) versus 0% (n = 0/851) on placebo.[112] As such, clinicians should closely monitor patients for adverse mood and behavioural changes during treatment, which may be of particular importance for those with co-morbid depression, as a 9-week controlled-study (n = 142) found atomoxetine to substantially improve ADHD symptoms, but not major depressive symptoms.[113]

4.5 Potential Non-Approved Uses of Atomoxetine

Atomoxetine may have utility for some children with certain co-morbid conditions, although it is not approved for these uses. For example, atomoxetine did not aggravate tic severity in a controlled study of ADHD children with Tourette's syndrome (n = 117).[114] In this study, the children receiving atomoxetine had mild gradual improvement in tic severity that was superior to placebo, which suggests that atomoxetine may not necessarily worsen tics of Tourette's syndrome. On the other hand, clinicians should remain cautious, as case reports indicate that atomoxetine may also induce or worsen facial and abdominal tics in some children.[115-118]

Atomoxetine may provide benefit for some children with ADHD with co-morbid anxiety. In a 12-week study of 8- to 17-year-olds (n = 176), atomoxetine was found to be superior to placebo in minimizing symptoms of ADHD as well as symptoms of generalized anxiety, separation anxiety or social phobia.[119] Adults have sometimes reported experiencing a new onset or worsening of anxiety when taking atomoxetine, whereas this is uncommonly reported in children.[8] As such, further data are required to clarify how atomoxetine may impact anxiety throughout a patient's lifespan.

Atomoxetine may also be helpful for oppositional or defiant symptoms.[120-123] In a 6-week study (n = 226), atomoxetine substantially decreased ADHD and ODD symptoms more than placebo.[119] Considering how commonly ODD presents as a co-morbidity with ADHD, further study is suggested that clarifies how such constructs might differentiate ODD from ADHD.

4.6 Clinical Application

While atomoxetine has been associated with a lower effect size than that of stimulant treatments, newer data demonstrate that some children may differentially respond to atomoxetine or stimulant treatment, while others may not respond to either treatment.[105] Unfortunately, we have a limited clinical profile for the type of patient who is more likely to respond well to atomoxetine. As co-morbidity in ADHD paediatric patients is common,

atomoxetine may possibly be useful as a dual treatment, although it is not approved for this use. Atomoxetine has a proven efficacy superior to placebo, with a durable treatment effect that appears to last over years in some children and adolescents.[107-109] Because atomoxetine is not associated with a significant abuse liability, it might prove useful for those with prior stimulant abuse or misuse, while some of those experiencing bothersome adverse effects from stimulant treatment, such as persistent insomnia, may better tolerate atomoxetine.

5. Potential Treatments of Paediatric Attention-Deficit Hyperactivity Disorder: α_2-Adrenoceptor Agonists

An XR formulation of the α_2-adrenoceptor agonist guanfacine[16] is now approved by the FDA in the US to treat paediatric ADHD, and another α_2-adrenoceptor agonist, clonidine,[15] is in development as a potential treatment for paediatric ADHD to offer more convenient once-daily dosing. Both clonidine and guanfacine are approved to treat adult hypertension.[15,16] These agonists stimulate post-synaptic α_2-adrenergic receptors, which are known to be involved in the modulation of attention and behaviour. Whereas clonidine provides general stimulation to α_{2A}-, α_{2B}- and α_{2C}-adrenergic receptors, guanfacine more selectively stimulates the α_{2A}-adrenoceptors.[124-126]

Clonidine has a rapid onset of action (30–60 minutes), an average t_{max} of 3–5 hours and a half-life that varies from 8 to 16 hours. Clonidine is manufactured as scored tablets that come in three dose strengths (0.1–0.3 mg).[15] Also available is a weekly transdermal patch, but clinicians are advised against this off-label use, as no controlled data are available on its use in paediatric ADHD.

5.1 Guanfacine

5.1.1 Guanfacine Immediate Release

Guanfacine has an average t_{max} of 2–3 hours and a plasma half-life that is longer than that of clonidine (10–30 hours).[16,127] Guanfacine is manufactured as 1 and 2 mg scored tablets in bottles of 100 tablets.[16] After several small studies purported guanfacine to have potential use in paediatric ADHD,[128,129] a controlled trial of 34 children and adolescents (aged 7–14 years) with ADHD and co-morbid Tourette's syndrome were treated with placebo or guanfacine (1–3 mg/day).[130] Based on teacher-rated ADHD-RS-IV[68] score reductions of 39% for guanfacine and 8% for placebo, guanfacine was found to be superior to placebo, with response rates of 53% for guanfacine versus 0% for placebo. Tic severity also improved with guanfacine (31%) compared with placebo (0%), which suggested that guanfacine may be useful for treating paediatric ADHD patients with co-morbid tics or Tourette's syndrome. In this study, 41% of subjects had at least some somnolence, which is only slightly less than the amount reported with clonidine. It could be that a slower dose titration may have lessened some of these sedating effects, as a pharmacokinetic study (n = 28) using weekly forced titration found dose-dependent rates of somnolence (89.3%), as well as insomnia (14.3%), blurred vision (7.1%) and headache (7.1%).[130] As such, clinicians should closely monitor for impairing effects and hypotension.

5.1.2 Guanfacine Extended Release

An XR formulation of guanfacine was recently approved on 4 Sep 2009 by the FDA in the US to treat ADHD in 6-17 year olds.[131] Guanfacine XR has a mean half-life of 18 hours in adolescents and 14 hours in children, with steady-state daily plasma concentrations usually reached within 5–7 days when taking 1–4 mg/day.[127]

Two controlled studies of guanfacine XR have been conducted.[132,133] In the first study, 345 children and adolescents (aged 6–17 years) were treated with one of three guanfacine XR doses (2–4 mg/day) or placebo for 8 weeks.[132] In the second study, 324 similar-aged subjects were treated with one of four doses of guanfacine XR (1–4 mg/day) or placebo for 9 weeks.[133] The last 3 weeks in each study were used for downward titration and discontinuation. Based on ADHD-RS-IV[68] change scores at end-of-treatment, both studies demonstrated that guanfacine XR was superior to placebo at all dosages, with resulting dose-based effect sizes ranging from 0.43 to 0.86. Response rates were 43% (3 mg/day)

and 56% (4 mg/day) for guanfacine XR versus 26% and 30% for placebo. Parents of patients participating in the first study reported that beneficial effects of guanfacine XR were noticed within 2–3 weeks of start of treatment and typically lasted 8–14 hours/day.[132] In both studies, the parents of subjects who were taking a higher dose (guanfacine XR 3–4 mg/day) noticed that benefit seemed to last up to 24 hours.[132,133]

When data from the second controlled study of guanfacine XR were stratified by weight, the resulting effect size per dose ranged from 0.41 to 1.34. While younger children (aged 6–8 years) had the greatest benefit, adolescents generally did not respond well in either study, which led investigators to theorize that adolescents may potentially require doses larger than 4 mg/day. Unfortunately, response rates were not reported by age group or weight categories, which may have yielded a better understanding of these data.

After completing these studies, participants in both published studies were offered enrolment in a 24-month extension study. About two-thirds decided to participate, including 446 who had previously participated in a placebo-controlled study and 53 who had been previously treated with open-label guanfacine XR while continuing to take their stimulant medication.[134,135] The mean ADHD-RS-IV total score at baseline was about 40.6 for monotherapy and 29.3 for combination treatment. The average ADHD-RS-IV change score was –20.1 points for monotherapy and –16.2 for combination treatment. This improvement was generally maintained over 8–24 months. At end-of-treatment, the mean ADHD-RS-IV total scores were 19.4 for monotherapy and 13.2 for combination treatment. Mean ADHD-RS-IV change scores (over pre-treatment) ranged from –18.9 to –25.5, with those weighing the least generally taking up to 1 month before responding well to treatment.[134,135]

The long-term adverse-effect profile of guanfacine XR is consistent with that reported during the controlled studies, including the most commonly reported adverse effects of dose-dependent somnolence (30–38%), headache (24–26%), fatigue (14–15%), sedation (13%), upper abdominal pain (11–13%) and lethargy (6%).[134,135] When the adverse effects of somnolence, sedation and fatigue were grouped together, 58.7% of those receiving monotherapy and 11.1% receiving combination therapy experienced at least one sedating effect, which typically began near the start of treatment and lasted intermittently for about 6–7 weeks.

Across both long-term studies,[134,135] seven participants experienced syncope. Several participants had ECG measurement changes, including one who developed sinus arrhythmia; another discontinued the study after developing a non-serious conduction disorder, although this patient had intraventricular delay at baseline. By treatment end, 20 patients had developed bradycardia (heart rate <50 beats/minute) and at least 9 others developed tachycardia (heart rate >100 beats/minute), but all of these cardiac changes either stopped on their own or when guanfacine XR treatment was stopped. None of the patients had a corrected QT interval (QTc) >60 msec above their baseline ECG measurement, a QRS complex of >120 msec or a QTc interval of >500 msec. Overall, the study results suggested that guanfacine XR may maintain efficacy and safety over time.[134,135]

5.2 Clonidine

5.2.1 Efficacy Data

The off-label use of clonidine has primarily been in pill form as an adjunct to enhance stimulant treatment or to treat co-morbid symptoms, such as impulsivity, insomnia or tics. A meta-analysis of 11 early studies calculated clonidine to have an effect size of 0.58, although this analysis combined studies with and without patients with varied co-morbid conditions.[136]

Two similarly designed, well controlled studies have been published on the use of clonidine in paediatric ADHD.[137-139] In the first study,[137] 136 children (aged 7–12 years) with ADHD and co-morbid Tourette's syndrome were randomly assigned to take one of four treatments: clonidine (up to 0.6 mg/day); IR methylphenidate (up to 60 mg/day); clonidine plus methylphenidate in combination; or placebo for 12–16 weeks. Based on the CADS for Teachers,[48] all active treatments

proved superior to placebo in improving ADHD and tic symptoms, while the combination treatment resulted in the greatest benefit. Based on teacher-rated change scores on the Children's Global Assessment Scale, response rates were 88% for the combination, 67% for IR methylphenidate, 56% for clonidine and 31% for placebo. These study investigators suggested that IR methylphenidate was most helpful for improving on-task and inattention, while clonidine seemed helpful for aggression, impulsivity and sleep problems.[137]

The subsequent controlled study[138] enrolled 122 ADHD children (aged 6– 12 years) without tics or other co-morbidity who received one of four of the same treatments (clonidine, IR methylphenidate, clonidine plus methylphenidate, or placebo). In this study, clonidine unfortunately did not prove statistically different from placebo; however, similar to the first study, the combination treatment generally provided a better response in reducing ADHD symptoms than did either active treatment by itself.

A recent study of 50 hospitalized children (aged 4–12 years) conducted in South India compared clonidine with carbamazepine. Children receiving clonidine had greater improvement in their hyperactivity and impulsivity symptoms, but not in symptoms of inattention.

Results of these acute treatment studies support the theory that clonidine may be used most effectively in ADHD as part of a combination treatment, such as when added to stable stimulant treatment.[140]

An XR preparation of clonidine is currently in development for use in paediatric ADHD. At time of writing, an application for marketing approval had been recently submitted to the FDA in the US.[141] In a recently completed but not yet published study, 228 patients (aged 6–17 years) were treated with clonidine XR monotherapy (0.2 mg, 0.4 mg) or placebo for 8 weeks. ADHD-RS-IV change scores demonstrated that clonidine XR was superior to placebo, with the therapeutic effects lasting about 12 hours.[142] A second recently completed, but not yet published, US placebo-controlled phase III study (n = 200) demonstrated that taking clonidine XR 0.1–0.4 mg/day provided more benefit in decreasing ADHD symptoms when taken in combination with stimulant treatment than taking stimulant monotherapy.[143]

5.2.2 Tolerability Data

An early meta-analysis of open-label and controlled studies reported that the most common adverse effects in children treated with clonidine were sedating effects, mood-related effects (nervousness, irritability, apathy) and hypotensive effects (small pulse and orthostatic blood pressure decreases).[144] Data from the controlled study of ADHD children without co-morbid conditions supported this earlier-described tolerability, including frequent sedating effects, such as somnolence (42%) and fatigue (32%), which often lasted 6–8 weeks, as presented in table V.[138,139] The children treated with the combination of clonidine plus methylphenidate had less impairing somnolence than those receiving clonidine, suggesting that IR methylphenidate may shield children from becoming as tired or sleepy as those treated with clonidine alone. The combined group of children receiving clonidine or the combination treatments gained weight (mean: 1.3 kg) and had lower than usual heart rates and small orthostatic blood pressure changes, with a greater difference between supine and standing systolic blood pressure over time than in those not receiving clonidine. No clinically important ECG changes or cardiovascular problems were reported in this study.

6. Summary and Conclusions

In this article, the data for the efficacy and tolerability of five novel, recently approved treatments for paediatric ADHD have been considered, along with one treatment this is currently under review by the FDA. Because paediatric patients sometimes remain on treatment for a long time, it is important to better understand the long-term effectiveness and safety of ADHD treatments taken over several years, including potential psychiatric and general medical outcomes over time.

For each reviewed treatment, there are data providing evidence of an effective response compared with placebo. Cost effectiveness of treatment

Table V. Most common adverse effects and physiological changes[a] associated with 16 weeks' treatment of paediatric attention-deficit hyperactivity disorder (n = 122)[139]

Parameter	CLN (n = 31)	COMB (n = 32)	MPH-IR (n = 29)	PL (n = 30)
Adverse effect (%)				
Nervousness	32.3	31.3	17.2	13.3
Somnolence	41.9	34.4	6.9	6.7
Apathy	32.3	18.8	13.8	16.7
Depression	22.6	12.5	17.2	20.0
Upset stomach	19.4	15.6	24.1	13.3
Sleep difficulty	16.1	12.5	3.4	16.7
Fatigue	22.6	15.6	0.0	10.0
Headache	16.1	15.6	3.4	10.0
Heart rate <60 bpm	22.6	12.5	3.5	3.3
Physiological change (over pre-treatment) [mean ± SD]				
Heart rate (bpm)	−6.8 ± 15.4	−1.6 ± 10.8	−0.3 ± 10.3	−1.2 ± 7.3
Standing systolic BP (mmHg)	−4.5 ± 10.9	2.0 ± 15.5	−0.5 ± 9.5	0.1 ± 8.6
Standing diastolic BP (mmHg)	−1.7 ± 8.7	−1.4 ± 8.5	0.1 ± 10.3	0.3 ± 6.3
Postural systolic BP[b] (mmHg)	3.5 ± 10.9	0.8 ± 12.7	−0.6 ± 8.3	−2.1 ± 7.8
Postural diastolic BP[b] (mmHg)	0.5 ± 10.3	2.4 ± 9.1	−2.2 ± 11.7	−1.6 ± 7.6
Body weight (kg)	2.0 ± 2.9	0.6 ± 2.3	0.3 ± 2.3	1.4 ± 1.6

a Adverse effects and physiological changes listed if occurred in at least 5% of patients within one or more treatment groups.

b Postural BP is change in BP from supine to standing position over baseline.

BP = blood pressure; **bpm** = beats per minute; **CLN** = clonidine; **COMB** = clonidine plus immediate release methylphenidate; **MPH-IR** = immediate release methylphenidate; **PL** = placebo.

is an important consideration. Cost analyses have found that approved ADHD treatments generally produce a similar efficacy, regardless of preparation or formulation. Therefore, IR formulations have been considered as providing the most cost savings, considering that 2008 wholesale costs of IR preparations were about $US100/month or less for two- or three-times-daily dosing versus $US200–500/month for once-daily XR formulations.[145-149]

Achieving remission rather than response has become standard clinical care, yet most controlled studies discussed in this review limited their report to that of response.[150] Few studies have compared the effectiveness of long-acting ADHD treatment in terms of quality of life and even fewer studies have compared across treatments.[151-154] Several studies that compared ADHD and healthy children and adolescents have found that most of those treated for ADHD still fare worse than healthy individuals on quality-of-life indicators, such as self-esteem, emotional behaviour and family cohesion.[155,156] As such, the choice of pharmacotherapy should be based on the individual's clinical profile with consideration of factors such as the extent of effectiveness and residual symptoms, presence and severity of co-morbidity (including substance misuse or abuse), history of treatment-related adverse effects, non-compliance with multiple daily dosing, need to avoid trough concentration fluctuations and subsequent impairment, family preference and financial considerations.[157-159]

The α_2-adrenoceptor agonist, guanfacine as an XR formulation was recently approved by the FDA in the US to treat paediatric ADHD, while another α_2-adrenoceptor agonist, clonidine, is currently under review at the FDA. IR clonidine has a fast onset and short half-life, and did not improve inattention well in early studies.[137,138] Its manufacturer recently announced the completion of studies in which clonidine XR proved useful as monotherapy and also in combination to extend benefit when taken with a stimulant.

Guanfacine has more specific neuronal actions, is longer acting than clonidine and has had success in improving ADHD symptoms; however, more data are needed regarding its tolerability, particularly as it has high rates of sedating effects compared with other approved treatments.[131-133,160] Further data are also needed about its weight-based dosing effect in relation to a stimulant-treated reference group.

These pharmacological developments provide additional treatment options for ADHD children and adolescents, with ongoing work towards additional novel interventions of paediatric ADHD.

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