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PSYCHOPHARMACOLOGY

Focus on Guanfacine Extended-release: A Review of its Use in Child and Adolescent Psychiatry

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Abstract

Objective: To review the basic pharmacology and published literature regarding use of guanfacine extended-release (GXR) for the treatment of attention deficit/hyperactivity disorder in children and adolescents. **Methods:** A literature review was conducted using the search terms: 'guanfacine', with limits set to: Human trials, English Language, and All Child (Age 0-18). Articles pertaining to guanfacine immediate-release or for indications other than attention deficit/hyperactivity disorder (ADHD) were not included for analysis. Additional articles were identified from reference information and poster presentation data. **Results:** Six prospective, randomized controlled trials (RCT) and four open-label trials (including two long-term safety extension trials) were identified for GXR in the treatment of ADHD. All published RCTs showed superiority over placebo on the primary outcome measure. Subgroup analysis of available RCT data showed no efficacy of GXR at any dose in adolescents. Adverse effects in GXR trials were generally mild to moderate. High rates of early discontinuation were observed in long-term open-label extension trials. **Conclusion:** GXR is an effective option for treatment of ADHD in patients 6-12 years of age as monotherapy, or as adjunctive treatment to psychostimulants.

Key Words: *guanfacine, alpha$_2$-agonist, ADHD, child, adolescent*

Résumé

Objectif: Effectuer une revue de la pharmacologie de base et de la littérature publiée sur l'utilisation de la guanfacine à action prolongée (GXR) pour le traitement du trouble de déficit de l'attention avec hyperactivité (TDAH) chez les enfants et les adolescents. **Méthodes:** Une revue de la littérature a été menée à l'aide des mots clés « guanfacine »', et des limites suivantes: essais sur des humains, langue anglaise, et tous les enfants (0-18 ans). Les articles traitant de la guanfacine à action immédiate ou pour indications autres que le TDAH n'ont pas été inclus dans l'analyse. Les articles additionnels ont été repérés dans des bibliographies et les données de présentations par affiches. **Résultats:** Six essais randomisés contrôlés (ERC) prospectifs, et quatre essais ouverts (y compris deux essais prolongés d'innocuité à long terme) ont été retenus pour la GXR dans le traitement du TDAH. Tous les ERC publiés montraient la supériorité sur le placebo à la première mesure du résultat. L'analyse par sous-groupe des données d'ERC disponibles n'indiquait aucune efficacité de la GXR à n'importe quelle dose chez les adolescents. Les effets indésirables des essais de la GXR étaient généralement de faibles à modérés. Des taux élevés d'interruption précoce ont été observés dans les essais ouverts prolongés du long terme. **Conclusion:** La GXR est une option efficace de monothérapie pour le traitement du TDAH chez les patients de 6 à 12 ans, ou comme traitement d'appoint des psychostimulants.

Mots clés: *guanfacine, agoniste alpha2, TDAH, enfant, adolescent*

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Introduction

While psychostimulant medications have large effect sizes for treatment of attention deficit/hyperactivity disorder (ADHD) symptoms (Banaschewski et al., 2006; Pringsheim & Steeves, 2011), and are the most commonly prescribed class of medications for ADHD, in approximately 25-30% of patients, ADHD symptoms are not adequately controlled by psychostimulant monotherapy (The MTA Cooperative Group, 1999). Additionally, some children and adolescents may not tolerate either of the two main classes of psychostimulants (methylphenidate and amphetamine based treatments), or there may be concurrent substance use disorder or drug diversion concerns that preclude stimulant prescription. In some cases, patients or caregivers may simply prefer use of a non-stimulant medication.

Guanfacine extended-release (Intuniv XR®, GXR) is a novel formulation of an alpha$_{2A}$-agonist which recently received Health Canada approval for the treatment of ADHD in children 6-12 years of age as adjunctive therapy to stimulants or monotherapy (Shire Canada Inc., 2013). The GXR formulation has been available in the United States since 2009 (Shire Pharmaceuticals, 2013), and is approved by the United States Food and Drug Administration (FDA) for treatment of ADHD in patients 6-17 years of age as adjunctive therapy to stimulants or monotherapy (Shire Pharmaceuticals, 2013). Guanfacine was originally approved by the FDA for treatment of hypertension, and has been available in the United States as an immediate-release (IR) tablet (Tenex®) since 1986 (Shire Pharmaceuticals, 2013) but has not been approved for use in Canada previously. Guanfacine is an agonist at alpha$_{2A}$-adrenergic receptors which are heavily concentrated in the prefrontal cortex and the locus coeruleus. Its beneficial actions are likely due to its ability to strengthen prefrontal cortical network connections for the regulation of attention, emotion and behavior through actions at post-synaptic alpha$_{2A}$ receptors.

At the British Columbia Children's Hospital Children's and Women's Mental Health Programs, inpatient utilization of the non-selective alpha$_2$-agonist clonidine has increased approximately 11-fold from fiscal year 2008/09 to 2012/13 (D. Elbe, personal communication, November 7, 2013). Possible reasons for this observed increase include: a resurgence in interest regarding IR non-selective alpha$_2$-agonist clonidine following the approvals of clonidine extended-release and GXR in the United States in 2009; recent publication of RCTs demonstrating benefit with clonidine extended-release and GXR in child and adolescent psychopharmacology journals; increased awareness and recognition of the adverse metabolic effects of second generation antipsychotics; and, the potential for additional benefits from alpha$_2$-agonist therapy in treatment of comorbid conditions to ADHD, such as insomnia (Kratochvil, Lake, Pliszka, & Walkup, 2005) oppositional defiant disorder (Hazell & Stuart, 2003), conduct disorder (Hazell & Stuart, 2003), tic disorders (Scahill et al., 2001) and irritability of autism (Jaselskis, Cook, Fletcher, & Leventhal, 1992). Until GXR was marketed in Canada in November 2013, IR clonidine was the only available alpha$_2$-agonist in Canada. For treatment of ADHD (an off-label indication), IR clonidine is often required to be administered three to four times daily. Such a dosing schedule is often difficult for patients and families to adhere to consistently, which is cause for concern as there is a risk for rebound hypertension to occur following abrupt cessation of clonidine therapy (Geyskes, Boer, & Dorhout Mees, 1979). The sedative and hypotensive effects of clonidine may also be dose-limiting in some children.

Pharmacology

The GXR tablet is formulated as a once-daily extended release matrix tablet (Cruz, 2010).It should be swallowed whole and not be split, crushed or chewed, as this will increase the rate of guanfacine release (Shire Canada Inc., 2013). Guanfacine is well absorbed from the GXR tablet following an oral dose (Bukstein & Head, 2012; Lexi-Comp Online™, 2013). After oral administration, the time to peak plasma concentration is approximately five hours in children and adolescents with ADHD (Bukstein & Head, 2012; Lexi-Comp Online™, 2013). Exposure to guanfacine from GXR tablets is significantly affected by food intake, with a 75% increase in peak plasma concentrations (Cmax) and 40% increase in area under the plasma concentration-time curve (AUC) when administered with a high-fat breakfast (Bukstein & Head, 2012). Administration with a high-fat meal should be avoided (Shire Canada Inc., 2013).

In plasma, guanfacine is approximately 70% bound to plasma proteins (Bukstein & Head, 2012; Lexi-Comp Online™, 2013). Guanfacine is primarily metabolized by hepatic cytochrome p450 (CYP) 3A4 microsomal enzymes, and exposure to guanfacine may potentially be increased by concurrent use of CYP 3A4 inhibitors (e.g. clarithromycin, fluvoxamine, itraconazole, grapefruit juice) or decreased by concurrent use of CYP 3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's Wort) (Bukstein & Head, 2012; Lexi-Comp Online™, 2013). Guanfacine does not inhibit or induce CYP enzymes (Bukstein & Head, 2012; Lexi-Comp Online™, 2013). The elimination half-life of guanfacine following GXR administration is 16-17 hours (Cruz, 2010; Lexi-Comp Online™, 2013) which permits once daily administration of GXR. Fifty percent of an administered GXR dose is excreted unchanged in the urine (Cruz 2010; Lexi-Comp Online™, 2013).

Pharmacokinetics of guanfacine in children and adolescents are linear (first-order) and dose proportional (Bukstein & Head, 2012). The pharmacokinetics following administration of GXR differs from those with guanfacine IR tablets with GXR resulting in 60% lower Cmax and up to 43% lower AUC compared to IR tablets (Bukstein & Head, 2012). The relative bioavailability of guanfacine from the

GXR tablet is approximately 58% compared to the IR formulation (Bukstein & Head, 2012), therefore the extended-release and IR formulations of guanfacine are considered non-interchangeable. With equal doses of GXR, children attain lower plasma concentrations compared to adolescents, a difference most likely attributable to lower body weight in children (Bukstein & Head, 2012).

Guanfacine is a selective alpha$_2$-agonist that shares some pharmacological properties with the non-selective alpha$_2$-agonist clonidine. It has 15 to 20 times higher affinity for alpha$_{2A}$-adrenergic receptors than for the alpha$_{2B}$ or alpha$_{2C}$ subtypes (Newcorn et al., 1999; Bukstein & Head, 2012). This selectivity may be the basis for reduced rates of sedation, hypotension and dizziness compared with clonidine. Guanfacine does not have central nervous system stimulant properties (Lexi-Comp Online™, 2013).

Guanfacine reduces sympathetic nerve impulses, resulting in reduced sympathetic outflow and a subsequent decrease in vasomotor tone and heart rate. In addition, guanfacine preferentially binds to postsynaptic alpha2A-adrenoreceptors in the prefrontal cortex and has been theorized to improve delay-related firing of prefrontal cortex neurons. As a result, underlying working memory and behavioral inhibition are affected; thereby improving symptoms associated with ADHD (Lexi-Comp Online™, 2013). Like norepinephrine, guanfacine acts at alpha$_{2A}$-receptors in the cortex to enhance the signal-to-noise ratio from environmental stimuli and may improve the ability to focus on a particular stimulus "above the noise" during periods of low arousal (Stahl, 2008).

Efficacy data

A review of the literature was conducted using the MEDLine search term: 'guanfacine' with limits: Human trials, English language, All Child (aged 0-18 years). Articles pertaining to the IR formulation of guanfacine were not included for analysis. Additional articles were identified from reference information and poster presentation data. Table 1 summarizes the published RCT and open-label trial literature pertaining to GXR. No head-to-head trials of GXR and clonidine IR were identified.

Six prospective RCTs were found for GXR in the treatment of ADHD. Biederman et al. (2008a) studied 345 children 6-17 years of age with a diagnosis of ADHD. Patients were randomly assigned to one of three treatment groups (GXR 2, 3 or 4 mg daily, fixed-dosage escalation) or placebo for eight weeks. The primary outcome measurement was the reduction in the ADHD Rating Scale IV (ADHD-RS-IV) total score at the last observed week of dose escalation period. Scoring and clinical relevance of the ADHD-RS-IV are discussed elsewhere (DuPaul, Power, Anastopoulos, & Reid, 1998; Goodman et al., 2010). Secondary measurements included Clinical Global Impression of Improvement (CGI-I), Parent's Global Assessment (PGA), Conners' Parent Rating Scale–Revised: Short Form (CPRS-R), and Conners' Teacher Rating Scale–Revised: Short Form (CTRS-R). All three treatment groups had significant reductions in ADHD-RS-IV scores compared to placebo, with primary outcome measure effect sizes (Cohen's *d)* ranging from 0.64-0.86 (Biederman et al., 2008a). Separation from placebo was first observed starting at week 2 of the dose titration phase for GXR 2 mg/day, and starting at week 3 for GXR 3 and 4 mg/day (Biederman et al., 2008a). Improvements were observed for all active treatment groups compared to placebo on all secondary outcome measures at study endpoint (Biederman et al., 2008a). The proportion of patients in this study representing the adolescent age cohort of 13-17 years of age was small, at 23.2% (Biederman et al., 2008a). Post-hoc subgroup analyses showed that children 6-8 years of age and children 9-12 years of age who received GXR (all doses) showed statistically significant improvement compared to patients receiving placebo, whereas this was not the case in children 13-17 years of age (Biederman et al., 2008a).

Sallee et al. (2009a) studied 322 children 6-17 years of age with a diagnosis of ADHD. Patients were randomly assigned to one of four treatment groups (GXR 1, 2, 3 or 4 mg/day, fixed-dosage escalation) or placebo in a trial of nine weeks duration. The primary outcome measurement was the reduction in the ADHD-RS-IV total score from baseline to endpoint (defined as the last post-randomization treatment week of the double-blind treatment period for which a valid ADHD-RS-IV score was obtained). Secondary measurements included CGI-I, PGA and CPRS-R. All four treatment groups had significant reductions in ADHD-RS-IV scores compared to placebo, with primary outcome measure effect sizes (Cohen's *d)* ranging from 0.43-0.62 (Sallee et al., 2009a). Separation from placebo was first observed starting at week 1 for GXR 1 mg/day and 4 mg/day groups (when all active treatment patients were receiving GXR 1 mg/day), and week 2 for the GXR 2 mg/day and 3 mg/day groups (Sallee et al., 2009a). Improvements were observed for all active treatment groups compared to placebo on all secondary outcome measures at study endpoint (Sallee et al., 2009a). The proportion of patients representing the adolescent age cohort of 13-17 years of age in this study was small, at 25% (Sallee et al., 2009a). Subgroup analysis showed that children 6-12 years of age who received GXR (all doses) showed statistically significant improvement compared to those receiving placebo, whereas this was not the case in children aged 13-17 years of age. However, the study was not powered to make statistical comparisons between subgroups (Sallee et al., 2009a).

Connor et al. (2010) studied 217 children 6-12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms. Patients were randomly assigned in a 2:1 ratio to treatment with flexibly-dosed GXR 1-4 mg daily (mean: 2.87 mg/day) or placebo in a trial of nine weeks duration. The primary outcome measure was change in the

oppositional subscale of the CPRS-R Long Form (CPRS-R:L) from baseline to endpoint (defined as the last post-randomization treatment week of the double-blind treatment period for which a valid score was obtained). Change in ADHD-RS-IV score from baseline to endpoint was a secondary outcome measure. Compared to those receiving placebo, patients receiving GXR had a significant mean reduction in CPRS-R:L oppositional subscale score compared to placebo, with an effect size (Cohen's *d)* of 0.59 (Connor et al., 2010). Separation from placebo was observed starting at week 3 of the dose titration phase (second post-baseline assessment) for GXR and persisted throughout the dose titration and dose maintenance periods (until week 8 of the trial) (Connor et al., 2010). The GXR treatment group also had a significant mean reduction in ADHD-RS-IV scores compared to placebo, with an effect size (Cohen's *d)* of 0.92 (Connor et al., 2010). A post-hoc correlation analysis determined that the reduction in the CPRS-R:L oppositional subscale scores and the ADHD-RS-IV scores were highly correlated (r=0.74) (Connor et al., 2010).

Kollins et al. (2011) studied 182 children 6-17 years of age with a diagnosis of ADHD in a non-inferiority safety study of psychomotor function, alertness and daytime sleepiness in a laboratory classroom. Patients were randomly assigned to treatment with flexibly-dosed GXR 1-3 mg daily (mean optimal daily dose: 2.45 mg/day, mean weight adjusted dose optimal dose of GXR: 0.052 mg/kg/day) or placebo in a trial of nine weeks duration.

The primary safety outcome was reaction time as measured by the Choice Reaction Time (CRT) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CRT results and other safety measures are discussed below. Efficacy outcome measures included the change from baseline to endpoint on the ADHD-RS-IV, the dichotomized CGI-I (where CGI-I scores of 1 or 2 = improved, and CGI-I scores of 3 or higher = not improved), and the Permanent Product Measurement of Performance (PERMP). Patients treated with optimally dosed GXR did not experience a significant mean reduction in CRT compared to patients receiving placebo (Kollins et al., 2011) or other safety measures despite spontaneously self-reported rates of (combined) sedation, somnolence or hypersomnia of 47.8% of the GXR treatment group, compared to 28.1% of patients receiving placebo (Kollins et al., 2011). In terms of efficacy measures, patients receiving GXR had a significant mean reduction in ADHD-RS-IV scores from baseline to endpoint compared to placebo, and significantly more patients receiving GXR were rated as improved (56.8%) compared to patients receiving placebo (35.1%)c (Kollins et al., 2011). Separation from placebo was observed starting at visit 2 (first post-baseline visit) (Kollins et al., 2011). For the PERMP, significant greater improvement was observed with GXR treatment compared to placebo only at visits 2 and 3 (first and second post-baseline visit) (Kollins et al., 2011). Neither a breakdown of the relative proportion of children 13-17 years of age, nor an age-based cohort subgroup data analysis was provided (Kollins et al., 2011).

Wilens et al. (2012) studied 461 children 6-17 years of age with a diagnosis of ADHD and partial but suboptimal response to psychostimulant monotherapy. Patients were randomly assigned to one of three treatment groups (flexibly dosed GXR up to 4 mg/day administered in the morning (GXR-AM, mean: 3.3 mg/day), evening (GXR-PM, mean: 3.2 mg/day) or placebo for eight weeks, taken adjunctively to a previously established regimen of a long-acting psychostimulant (methylphenidate (53% of patients) or amphetamine (47% of patients) class) at a dose in keeping with the FDA-approved package insert for the particular stimulant. The primary outcome measurement was the reduction in ADHD-RS-IV total score at the last observed week of dose escalation period. Secondary outcome measurements included the CGI-I. The study was not designed or powered to make statistical comparisons between GXR treatment groups. Both the GXR-AM and GXR-PM treatment groups had significant reductions in ADHD-RS-IV scores compared to placebo, with primary outcome measure effect sizes (Cohen's *d)* ranging from 0.38 for GXR-AM to 0.45 for GXR-PM (Wilens et al., 2012). Separation from placebo was observed starting at visit 4 (second post-baseline visit) of the dose titration phase and onwards for the GXR-PM group, and at visit 5 (third post-baseline visit) and then visit 7 (fifth post-baseline visit) onwards for the GXR-AM group (Wilens et al., 2012). A significantly greater proportion of patients had CGI-I scores of 2 or less (much improved or very much improved) in both the GXR-AM (70.5%) and GXR-PM (74.3%) treatment groups compared to placebo (57.9%) (Wilens et al., 2012). The proportion of patients representing the adolescent age cohort of 13-17 years of age in this study was small, at 21% (Wilens et al., 2012). However, an age-based cohort subgroup data analysis was not provided (Wilens et al., 2012).

Newcorn et al. (2013) studied 333 children 6-12 years of age with a diagnosis of ADHD in a multi-center RCT. Patients were randomly assigned to one of three treatment groups (flexibly dosed GXR up to 4 mg/day administered in the morning (GXR-AM, mean: 2.9 mg/day), evening (GXR-PM, mean: 3 mg/day) or placebo for eight weeks. The primary outcome measurement was the reduction in the ADHD-RS-IV total score from baseline to week 8. The study was not designed or powered to make statistical comparisons between GXR treatment groups. Both the GXR-AM and GXR-PM treatment groups had significant reductions in ADHD-RS-IV scores compared to placebo, with primary outcome measure effect sizes (Cohen's *d)* of 0.75 for GXR-AM and 0.78 for GXR-PM (Newcorn et al., 2013). Separation from placebo was first observed for both GXR-AM and GXR-PM treatment groups starting at visit 3 (first post-baseline visit) (Newcorn et al., 2013).

Table 1 Review of guanfacine XR (GXR) trials involving children and adolescents

Year; Lead Author; Journal	# of pts; % ♂; Age (years)	Diagnosis	Drug/Dose; Design; Duration	Efficacy results **(bold=primary outcome measure(s))**	Adverse effects
2008a; Biederman; Pediatrics	n=345; 75% ♂; mean age: 10.5 (range 6-17)	ADHD-CT: 72% ADHD-IA: 26% ADHD-HI: 2%	GXR 2-4 mg/day vs PL; Prospective **RCT**, monotherapy, fixed dose escalation; 8 weeks	**ADHD-RS-IV†:** **GXR2: -16.18**, GXR3: -16.43**** **GXR4: -18.87**, PL: - 8.48** **Primary outcome effect size (*d*):** **GXR2: 0.64, GXR3: 0.66** **GXR4: 0.86** Responders: (30% ↓ ADHD-RS-IV and CGI-I ≤ 2): GXR2: 56%, GXR3: 50% GXR4: 56%, PL: 26% PGA: ('significant improvement') GXR2: 62%, GXR3: 51% GXR4: 66%, PL: 23% CPRS-R†: (placebo adjusted) GXR2: -6.55, GXR3: -7.36 GXR4: -12.7 CTRS-R†: (placebo adjusted) GXR2: -11.57, GXR3: -13.48 GXR4: -12.53	(% above PL): somnolence (18-30%), fatigue (10-15%), sedation (5-11%), abdominal pain (4-9%), appetite decrease (3-6%), dizziness (2-7%), lethargy (2-5%), dry mouth (1-7%)
2009a; Sallee; J Am Acad Child Adolesc Psychiatry	n=322; 72% ♂; mean age: 11 (range 6-17)	ADHD-CT: 73% ADHD-IA: 26% ADHD-HI: 2%	GXR 1-4 mg/day vs PL; Prospective **RCT**, monotherapy, fixed dose escalation (1 mg group restricted to pts < 50 kg only); 9 weeks	**ADHD-RS-IV†:** **GXR1: -20.4**, GXR2: -18**** **GXR3: -19.4**, GXR4: -20.9** PL: -12.2** **subgroup analysis: benefit seen only in pts 6-12 years of age** **Primary outcome effect size (*d*):** **GXR1: 0.53, GXR2: 0.43** **GXR3: 0.58, GXR4: 0.62** % of pts with CGI-I ≤ 2: GXR1: 54% GXR2: 43% GXR3: 55% GXR4: 56% PL: 30% PGA: ('improvement') GXR1: 51% GXR2: 36% GXR3: 62% GXR4: 57% PL: 30% CPRS-R†: (placebo adjusted) GXR1: -12.8 at 8 hours GXR2: -9 at 8 hours GXR3: -9.6 at up to 12 hours GXR4: -7.5 at up to 12 hours	(% above PL): somnolence (15%), headache (10%), fatigue (6%), nausea (3%), vomiting (3%), sedation (1%), irritability (1%)

2010; Connor; CNS Drugs	n=217; 69% ♂; mean age: 9.4 (range 6-12)	ADHD-CT: 84% ADHD-IA: 13% ADHD-HI: 3% Oppositional symptoms (per CPRS-R:L) present in all pts	GXR 1-4 mg/day (mean: 2.87 mg/day) vs PL; Prospective **RCT**, monotherapy, flexible dose; 9 weeks	**CPRS-R:L (oppositional subscale)†:** **GXR (all doses): -10.9** PL: -6.8** **Primary outcome effect size (*d*):** **GXR (all doses): 0.59** ADHD-RS-IV†: GXR (all doses): -23.8 PL: -11.5	(% above PL): somnolence (46%), sedation (12%), upper abdominal pain (9%), fatigue (6%), irritability (5%), decreased DBP (5%), headache (4%) No serious QTc abnormalities noted with GXR treatment. One subject discontinued treatment following bradycardia, hypotension and sinus arrhythmia.
2011; Kollins; J Child Adolesc Psychopharmacol	n=182; 70% ♂; mean age: 12.6 (range 6-17)	ADHD-CT: 75% ADHD-IA: 24% ADHD-HI: 2%	GXR 1-3 mg/day (mean: 2.46 mg/day) vs PL; Prospective **RCT** non-inferiority safety study, monotherapy, flexible dose; 6 weeks	ADHD-RS-IV†: GXR (all doses): -18 PL: -11.9 % of pts with CGI-I ≤ 2: GXR (all doses): 57% PL: 35% PERMP†: (placebo adjusted): GXR (all doses): week 2: -22.1 week 3: -36.5 other weeks: non-significant differences	(% above PL): somnolence (19%), headahce (6%), abdominal pain (5%), sedation (2%) No significant effects on reaction time, strategy/working memory, DSST, subjective sleepiness at endpoint
2012; Wilens; J Am Acad Child Adolesc Psychiatry	n=461; 72% ♂; mean age: 10.8 (range: 6-17)	ADHD (subtype distribution not specified) with partial response to long-acting stimulant therapy	GXR-AM (1-4 mg/day) (mean 3.3 mg/day) or GXR-PM (1-4 mg/day) (mean 3.2 mg/day) vs PL; Prospective **RCT**, adjunct to long-acting stimulant (AMP or MPH based regimen), flexible dose; 9 weeks	**ADHD-RS-IV†:** **GXR-AM: -20.3** GXR-PM: -21.1**** **PL: -15.8** **Primary outcome effect size (*d*):** **GXR-AM: 0.377 GXR-PM: 0.447** % of pts with CGI-I ≤ 2: GXR-AM:71% GXR-PM:74% PL:58%	(% above PL): GXR-AM: somnolence (9%), fatigue (9%), headache (8%), dizziness (6%), abdominal pain (6%) GXR-PM: somnolence (9%), insomnia (8%), headache (8%), abdominal pain (7%), fatigue (5%) 1 pt had serious syncopal episode
2013; Newcorn; J Am Acad Child Adol Psychiatry;	n=333; 71% ♂; mean age: 9.1 (range: 6-12)	ADHD (subtype distribution not specified)	GXR-AM (1-4 mg/day) or GXR-PM (1-4 mg/day) vs PL; Prospective **RCT**, monotherapy, dose-optimization design; 8 weeks	**ADHD-RS-IV†:** **GXR-AM: -19.8** GXR-PM: -20.1**** **PL: -11** **Primary outcome effect size (*d*):** **GXR-AM: 0.75, GXR-PM: 0.78** % of pts with CGI-I ≤ 2: GXR-AM: 66.3% GXR-PM: 67% PL: 31.8%	(% above PL): GXR-AM: somnolence (34%), sedation (11%), fatigue (8%), headache (7%), nausea (5%), vomiting (5%), irritability (5%), syncope (1%) GXR-PM: somnolence (30%), sedation (12%), abdominal pain (10.5%), fatigue (9%), headache (5%), syncope (1%), suicidal ideation (1%)

Table 1 (continued)

Year; Lead Author; Journal	# of pts; % ♂; Age (years)	Diagnosis	Drug/Dose; Design; Duration	Efficacy results **(bold=primary outcome measure(s))**	Adverse effects
2007; Boellner; Pharmacother	n=28; 68% ♂; mean age: 11.8 (range: 7-16)	ADHD (subtype distribution not specified)	GXR 2-4 mg/day; open-label safety and pharmacokinetic dose-escalation study, montherapy; 4 weeks	No efficacy outcomes studied	Somnolence (89%), insomnia (14%), headache (7%), blurred vision (7%), alteration in mood (7%)
2008b; Biederman; CNS Spectr	n=240; 77% ♂; mean age: 10.5	ADHD-CT: 73% ADHD-IA: 26% ADHD-HI: 1%	GXR 2-4 mg/day; open-label safety extension of Biederman 2008 GXR RCT, monotherapy; 52-104 weeks	ADHD-RS-IV†: GXR (all doses): -18.1 (compared to RCT baseline values) benefits observed in children and adolescent age groups PGA: GXR (all doses): 58.6% 'improved' CHQ-PF50: physical summary scores: 'not improved' psychosocial summary scores: 'improved'	Somnolence (30%), headache (26%), fatigue (14%), sedation (13%), cough (12%), abdominal pain (11%), pharyngitis (10%), weight increased (9%), pyrexia (8%), vomiting (8%), nasopharyngitis (8%), dizziness (7%), nasal congestion (6%), lethargy (6%), nausea (6%), irritability (5%), insomnia (5%)
2009; Spencer; J Child Adolesc Psychopharmacol	n=75; 73% ♂; mean age: 11.4 (range: 6-17)	ADHD-CT: 75% ADHD-IA: 21% ADHD-HI: 4%	GXR (1-4 mg/day) (mean); open-label safety study, adjunctive to stimulants (AMP or MPH based regimen), dose-optimization design; 9 weeks	ADHD-RS-IV†: GXR+AMP: -13.8 GXR+MPH: -17.8 % of pts with CGI-I ≤ 2: GXR (all pts): 73% PGA: ('much or very much improved'): GXR (all pts): 84% CPRS-R:S:†: GXR (all pts): mean day total score: -19.8 CHQ-PF50: GXR (all pts): physical summary scores: 'not improved' psychosocial summary scores: 'improved'	GXR+AMP: Irritability (33%), nausea (27%), somnolence (24%), headache (21%), fatigue (18%), insomnia (12%), anxiety (9%), depressed mood (9%), sedation (6%), appetite increased (6%) GXR+MPH: Fatigue (28%), abdominal pain (24%), headache (19%), somnolence (14%), irritability (14%), insomnia (14%), nausea (7%), anorexia (7%), social avoidant behavior (7%). One pt experienced severe fatigue, distored equilibrium, fatigue and fecal incontinence resulting in discontinuation.

2009b; Sallee; J Child Adolesc Psychopharmacol	n=259; 73% ♂; mean age: 10.7 (range 6-17)	ADHD-CT: 73% ADHD-IA: 24% ADHD-HI: 3%	GXR 1-4 mg/day; open-label safety extension of Sallee 2008 GXR RCT or Spencer 2008 open-label trial, flexible-dose, stimulant therapy allowed; 104 weeks	ADHD-RS-IV†: GXR monotherapy (all doses): -21.2 GXR plus stimulant (all doses): -16.1 % of pts with CGI-I ≤ 2: GXR (all conditions): 58% PGA: ('much or very much improved') GXR (all conditions): 60% CPRS-R†: GXR (all conditions):-18.2 CHQ-PF50: GXR (all conditions): physical summary scores: 'not improved' psychosocial summary scores: 'improved'	Monotherapy group: somnolence (38%), headache (25%), URTI (16%), fatigue (15%), nasopharyngitis (14%), sedation (13%), abdominal pain (12%), hypotension (5%) GXR plus stimulant group: URTI (25%), headache (23%), nasopharyngitis (15%), abdominal pain (15%), irritability (13%), decreased appetite (13%), pharyngitis (11%), hypotension (5%)

Abbreviations

ADHD-CT: ADHD, combined subtype, ADHD-HI: ADHD, hyperactive/impulsive subtype, ADHD-IA: ADHD, inattentive subtype AMP=amphetamine and derivatives

DBP=Diastolic Blood Pressure GXR=Guanfacine XR GXR-AM=Guanfacine XR given in the morning GXR-PM=Guanfacine XR given in the evening

MPH=methylphenidate and derivatives ODD=Oppositional Defiant Disorder PL=placebo pt=patient RCT=Randomized Controlled Trial vs=versus

♂ = male †=negative score denotes improvement **=statistically significant result (primary outcome measure only)

Abbreviations of Rating Scales used

ADHD-RS-IV: Attention Deficit/Hyperactivity Disorder Rating Scale version 4

CHQ-PF50: Child Health Questionnaire-Parent Form 50

CGI-I: Clinical Global Impression: Improvement

CPRS-R: Conners' Parent Rating Scale-Revised

CPRS-R:L: Conners' Parent Rating Scale-Revised:Long Form

CPRS-R:S: Conners' Parent Rating Scale-Revised:Short Form

CTRS-R: Conners' Teacher Rating Scale-Revised

DSST: Digit Symbol Substitution Test

HUI-2/3: Health Utility Index Mark 2/3

PERMP: Permanent Product Measure of Performance

PGA: Parents' Global Assessment

WFIRS-P: Weiss Functional Impairment Rating Scale-Parent Report

Four open-label trials for GXR in the treatment of ADHD were found. Boellner, Pennick, Fiske, Lyne and Shojaei (2007) studied 14 children 6-12 years of age and fourteen adolescents 13-17 years of age with ADHD in a phase I-II open-label dose escalation pharmacokinetic evaluation study. After a 2 mg test dose, all patients received GXR 2 mg/day for one week, followed by 3 mg/day for one week and then 4 mg/day for one week. Observed guanfacine plasma concentrations were higher in children than in adolescents, proportional to differences in body weight. Efficacy parameters were not assessed in this study.

Biederman et al. (2008b) studied 240 children 6-17 years of age with ADHD in a long-term open-label extension of the prior RCT (Biederman et al., 2008a) conducted by this research group. Patients started GXR at 2 mg/day and were titrated in 1 mg increments to a maximum of 4 mg/day to achieve optimal clinical response, and were continued on this dosage for up to two years duration. Scores on the ADHD-RS-IV improved significantly from baseline to endpoint for all dose groups. Secondary efficacy measures included the PGA and the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), a measure of quality of life. Patients demonstrated a mean reduction on the ADHD-RS-IV scale of 18.1 points compared to their baseline scores in the RCT. Reductions in symptoms were apparent at one month, and were sustained for up to 24 months with continued treatment (Biederman et al., 2008b). Significant decreases were observed in both the child and adolescent age groups (Biederman et al., 2008b). On the PGA, 58.6% of patients were considered improved (all GXR doses), and significant improvement on the CHQ-PF50 psychosocial subscale (but not the physical subscale) was observed (Biederman et al., 2008b).

Spencer, Greenbaum, Ginsberg and Murphy (2009) studied 75 children 6-17 years of age with ADHD who had been taking a stable medication regimen of either an amphetamine or methylphenidate based psychostimulant for at least one month with suboptimal control of ADHD symptoms. Patient received adjunctive flexibly-dosed GXR 1-4 mg/day (mean: 3.1 mg/day, 0.07 mg/kg/day) titrated up to the highest tolerated dose in a nine week open-label safety study. Assessment of efficacy parameters included the ADHD-RS-IV scale, CGI-I, PGA and CHQ-PF50. Mean change in ADHD-RS-IV score from baseline to endpoint was -16.1 (methylphenidate-based treatment plus GXR: -17.8, amphetamine-based treatment plus GXR: - 13.8) (Spencer et al., 2009). At endpoint, 73% of patients in the study were rated as CGI-I of 2 or less (much improved or very much improved), and 84% of patients were rated on the PGA as much improved or very much improved (Spencer et al., 2009). Significant improvement on the CHQ-PF50 psychosocial subscale, but not the physical subscale was observed (Spencer et al., 2009).

Sallee, Lyne, Wigal and McGough (2009b) studied 259 children 6-17 years of age with ADHD in a long-term open-label extension trial. Patients who entered the trial had either participated in a prior RCT conducted by this research group (Sallee et al., 2009b) or a prior open-label GXR safety study (Spencer et al., 2009). Patient received flexibly-dosed GXR 1-4 mg/day (adjunctive to an amphetamine or methylphenidate psychostimulant regimens or as monotherapy) titrated up to their optimal dose for up to two years duration. Assessment of efficacy parameters included the ADHD-RS-IV scale, CGI-I, PGA and CHQ-PF50. Mean change in ADHD-RS-IV score from baseline to endpoint was -20.1 (GXR monotherapy: -21.2, psychostimulant plus GXR: -16.1) (Sallee et al., 2009b). At endpoint, 58% of patients in the study were rated as CGI-I of 2 or less (much improved or very much improved), and 60% of patients were rated on the PGA as much improved or very much improved (Sallee et al., 2009b). Significant improvement on the CHQ-PF50 psychosocial subscale, but not the physical subscale was observed (Sallee et al., 2009b).

Safety data

General adverse effect data is presented in Table 1, while cardiovascular effect data is presented in Table 2. Overall, high rates of treatment-emergent adverse effects were observed in both GXR and placebo groups in RCTs. Sedation, somnolence, fatigue, drowsiness, headache and upper abdominal pain were adverse effects that consistently occurred with the highest frequency in GXR RCTs and open-label trials. Most sedation-related adverse effects were dose-related, mild to moderate in severity and decreased over time (Sallee & Eaton, 2010).

In the Kollins safety study (Kollins et al., 2011) the primary safety outcome was reaction time as measured by the CRT test from the CANTAB. Compared with placebo, GXR treatment non-significantly reduced CRT by 2.5 msec, indicating psychomotor function and alertness were not impaired by GXR treatment (Kollins et al., 2011). Additional safety measures included tests of spatial working memory (SWM), the Digit Symbol Substitution Task/Coding Test (DSST/Coding), the Pictorial Sleepiness Scale (PSS), the Pediatric Daytime Sleepiness Scale (PDSS) and subjective reports of sedative-related effects, though no significant impact of GXR treatment was observed on these measures (Kollins et al., 2011). These results, taken with the significant improvement observed on efficacy measures for ADHD symptoms in this trial suggests that GXR efficacy is independent of general sedation (Kollins et al., 2011). Spontaneously reported sedative effect rates may vary from validated objective and subjective measures of sleepiness (Kollins et al., 2011).

Table 2. Summary of cardiovascular parameters in guanfacine XR (GXR) Trials

	Year; Lead Author; Journal	Peak SBP change	Peak DBP change	Peak HR change	QTcF change
RCTs	2008a; Biederman; Pediatrics	[3]GXR2: -7 mm Hg [3]GXR3: -7 mm Hg [4]GXR4: -10.1 mm Hg	[2]GXR2: -3.8 mm Hg [3]GXR3: -4.7 mm Hg [4]GXR4: -7.1 mm Hg	[3]GXR2: -5.7 bpm [3]GXR3: -8.1 bpm [4]GXR4: -8 bpm	GXR2: +2.4 msec* GXR3: +5.4 msec*
	2009a; Sallee: J Am Acad Child Adolesc Psychiatry	[4-6]GXR1: -0.5 mm Hg [4-6]GXR4: -7.4 mm Hg	[4-6]GXR1: -5.4 mm Hg [4-6]GXR4: +1.2 mm Hg	[4-6]GXR2: -1.3 bpm [4-6]GXR4: -9.5 bpm	GXR1: +4 msec* GXR2: +2.1 msec* GXR3: +6.8 msec* GXR4: +10 msec*
	2010; Connor; CNS Drugs	[8]GXR: -3 mm Hg* (all doses)	[8]GXR: -1.4 mm Hg* (all doses)	[8]GXR: -3.6 bpm* (all doses)	GXR: +3.1 msec* (all doses)
	2011; Kollins; J Child Adolesc Psychopharmacol	[4]GXR: -2.8 mm Hg (all doses)	[4]GXR: -3.7 mm Hg (all doses)	[4]GXR: -7.3 bpm (all doses)	no meaningful differences observed
	2012; Wilens; J Am Acad Child Adolesc Psychiatry	[8]GXR-AM: -0.9 mm Hg* [8]GXR-PM: -2.3 mm Hg* (all doses)	[8]GXR-AM: -1.1 mm Hg* [8]GXR-PM: -1.2 mm Hg* (all doses)	[8]GXR-AM: -7.9 bpm* [8]GXR-PM: -7.5 bpm* (all doses)	no subjects with QTcF of 480 msec or above
	2013; Newcorn; J Am Acad Child Adol Psychiatry;	not reported	not reported	not reported	not reported
Open-label	2007; Boellner; Pharmacother	not reported	not reported	not reported	no clinically significant change in ECG parameters or vital signs
	2008b; Biederman; CNS Spectr	GXR: -0.8 mm Hg (all doses, compared to baseline values in RCT)	GXR: -0.4 mm Hg (all doses, compared to baseline values in RCT)	GXR: -1.9 bpm (all doses, compared to baseline values in RCT)	GXR: -0.1 msec (all doses, compared to baseline values in RCT)
	2009; Spencer; J Child Adolesc Psychopharmacol	GXR1: -1.3 mm Hg GXR2: -3.9 mm Hg GXR3: -5.8 mm Hg GXR4: - 6.8 mm Hg	GXR1: +0.8 mm Hg GXR2: -1.7 mm Hg GXR3: -3 mm Hg GXR4: - 4.1 mm Hg	GXR1: +0.1 bpm GXR2: -3.9 bpm GXR3: -6.8 bpm GXR4: -9.9 bpm	GXR: +3.3 msec (all doses)
	2009b; Sallee; J Child Adolesc Psychopharmacol	GXR: +1.2 mm Hg (all doses, compared to baseline values in RCT)	GXR: +0.9 mm Hg (all doses, compared to baseline values in RCT)	GXRmonoTx: -0.8 bpm GXR+stimulant: +2.6 bpm (all doses, compared to baseline values in RCT)	no subject with QTcF above 500 msec or an increase from baseline of greater than 60 msec.

Abbreviations

bpm = beats per minute (pulse rate) DBP = diastolic blood pressure, GXR = guanfacine XR, HR = heart rate, mm Hg = millimeters of Mercury, msec = milliseconds, QTcF = corrected QT interval (Friedericia correction), SBP = systolic blood pressure, RCT = randomized controlled trial, * = placebo adjusted value

For RCTs, superscript numbers denote post-basline visit(s)/week(s) when peak effects observed; for open-label trials, measurement represents change from baseline to study endpoint

Cardiovascular safety

Cardiovascular safety data from GXR trials are summarized in Table 2. Compared to placebo, mean reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were observed in GXR treated patients, mostly in a dose-dependent fashion.

No serious QTc abnormalities noted with GXR in the five RCTs where this parameter was evaluated. Mean net QTc interval change (reported as QTc with Friedericia correction (QTcF)) from baseline in GXR treated patients compared to placebo ranged from increases of 2.4-5.4 msec (Biederman et al., 2008a), 2.7-10 msec (Sallee et al., 2009a) and 3.1 msec (Connor et al., 2010) where detailed QTcF reporting was provided. No "meaningful difference" in QTc intervals were reported in two RCTs (Kollins et al., 2011; Wilens et al., 2012) and one RCT did not assess QTc intervals (Newcorn et al., 2013). A precautionary statement regarding QTc prolongation was included in the Canadian product monograph (Shire Canada Inc., 2013) advising that mean placebo-adjusted QTc interval increase of 5 msec from GXR be considered in patients with a known history

of QT prolongation, risk factors for torsades de pointes (e.g. heart block, bradycardia, hypokalemia) or patients who are taking medications known to prolong the QT interval.

Rebound hypertension is a potential concern with sudden discontinuation of alpha$_2$-agonists. Persistent blood pressure increases of up to 10 mm Hg have been observed in a few individuals at 30 days post-discontinuation (Shire Canada Inc., 2013). All reviewed trials had a dose tapering period following the maintenance phase, in keeping with the manufacturer's recommendations for gradual dosage decrements of no more than 1 mg every 3-7 days when tapering off GXR (Shire Pharmaceuticals 2013; Shire Canada Inc., 2013).

Discontinuations

Altogether, 12% of GXR patients discontinued from RCTs due to adverse events, compared with 4% in the placebo group. The most common adverse reactions leading to discontinuation of GXR were somnolence/sedation (6%) and fatigue (2%) (Sallee & Eaton, 2010). Higher discontinuation rates were observed in the two-year open-label extension trials, where 82.5% (Biederman et al., 2008b) and 77.1% (Sallee et al., 2009b) of patients discontinued from these studies early mostly due to withdrawal of consent or adverse events (Biederman et al., 2008b; Sallee et al., 2009b).

Four patients in the Biederman RCT (Biederman et al., 2008a) discontinued from the trial due to QTc prolongation (one each in each GXR dosage group and placebo group), though none of these observed prolongations were considered clinically significant.

Two clinically significant ECG abnormalities possibly related to GXR occurred in the Sallee RCT (Sallee et al., 2009a). One patient experienced first-degree atrioventricular block, and one patient experienced symptomatic sinus bradycardia (Sallee et al., 2009a). While no patients receiving placebo in this study had a documented heart rate below 50 beats per minute (bpm), 12 patients receiving GXR experienced a heart rate below 50 bpm, with a higher frequency of this event in the GXR 3 and 4 mg/day groups (Sallee et al., 2009a).

One patient receiving GXR 2 mg/day withdrew from the Connor RCT (Connor et al., 2010) following an episode of bradycardia, hypotension and sinus arrhythmia that resolved without treatment. Two subjects in the Newcorn RCT (Newcorn et al., 2013) experienced syncope of mild to moderate intensity and were withdrawn from the trial, one each in the morning and evening dosing groups.

In the open-label trials, no clinically significant ECG changes were observed in patients in the Boellner study (Boellner et al., 2007). In the Biederman long-term extension study (Biederman et al., 2008b) one patient experienced orthostatic hypotension, and two patients experienced syncope. In addition, two patients experienced bradycardia, and one patient experienced junctional escape complexes, which resolved without treatment (Biederman et al., 2008b). In the Spencer open-label study (Spencer et al., 2009), 11.8% of patients experienced a heart rate of greater than 100 bpm, while 10.3% of patients experienced a heart rate below 50 bpm. The incidence of heart rate below 50 bpm was higher in the GXR plus methylphenidate group compared to the GXR plus amphetamine group (Spencer et al., 2009). In the Sallee long-term extension trial (Sallee et al., 2009b) one subject experienced atrioventricular block (which was originally reported in the RCT (Sallee et al., 2009a) and one subject experienced sinus bradycardia. Also, in this study 3.5% of patients experienced a heart rate of greater than 100 bpm, while 5.8% of patients experienced a heart rate below 50 bpm (Sallee et al., 2009b).

Discussion and recommendations

GXR has been shown to be effective as monotherapy or adjunctive therapy in the treatment of ADHD. The findings of Spencer and his group (Spencer et al., 2009) support the safety and effectiveness of co-administration of GXR and amphetamine-based stimulants (AMP) or methylphenidate (MPH) for the treatment of ADHD in patients with suboptimal responses to stimulants.

Until recently, IR clonidine was the only alpha$_2$-agonist available in Canada, and this formulation usually requires administration three to four times daily. However, non-adherence with resulting possible rebound hypertension is a concern with this dosing frequency of IR clonidine. Atypical antipsychotics are prescribed for patients with severe comorbidities including oppositional defiant disorder, conduct disorder, and symptoms of irritability and aggression (Weiss et al., 2009) and this class of medications are now well documented to lead to increased risk for metabolic adverse effects (De Hert, Dobbelaere, Sheridan, Cohen, & Correll, 2011).

Use of GXR in patients in age groups outside the Health Canada approved range of 6-12 years is likely to be considered by clinicians. GXR has had the approval of the US FDA for the range of 6-17 years of age since 2009 (Shire Pharmaceuticals, 2013). The lack of Health Canada approval for the adolescent age group stems from statistically non-significant results observed in the adolescent age cohort subgroup analyses in both the Biederman and Sallee RCTs (Biederman et al., 2008a; Sallee et al., 2009a). Both groups showed that children 6-12 years of age who received all doses of GXR showed statistically significant improvement whereas this was not the case in their small cohorts ranging from 13-17 years of age (Biederman et al., 2008a; Sallee et al., 2009a).

Coadministration of GXR with either MPH or AMP did not produce a unique pattern of adverse effects apart from what has been observed during monotherapy with either

psychostimulant or GXR alone. Common adverse effects of psychostimulant pharmacotherapy include irritability, headache, abdominal pain, and insomnia (Lexi-Comp Online™, 2013). While a small, non-statistically significant increase in effect size was observed for evening administration compared to morning administration of GXR (Newcorn et al., 2013) it is possible that patients with insomnia associated with psychostimulant use may benefit from evening administration of GXR. However, at present, there is no data supporting efficacy of evening administration of GXR as a sleep aid for insomnia. While guanfacine is rated as a strong recommendation/moderate-quality evidence in recent Canadian pharmacotherapy guidelines for treatment of tic disorders (Pringsheim et al., 2012) the IR guanfacine formulation was used in the RCT that demonstrated positive results for treatment of tic disorders (Scahill et al., 2001) and at present there are no published RCTs of GXR for the treatment of tic disorders.

In RCTs, fatigue and somnolence have been reported as adverse effects of GXR generally occurring within two to three weeks of starting therapy and these adverse effects tended to decrease over time. Slow upward titration of the GXR dosage may help to lessen or avoid these adverse effects. Co-administration of GXR and psychostimulants did not increase sleepiness (Wilens et al., 2012). Higher doses of GXR were associated with greater mean decreases in systolic blood pressure, diastolic blood pressure, and heart rate, although this relationship was not seen in the GXR+AMP group at the highest actual dose of GXR analyzed (Wilens et al., 2012). QTc prolongation observed to date with GXR was mild (mean increase of 5 msec, greatest reported mean increase in an RCT was 10 msec with GXR 4 mg/day) (Sallee et al., 2009a; Shire Canada Inc., 2013). Such prolongations are not of clinical concern for most children, but should be considered in those with known prolonged QTc interval, risk factors for torsades de pointes, or who take other medications that prolong the QTc interval.

Abrupt withdrawal of guanfacine should be avoided to decrease the risk of notable increases in blood pressure (Shire Canada Inc., 2013). Although few syncopal events were observed in RCTs, measurement of pulse and blood pressure should be performed prior to initiating therapy, following dose adjustments, periodically during treatment and following drug discontinuation (Shire Canada Inc., 2013).

GXR administered once daily either in the morning or evening was associated with significant and clinically meaningful improvements and level of response in ADHD symptoms. The recommended starting dosage of GXR is 1 mg per day (Shire Canada Inc., 2013). The dosage can be titrated up in weekly increments of 1 mg to a maximum dosage of 4 mg per day (Shire Canada Inc., 2013).

Guanfacine extended-release tablets should be swallowed whole and should not be chewed or crushed. This medication should be given on a daily basis for the entire week, not just on school days, to avoid issues with returning or worsening somnolence and potential, but rare, increases in blood pressure. Patients who miss two or more consecutive doses of GXR may need to restart therapy at 1 mg per day and then the dosage should be re-titrated based on patient tolerability. To discontinue GXR, the dosage should be tapered down by 1 mg decrements every three to seven days (Shire Canada Inc., 2013).

Canadian pricing of the available GXR dosage forms ranges from just over $3/day for the 1 mg tablet to just over $5/day for the 4 mg tablet. Atomoxetine, a non-stimulant medication with a different mechanism of action used to treat ADHD has demonstrated similar effect sizes in RCTs (Newcorn et al., 2008) and is similarly priced in Canada, though onset of response with atomoxetine is often delayed, while in GXR RCTs response occurred as early as post-randomization week 1. The pricing of GXR is similar to the cost of long-acting stimulant formulations available in Canada if used as monotherapy but may more than double the cost of ADHD treatment if used adjunctively with a long-acting stimulant. Medication cost may pose a barrier to widespread use and provincial formulary uptake of GXR as a benefit drug. Conversely, as a non-stimulant treatment for ADHD, GXR has low potential for abuse, and may be an attractive alternative to parents, clinicians, schools and governments struggling with substance use disorders.

Conclusion

In conclusion, the available evidence for efficacy and safety of GXR indicates that it is an effective treatment option for ADHD in children 6-12 years of age as monotherapy or as an adjunct to psychostimulants. Sedation is an adverse effect observed in many children but improves with time. Patients should take GXR regularly on a daily basis to avoid adverse effects that occur with abrupt discontinuation or when GXR is restarted.

Acknowledgements/Conflicts of Interest

The authors have no financial relationships to disclose.

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