

Guanfacine extended release for ADHD

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Guanfacine extended release (GXR)—a selective α -2 adrenergic agonist FDA-approved for the treatment of attention-deficit/hyperactivity disorder (ADHD)—has demonstrated efficacy for inattentive and hyperactive/impulsive symptom domains in 2 large trials lasting 8 and 9 weeks.^{1,2} GXR's once-daily formulation may increase adherence and deliver consistent control of symptoms across a full day (*Table 1*).

Clinical implications

GXR exhibits enhancement of noradrenergic pathways through selective direct receptor action in the prefrontal cortex.³ This mechanism of action is different from that of other FDA-approved ADHD medications. GXR can be used alone or in combination with stimulants or atomoxetine for treating complex ADHD, such as cases accompanied by oppositional features and emotional dysregulation or characterized by partial stimulant response.

How it works

Guanfacine—originally developed as an immediate-release (IR) antihypertensive—reduces sympathetic tone, causing centrally mediated vasodilation and reduced heart rate. Although GXR's mechanism of action in ADHD is not known, the drug is a selective α -2A receptor agonist thought to directly engage postsynaptic receptors in the prefrontal cortex (PFC), an area of the

Table 1

Guanfacine extended release: Fast facts

Brand name: Intuniv
Indication: Attention-deficit/hyperactivity disorder
Approval date: September 3, 2009
Availability date: November 2009
Manufacturer: Shire
Dosing forms: 1-mg, 2-mg, 3-mg, and 4-mg extended-release tablets
Recommended dosage: 0.05 to 0.12 mg/kg once daily

Once-daily formulation may improve adherence and control symptoms across a full day

brain believed to play a major role in attentional and organizational functions that preclinical research has linked to ADHD.³

The postsynaptic α -2A receptor is thought to play a central role in the optimal functioning of the PFC as illustrated by the "inverted U hypothesis of PFC activation."⁴ In this model, cyclic adenosine monophosphate (cAMP) levels build within the prefrontal cortical neurons and cause specific ion channels—hyperpolarization-activated cyclic nucleotide-gated (HCN) channels—to open on dendritic spines of these neurons.⁵ Activation of HCN channels effectively reduces membrane resistance, cutting off synaptic inputs and disconnecting PFC network connections. Because α -2A receptors are

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Clinical Point

GXR provides a broad but flat concentration profile

Table 2

Randomized, controlled trials supporting GXR's effectiveness for treating ADHD symptoms

Study	Subjects	GXR dosages	Results
Biederman et al, 2008 ⁷ ; phase III, forced-dose parallel-design	345 ADHD patients age 6 to 17	2, 3, or 4 mg given once daily for 8 weeks	GXR was associated with significantly lower ADHD-RS-IV score compared with placebo (-16.7 vs -8.9)
Sallee et al, 2009 ⁸ ; phase III, forced-dose parallel-design	324 ADHD patients age 6 to 17	1,* 2, 3, or 4 mg given once daily for 9 weeks	GXR was associated with significantly lower ADHD-RS-IV score compared with placebo (-19.6 vs -12.2)
Connor et al, 2009 ⁹ ; collateral study	217 complex ADHD patients age 6 to 12 with oppositional symptoms	Starting dose 1 mg/d, titrated to a maximum of 4 mg/d for a total of 8 weeks	GXR was associated with significantly lower scores on CPRS-R:L oppositional subscale (-10.9 vs -6.8) and ADHD-RS-IV (-23.8 vs -11.4) compared with placebo

*1-mg dose was given only to subjects weighing <50 kg (<110 lbs)
 ADHD: attention-deficit/hyperactivity disorder; ADHD-RS-IV: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV;
 CPRS-R:L: Conners' Parent Rating Scale-Revised: Long Form; GXR: guanfacine extended release

located in proximity to HCN channels, their stimulation by GXR closes HCN channels, inhibits further production of cAMP, and reestablishes synaptic function and the resulting network connectivity.⁵ Blockade of α -2A receptors by yohimbine reverses this process, eroding network connectivity, and in monkeys has been demonstrated to impair working memory,⁶ damage inhibition/impulse control, and produce locomotor hyperactivity.

Direct stimulation by GXR of the post-synaptic α -2A receptors is thought to:

- strengthen working memory
- reduce susceptibility to distraction
- improve attention regulation
- improve behavioral inhibition
- enhance impulse control.⁷

Pharmacokinetics

GXR offers enhanced pharmacokinetics relative to IR guanfacine. IR guanfacine exhibits poor absorption characteristics—peak plasma concentration is achieved too rapidly and then declines precipitously, with considerable inter-individual variation.

GXR's once-daily formulation is implemented by a proprietary enteric-coated sustained release mechanism⁸ that is meant to:

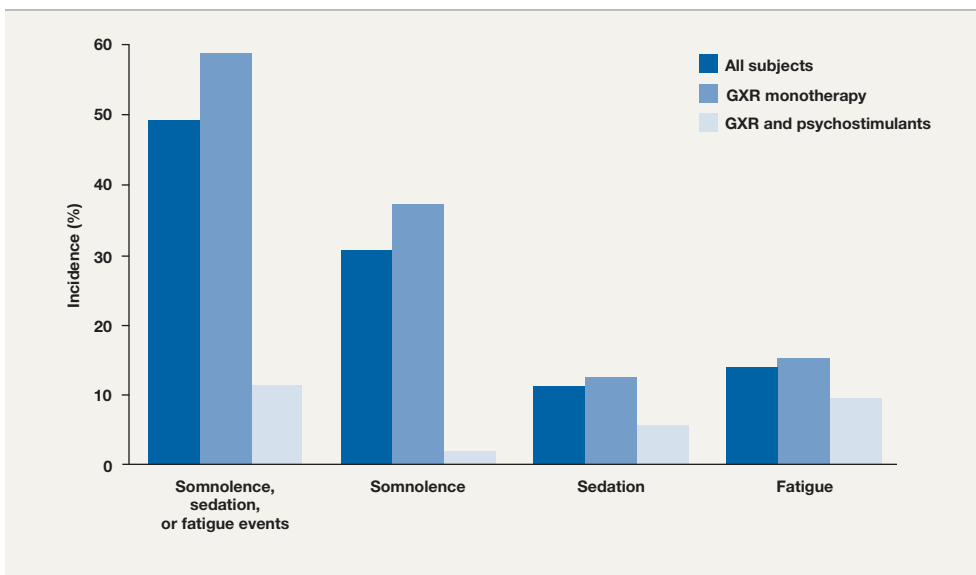
- control absorption
- provide a broad but flat plasma concentration profile
- reduce inter-individual variation of guanfacine exposure.

Compared with IR guanfacine, GXR exhibits delayed time of maximum concentration (Tmax) and reduced maximum concentration (Cmax). Therapeutic concentrations can be sustained over longer periods with reduced peak-to-trough fluctuation,⁸ which tends to improve tolerability and symptom control throughout the day. The convenience of once-daily dosing also may increase adherence.

GXR's pharmacokinetic characteristics do not change with dose, but high-fat meals will increase absorption of the drug—Cmax increases by 75% and area under the plasma concentration time curve increases by 40%. Because GXR primarily is metabolized through cytochrome P450 (CYP) 3A4, CYP3A4 inhibitors such as ketoconazole will increase guanfacine plasma concentrations

Figure

Incidence of somnolence, sedation, and fatigue in study patients receiving GXR with or without psychostimulants



In an open-label continuation study of 259 patients treated with guanfacine extended release (GXR), somnolence, sedation, or fatigue was reported by 49% of subjects overall, 59% of those who received GXR monotherapy, and 11% of those given GXR with a psychostimulant.

GXR: guanfacine extended release

Source: Reprinted with permission from Sallee FR, Lyne A, Wigal T, et al. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2009;19(3):215-226

Clinical Point

In 2 trials, patients experienced significant improvements in ADHD-RS-IV score 1 to 2 weeks after starting GXR

and elevate the risk of adverse events such as bradycardia, hypotension, and sedation. Conversely, CYP3A4 inducers such as rifampin will significantly reduce total guanfacine exposure. Coadministration of valproic acid with GXR can result in increased valproic acid levels, producing additive CNS side effects.

Efficacy

GXR reduced both inattentive and hyperactive/impulsive symptoms in 2 phase III, forced-dose, parallel-design, randomized, placebo-controlled trials (Table 2). In the first trial,¹ 345 children age 6 to 17 received placebo or GXR, 2 mg, 3 mg, or 4 mg once daily for 8 weeks. In the second study,² 324 children age 6 to 17 received placebo or GXR, 1 mg, 2 mg, 3 mg, or 4 mg, once daily for 9 weeks; the 1-mg dose was given only to patients weighing <50 kg (<110 lbs).

In both trials, doses were increased in

increments of 1 mg/week, and investigators evaluated participants' ADHD signs and symptoms once a week using the clinician administered and scored ADHD Rating Scale-IV (ADHD-RS-IV). The primary outcome was change in total ADHD-RS-IV score from baseline to endpoint.

In both trials, patients taking GXR demonstrated statistically significant improvements in ADHD-RS-IV score starting 1 to 2 weeks after they began receiving once-daily GXR:

- In the first trial, the mean reduction in ADHD-RS-IV total score at endpoint was -16.7 for GXR compared with -8.9 for placebo ($P < .0001$).

- In the second, the reduction was -19.6 for GXR and -12.2 for placebo ($P = .004$).

Placebo-adjusted least squares mean changes from baseline were statistically significant for all GXR doses in the randomized treatment groups in both studies.

Secondary efficacy outcome measures

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INVEGA® (paliperidone) Extended-Release Tablets

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment [see *Clinical Pharmacology* (12.3) in full PI], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration* (2.5) in full PI].

Renal Impairment: Dosing must be individualized according to the patient's renal function status [see *Dosage and Administration* (2.5) in full PI].

Hepatic Impairment: No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA® (paliperidone) is not a controlled substance.

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of INVEGA® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Dependence: Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE

Human Experience: While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

Manufactured by:

ALZA Corporation, Vacaville, CA 95688 OR
Janssen Cilag Manufacturing, LLC, Gurabo, Puerto Rico 00778

Manufactured for:

Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.,
Titusville, NJ 08560

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included the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R).

Significant improvements were seen on both scales. On the CPRS-R, parents reported significant improvement across a full day (as measured at 6 PM, 8 PM, and 6 AM the next day). On the CTRS-R—which was used only in the first trial—teachers reported significant improvement throughout the school day (as measured at 10 AM and 2 PM).

Treating oppositional symptoms. In a collateral study,⁹ GXR was evaluated in complex ADHD patients age 6 to 12 who exhibited oppositional symptoms. The primary efficacy measure was change from baseline to endpoint in the oppositional subscale of the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L) score.

All subjects randomized to GXR started on a dose of 1 mg/d—which could be titrated by 1 mg/week during the 5-week, dose-optimization period to a maximum of 4 mg/d—and were maintained at their optimal doses for 3 additional weeks. Among the 217 subjects enrolled, 138 received GXR and 79, placebo.

Least-squares mean reductions from baseline to endpoint in CPRS-R:L oppositional subscale scores were -10.9 in the GXR group compared with -6.8 in the placebo group ($P < .001$; effect size 0.590). The GXR-treated group showed a significantly greater reduction in ADHD-RS-IV total score from baseline to endpoint compared with the placebo group (-23.8 vs -11.4, respectively, $P < .001$; effect size 0.916).

Tolerability

In the phase III trials, the most commonly reported drug-related adverse reactions (occurring in $\geq 2\%$ of patients) were:

- somnolence (38%)
- headache (24%)
- fatigue (14%)
- upper abdominal pain (10%)
- nausea, lethargy, dizziness, hypotension/decreased blood pressure, irritability (6% for each)
- decreased appetite (5%)
- dry mouth (4%)
- constipation (3%).

Many of these adverse reactions appear to be dose-related, particularly somnolence, sedation, abdominal pain, dizziness, and hypotension/decreased blood pressure.

Overall, GXR was well tolerated; clinicians rated most events as mild to moderate. Twelve percent of GXR patients discontinued the clinical studies because of adverse events, compared with 4% in the placebo groups. The most common adverse reactions leading to discontinuation were somnolence/sedation (6%) and fatigue (2%). Less common adverse reactions leading to discontinuation (occurring in 1% of patients) included hypotension/decreased blood pressure, headache, and dizziness.

Open-label safety trial. Sallee et al¹⁰ conducted a longer-term, open-label, flexible-dose safety continuation study of 259 GXR-treated patients (mean exposure 10 months), some of whom also received a psychostimulant. Common adverse reactions (occurring in ≥5% of subjects) included somnolence (45%), headache (26%), fatigue (16%), upper abdominal pain (11%), hypotension/decreased blood pressure (10%), vomiting (9%), dizziness (7%), nausea (7%), weight gain (7%), and irritability (6%).¹⁰ In a subset of patients, the onset of sedative events typically occurred within the first 3 weeks of GXR treatment and then declined with maintenance to a frequency of approximately 16%. The rates of somnolence, sedation, or fatigue were lowest among patients who also received a psychostimulant (*Figure, page 51*).

Distribution of GXR doses before the end of this study was 37% of patients on 4 mg, 33% on 3 mg, 27% on 2 mg, and 3% on 1 mg, suggesting a preference for maintenance doses of 3 to 4 mg/d. The most frequent adverse reactions leading to discontinuation were somnolence (3%), syncope events (2%), increased weight (2%), depression (2%), and fatigue (2%). Other

Related Resource

• Guanfacine extended release (Intuniv) prescribing information. www.intuniv.com/documents/INTUNIV_Full_Prescribing_Information.pdf.

Drug Brand Names

Atomoxetine • Strattera	Ketoconazole • Nizoral
Guanfacine extended release • Intuniv	Rifampin • Rifadin, Rimactane
Guanfacine immediate release • Tenex	Valproic acid • Depakene, Depakote

Disclosure

Dr. Sallee receives grant/research support from the National Institutes of Health. He is a consultant to Otsuka, Nextwave, and Sepracor and a consultant to and speaker for Shire. Dr. Sallee is a consultant to, shareholder of, and member of the board of directors of P2D Inc. and a principal in Satiety Solutions.

adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included hypotension/decreased blood pressure, sedation, headache, and lethargy. Serious adverse reactions in the longer-term study in >1 patient included syncope (2%) and convulsion (0.4%).

Safety warnings relating to the likelihood of hypotension, bradycardia, and possible syncope when prescribing GXR should be understood in the context of its pharmacologic action to lower heart rate and blood pressure. In the short-term (8 to 9 weeks) controlled trials, the maximum mean changes from baseline in systolic blood pressure, diastolic blood pressure, and pulse were -5 mm Hg, -3 mm Hg, and -6 bpm, respectively, for all dose groups combined. These changes, which generally occurred 1 week after reaching target doses of 1 to 4 mg/d, were dose-dependent but usually modest and did not cause other symptoms; however, hypotension and bradycardia can occur.

In the longer-term, open-label safety study,¹⁰ maximum decreases in systolic and diastolic blood pressure occurred in the first

Clinical Point

Instruct patients to swallow GXR whole because chewing or crushing the tablet will markedly enhance the drug's release

Bottom Line

In clinical trials, guanfacine extended release significantly reduced inattentive and hyperactive/impulsive symptoms in patients with attention-deficit/hyperactivity disorder. The most common adverse reactions are somnolence, headache, and fatigue.

Clinical Point

Adverse events such as hypotension, bradycardia, and sedation are dose-related

month of treatment; decreases were less pronounced over time. Syncope occurred in 1% of pediatric subjects but was not dose-dependent. Guanfacine IR can increase QT interval but not in a dose-dependent fashion.

Dosing

The approved dose range for GXR is 1 to 4 mg once daily in the morning. Initiate treatment at 1 mg/d, and adjust the dose in increments of no more than 1 mg/week, evaluating the patient weekly. GXR maintenance therapy is frequently in the range of 2 to 4 mg/d.

Because adverse events such as hypotension, bradycardia, and sedation are dose-related, evaluate benefit and risk using mg/kg range approximation. GXR efficacy on a weight-adjusted (mg/kg) basis is consistent across a dosage range of 0.01 to 0.17 mg/kg/d. Clinically relevant improvements are usually observed beginning at doses of 0.05 to 0.08 mg/kg/d. In clinical trials, efficacy increased with increasing weight-adjusted dose (mg/kg), so if GXR is well-tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit up to the maximum of 4 mg/d.

Instruct patients to swallow GXR whole because crushing, chewing, or otherwise breaking the tablet's enteric coating will markedly enhance guanfacine release.

Abruptly discontinuing GXR is associated with infrequent, transient elevations

in blood pressure above the patient's baseline (ie, rebound). To minimize these effects, GXR should be gradually tapered in decrements of no more than 1 mg every 3 to 7 days. Isolated missed doses of GXR generally are not a problem, but ≥ 2 consecutive missed doses may warrant reinitiation of the titration schedule.

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PROMISING NEW INVESTIGATORS TRAVEL SCHOLARSHIPS

The Neuroleptic Malignant Syndrome Information Service (NMSIS) announces a competition to recognize promising new investigators based on a scholarly paper addressing "New insights on psychotropic drug safety and side effects."

Consistent with its mission to advance pharmacotherapy and patient safety, NMSIS offers these scholarships to promote education and research by early career psychiatrists. Two prizes of \$2,000 and \$1,000 will be awarded to cover travel costs to the American Psychiatric Association (APA) Annual Meeting in New Orleans, LA, in May 2010. Winners will be announced on March 8, 2010, and the scholarships will be presented during the APA event.

- Papers should address specific issues related to the award theme and be no longer than 15 double-spaced typed pages.
- Literature reviews, case reports, or original studies that are not in press or published are acceptable.
- Primary author must be a student, resident, or fellow.
- Papers will be judged on originality, scholarship, relevance, and methodology.

Submit paper and the primary author's curriculum vitae to Michael Wesolowski, 11 East State St., Sherburne, NY 13460, fax 607-674-7910, or via e-mail to michael@mhaus.org. Deadline is February 6, 2010. To learn more about NMSIS, visit www.nmsis.org.

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