Clonidine and guanfacine IR vs ER: Old drugs with "new" formulations

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ABSTRACT

After a long history of use for hypertension, clonidine and guanfacine have re-emerged on the market as treatment options for attention-deficit/hyperactivity disorder, particularly in patients who are unable to tolerate or need an alternative to stimulant medications as well as those who have residual symptoms despite adequate therapy with stimulants. In recent years, new formulations of long-acting clonidine and guanfacine have come to market. The purpose of this article is to review the pharmacokinetic properties and clinical utility of these new agents while comparing the medications and parent compounds in terms of dosing, adverse effects, and costs of treatment.

KEYWORDS

Alpha agonist, attention-defecit/hyperactivity disorder, clonidine, guanfacine

INTRODUCTION

Clonidine and guanfacine are central alpha agonists that were initially developed for the management of hypertension. However, as other medications have come to market, the alpha agonists have fallen out of favor, and are now reserved for use in emergent settings or as add-on agents for treatment resistant hypertension.[1] Although no longer preferred therapy for blood pressure management, numerous studies have indicated the safety and efficacy of these medications for the treatment of hallmark symptoms of ADHD.

The activity of these medications has been attributed to their effects on pre- and post-synaptic alpha-2 receptors, particularly as they relate to the prefrontal cortex (PFC) and its mediation of key ADHD symptoms, such as inattention, distractibility, and impulsivity.[2,3] While both medications work specifically on the alpha-2 receptors, differences in binding affinity and selectivity between the two medications may lead to differences in side effect profiles.[2] Regardless of these differences, both clonidine and guanfacine are used frequently in the treatment of ADHD, whether as adjuncts for patients with a partial response to treatment with stimulants or atomoxetine, or as monotherapy in patients who are unable to tolerate other medications used in the treatment of ADHD.

Clonidine

Clonidine is an alpha-2 agonist with affinity for alpha receptors at both pre- and post-synaptic terminals.[2,3] The nonselectivity of clonidine at postsynaptic alpha-2A, 2B, and 2C receptors is believed to contribute to the high incidence of side effects such as dry mouth, sedation, dizziness, and hypotension.[2-4] These effects are most common with initiation of therapy and dose increases; thus, these side effects may lessen as the patient continues the medication.[4]

When used for ADHD, clonidine is usually initiated at a low dose of 0.05 – 0.1 mg daily with a maximum dose of 0.4 mg daily (Table 1). These doses may be given once daily or divided into twice daily dosing. Patients who are starting on clonidine should be titrated in increments of 0.05 mg (for patients weighing ≤ 45 kg) or 0.1 mg (for patients > 45 kg) every 3-7 days. Patients who are discontinuing clonidine treatment should be tapered off over several days and should be counseled to avoid abrupt discontinuation due to the risk of rebound hypertension.[4] This risk is increased in patients on higher doses of clonidine or concomitant beta blockers.[4]

In 2010, an extended-release formulation of clonidine (CXR; Kapvay®) was approved for use in the treatment of ADHD as either monotherapy or adjunctive therapy to stimulant medications in children ages 6-17 years old.[6] CXR has not been studied in children younger than 6 years old or in adult patients. Dosing should be initiated with one 0.1 mg tablet at bedtime and titrated by 0.1 mg in weekly intervals until the desired response is achieved (Table 2). Despite the extended-release formulation of CXR, doses are still administered twice a day, with higher doses given at bedtime to minimize the effects of sedation and dry mouth.[4,6] Doses higher than 0.2 mg

Table 1. Dosing and cost comparison of immediate- and extended-release clonidine and guanfacine[4,6,11,15,16]

	Initial Dosing	Dosing Range	AWP Cost	Available on Discount Rx Programs
Clonidine IR (generic)	≤ 45 kg: 0.05 mg qhs > 45 kg: 0.1 mg qhs	0.1 – 0.4 mg daily in multiple divided doses	$23.62 for 100 0.1 mg tablets	Yes
Clonidine XR (Kapvay®)	Children ≥ 6 years of age: 0.1 mg qhs	0.1 – 0.4 mg daily in 2 divided doses	$226.31 for 100 0.1 mg tablets	No
Guanfacine IR (generic)	≤ 45 kg: 0.5 mg qhs > 45 kg: 1 mg qhs	1 – 4 mg daily in 2 divided doses	$87.20 for 100 1 mg tablets	Yes
Guanfacine XR (Intuniv®)	1 mg daily	1 – 4 mg daily	$884.11 for 100 1 mg tablets	No

Table 2. Dose adjustments for initiation of extended-release guanfacine (GXR; Intuniv®)[12]

Co-medication Type	When adding GXR to co-medication	When starting co-medication and continuing GXR	When stopping co-medication and continuing GXR
Strong 3A4 Inhibitor	GXR dose should be limited to 2 mg daily	GXR dose should be decreased by half	GXR dose should be doubled (if patient tolerates). Max daily dose should not exceed 4 mg
Strong 3A4 Inducer	GXR dose may be titrated up to 8 mg daily. May consider faster titration (2 mg/ week)	Increase GXR dose gradually (1-2 weeks) to 2x the original dose (if patient tolerates)	GXR dose should be decreased by half in 1-2 weeks (if patient tolerates). Max daily dose should not exceed 4 mg

twice a day (0.4 mg/day) were not evaluated in CXR clinical trials and are not currently recommended.[6]

Two placebo-controlled trials examined the efficacy of CXR in the treatment of ADHD. These studies were conducted in patients aged 6-17, who met DSM-IV criteria for ADHD hyperactive or combined hyperactive/inattentive subtypes. To evaluate symptoms of ADHD, the ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score was used.[7,8] The first study was an 8-week randomized, double-blind, placebo-controlled, fixed dose study of 236 children and adolescents. The primary endpoint was mean change in ADHD-RS-IV total score from baseline to week 5 versus placebo. Both the 0.2- and the 0.4 mg/day doses were effective, showing significant improvement in the ADHD-RS-IV score when compared to placebo-treated patients.[7] However, due to adverse effects associated with CXR (predominantly noted as somnolence, sedation, and fatigue), 13% of patients receiving the medication discontinued use, compared to 1% in the placebo group.[7] Discontinuation due to adverse effects was three times higher in the 0.4 mg group compared to the 0.2 mg group, indicating that these effects may have been dose-related. Incidence of adverse effects for CXR were similar to that of immediate release clonidine, with rates of somnolence ranging from 39.5% with the 0.2 mg dose to 30.8% with the 0.4 mg dose (compared to 33% noted in the prescribing information for immediate-release clonidine when used in adult patients for treatment of hypertension).[4,7] The authors also report rates of sinus bradycardia at 6% in the 0.2 mg group and 21% in the 0.4 mg, compared to 5% in the placebo group. These rates are higher with CXR than what has been previously described for immediate release clonidine (rates reported as <10% in prescribing information).[4]

Kollins and colleagues examined the efficacy of CXR in an 8-week study in 198 patients aged 6 to 17 with a 5-week primary efficacy end point of mean change in ADHD-RS-IV total score from baseline to week 5 versus placebo.[8] Patients had been treated with a stimulant, either methylphenidate or amphetamine, for four weeks with an inadequate response. All stimulant agents were included; the most common stimulants included Concerta® (32%), Vyvanse® (18%), Adderall XR® (15%), and Focalin XR® (10%). Patients were randomly assigned to receive flexible-dosed CXR (0.1 to 0.4 mg daily) as an adjunct to their stimulant or continue the stimulant with placebo. ADHD symptoms were significantly improved in the combination group, with changes in both the hyperactivity/impulsivity and inattention subscales showing statistically significant improvement at the end of 5 weeks (hyperactivity/impulsivity score changes of -5.8 for the placebo plus stimulant group and -7.9 in the CXR and stimulant group; inattention score changes of -5.8 for the placebo plus stimulant group and -7.8 in the CXR and stimulant group; p=0.017 and p=0.014, respectively).[8] In this trial, CXR had lower rates of somnolence, fatigue, and sedation than the authors reported in the monotherapy study. However, rates of

these side effects were more than double in frequency for the CXR plus stimulant groups than for stimulant plus placebo.[8] The authors note rates of somnolence and sedation for the stimulant and placebo group at 8% compared to 20% in the clonidine and stimulant group. Likewise, rates of fatigue were 4% in the stimulant and placebo group and 16% in the clonidine and stimulant group.[8]

A potential limitation of the immediate-release formulation of alpha-2-adrenergic agonists stem from their rapid absorption and high peak plasma concentration that can lead to side effects. In pharmacokinetic studies conducted by the manufacturer, the extended-release product had a maximum concentration (C_{max}) 50% lower and a time to maximum concentration (t_{max}) 5 hours later than immediate-release clonidine.[6] No difference was noted in terms of elimination rate.[6] Bioavailability of CXR is 89% of immediate release clonidine, with no effect by food. CXR clearance is slightly higher in the presence of methylphenidate, and slightly lower in the presence of amphetamine.[7] Due to these varying pharmacokinetic properties, the manufacturer of CXR warns against the substitution of immediate-release tablets in place of the extended-release formulation.[6] The XR formulation should be swallowed whole, not crushed or chewed.

Another distinct difference between clonidine formulations is a 10-fold higher cost for the CXR compared to the immediate-release formulation (Table 1). However, it was announced in mid-October 2013 that the patent on brand-name CXR has expired, which will soon allow for other manufacturers to produce CXR and decrease cost to consumers.[9]

Guanfacine

Guanfacine is a postsynaptic alpha-2 adrenergic receptor agonist that is more selective than clonidine and has a greater affinity for the alpha-2A receptor subtype than for other subtypes.[2,3] Compared to clonidine, guanfacine also has 10-fold weaker affinity for presynaptic receptors, which has been attributed to lower rates of sedation.[10] Guanfacine has been studied off-label for treatment of ADHD symptoms at starting doses of 0.5 to 1 mg daily and a max dose of 4 mg daily.[3,5,10] Patients should be titrated by 0.5 to 1 mg each week to minimize sedating effects of the medication. For patients needing to discontinue the medication, a taper of ≤ 1 mg every 3 – 7 days is suggested to minimize risk of rebound hypertension.[11]

Side effects associated with guanfacine appear to be similar to those seen with clonidine use but occur at lower frequency. Sedation, dizziness, dry mouth, and constipation were most commonly reported in clinical trials conducted by the manufacturer.[11] Decreases in blood pressure are dose-related, and patients should be counseled on the risk of orthostasis or syncope with initiation of treatment or with dose increases.

Guanfacine extended release (GXR) was approved in 2009 and is indicated for the treatment of ADHD as both monotherapy and adjunctive therapy to stimulant medications.[12] The use of GXR in pediatric patients has been evaluated in two clinical trials conducted in patients aged 6 -17 years who met DSM-IV criteria for ADHD. The first study, conducted by Biederman and colleagues, was an eight-week, placebo-controlled safety and efficacy study of GXR in 345 patients aged 6 to 17 years. The primary outcome of this study was improvement in total scores on the ADHD-RS IV from baseline compared with placebo. GXR was initiated at 1 mg/day and increased to a dose of 2 – 4 mg per day. ADHD-RS IV scores at study completion showed a statistically significant decrease in the GXR group (-16.7 points) compared with placebo (-8.9 points; p<0.0001). Common adverse effects associated with guanfacine included sedation, fatigue, upper abdominal pain, and somnolence.[13] Withdrawal from the study due to adverse effects appeared to be dose-related, with one patient withdrawing from the placebo group as compared to nine patients in the GXR 2 mg group, 13 in the 3 mg group, and 20 in the 4 mg group.[13] Treatment-emergent adverse effects were also dose-related, with 3.5% of patients experiencing somnolence in the placebo group as compared to 24.1%, 33.7%, and 38.4% in the 2 mg, 3 mg, and 4 mg GXR doses, respectively. These rates are similar to what has been reported in the prescribing information for immediate release guanfacine, with 39% of patients taking a 3 mg dose reporting somnolence.[11] Fatigue was also a common adverse effect in the GXR study, affecting 3.5% of patients in the placebo group compared to over 20% in the GXR 3 mg group.[13] These rates of fatigue may be higher than what has been reported for the immediate release formulation, with only 10% of patients reporting this side effect in initial dose-response studies of patients with hypertension.[11]

A study conducted by Sallee and colleagues examined the use of GXR in 324 patients 6 to 17 years of age over a 25-month time period. Patients were randomized to receive GXR alone or in combination with a stimulant (either amphetamine or methylphenidate products) and were titrated up to 4 mg of GXR per day. In this study, ADHD-

RS IV total scores showed statistically significant improvement from baseline in patients taking GXR as monotherapy or in combination with stimulants (mean change overall, -20.1 points; p<0.001).[14] Statistically significant score improvement was seen at each monotherapy dose compared to baseline (-24.3 points for the 1 mg, -23.8 dose for the 2 mg, -22.1 for the 3 mg, and -18.0 for the 4 mg arms; all p<0.001). Statistically significant improvement was also noted in the combination therapy groups for the 2 mg, 3 mg, and 4 mg arms as compared to baseline (p=0.006, p<0.001, p<0.001, respectively) but not in the 1 mg group. Treatment-emergent adverse effects were reported in 87.4% of patients on monotherapy and 86.8% of patients in the combination therapy group. Common adverse effects reported in patients receiving the study medication were somnolence, headache, and fatigue.[14] The side effects of sedation, somnolence, and fatigue occurred in approximately 58.7% of patients on guanfacine monotherapy and 11.3% of patients on combination therapy. The lower incidence of side effects in the combination group may be due to the stimulating effects of the psychostimulant used, which could combat some of the sedation and fatigue seen with monotherapy. When examining rates of somnolence alone in patients on GXR as monotherapy, the effects appear to have similar frequency as that reported with immediate-release guanfacine in early dose-response studies.[11]

Despite the availability of tablets in identical strengths and daily doses in the same dosing range, the manufacturer of GXR warns against the substitution of immediate-release guanfacine in place of the extended-release formulation due to varying pharmacokinetic properties of the two medications.[12] In kinetic studies conducted by the manufacturer, the extended-release product was found to have a Cmax that is 60% lower and occurred three hours after that of immediate-release guanfacine.[12] Due to the extended-release properties of GXR, the tablet should be swallowed whole and should not be crushed or chewed. High fat intake at the time of dosing has been shown to increase the amount of medication absorbed in initial pharmacokinetic studies (C_{max} increased by ~75%, area under the curve (AUC) by ~40%) and may increase side effects. GXR should be taken once daily at the same time each day, and the patient should avoid taking it with a high fat meal. Another difference between immediate release guanfacine and GXR is the increased cost associated with GXR use (Table 1). The substantial cost difference between these formulations may be a significant limitation to the use of GXR.

Dosing adjustments are recommended if guanfacine is used with concomitant medications known to alter hepatic metabolism, such as potent inducers or inhibitors of the cytochrome P450 system. Prescribing information for immediate-release guanfacine (Tenex®) includes information on the use of guanfacine with phenobarbital or phenytoin in two patients with renal impairment. The manufacturer reports a significant (though unspecified) reduction in elimination half-life, and suggest more frequent daily dosing to combat the shortened duration of action. However, specific dosing suggestions are not given.[11] For patients currently prescribed strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, grapefruit juice) and starting on GXR, the dose should be limited to 2 mg daily. For patients taking 3A4 inducers (e.g., carbamazepine, phenytoin, St. John's wort) and starting GXR, the titration may occur at 2 mg/week and total daily dose may be titrated up to 8 mg.[12] See Table 2 for additional dosing recommendations.

CONCLUSION

Clonidine and guanfacine have demonstrated efficacy and tolerability for use in both immediate-release and extended-release formulations for treatment of ADHD symptoms. For patients who have difficulty remembering to take multiple doses, GXR may be the best treatment option due to once daily dosing. However, when comparing estimated cost (Table 1), the extended-release formulations of both agents are much more costly options. Immediate-release clonidine and guanfacine are the least expensive options, with both 0.1 mg and 0.2 mg clonidine tablets and 1 mg guanfacine tablets available on many discount medication programs at community pharmacies. As the healthcare climate changes and more patients are provided with insurance coverage, companies will be looking to further compare and assess the costs and benefit of these varying dosage forms. When comparing the rates of side effects between formulations for each medication, the extended-release products do appear to have lower rates of common side effects (e.g., sedation, dry mouth, somnolence, headache), particularly with initiation of treatment; however, the clinical applicability of this data is unclear.[4,6,11,12] Initiation of IR formulations at low doses and with slow dose titration may minimize the emergence of common side effects associated with these medications. Determining which medication formulation to use for a particular patient may depend on his or her specific factors, such as willingness to take a medication that requires repeated dosing, concomitant medications, and cost considerations.

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