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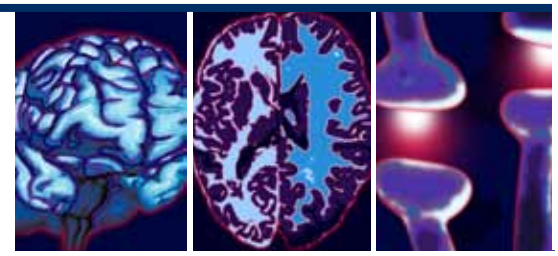

Clonidine extended-release tablets for the treatment of ADHD

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Practice points

- Stimulant medications remain the first-line treatment for ADHD.
- Based on two recent studies, clonidine extended release is efficacious and relatively well-tolerated on a short-term basis for the treatment of ADHD as a monotherapy as well as an adjunctive therapy.
- Sedation/fatigue was problematic for many children in the studies, particularly in the acute phase of treatment.
- Long-term follow-up and additional trials are necessary to more fully assess the efficacy, tolerability and safety of clonidine extended release in patients with ADHD.
- It would be useful to assess its efficacy and tolerability in patients with comorbid psychiatric disorders and those with the inattentive subtype of ADHD.

SUMMARY Treatment guidelines for ADHD recommend stimulants as a first-line therapy. However, as many as 15% of patients are unresponsive to these medications, while others are unable to tolerate stimulants. For some patients with ADHD, there is a clear need for nonstimulant therapies. This article aims to summarize the current evidence regarding the use of clonidine extended release (Kapvay™, Shionogi Pharma, GA, USA) in the treatment of children and adolescents with ADHD.

ADHD is the most common childhood neurobehavioral disorder, with the most recent National Survey of Children's Health suggesting a prevalence of 9.5% among children in the USA [1]. It causes significant impairment in academic performance and social functioning in affected youth, with symptoms frequently persisting into adolescence and adulthood [2]. Stimulant medications represent first-line pharmacotherapy for ADHD, with 70% of children and adolescents responding to a single stimulant trial, and up to 80–90% responding if both stimulant classes are prescribed consecutively [3]. The average effect size for stimulant treatment versus placebo is calculated to be 1.0, which represents one of the largest effect sizes in psychiatric treatment [2].

Although stimulants are highly effective, they are also associated with common adverse effects such as appetite suppression, insomnia and irritability. In addition, they carry a risk of misuse and diversion [4]. If patients do not respond

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adequately to treatment with stimulant medications or cannot tolerate stimulant medications, the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters recommend treatment with a nonstimulant medication [2]. Currently, the most studied nonstimulant medication for the treatment of ADHD is atomoxetine, which selectively blocks reuptake at noradrenergic neurons, with more than a dozen double-blind, placebo-controlled trials demonstrating safety and efficacy in ADHD and a calculated medium effect size of 0.7 [3].

α-2 agonists have emerged as an alternate ADHD medication strategy, either as monotherapy or as an adjunct to stimulant medications. Notably, the α-2 agonists are the only medications US FDA-approved as an adjunctive therapy for the treatment of ADHD. While immediate-release α-2 agonists have been available for some time, adherence with short-acting versions of oral clonidine (CLON) and guanfacine has been limited by the need for multiple daily dosing. In 2009, guanfacine extended release (XR) (Intuniv™, Shire Specialty Pharmaceuticals, Dublin, Ireland) was approved by the FDA for the treatment of ADHD in children 6–17 years of age [5]. In 2010, an oral, XR version of CLON (Kapvay™, Shionogi Pharma, GA, USA) was approved for the treatment of ADHD in children aged 6–17 years [6]. Both medications reduce the need for multiple daily dosing.

Indications & usage

CLON-XR is FDA-approved for the treatment of ADHD as monotherapy or as adjunctive therapy to stimulant medications for children and adolescents aged 6–17 years [7]. The two clinical trials which led to FDA approval assessed end point efficacy measures at 5 weeks, while total study duration was 8 weeks in length (allowing for tapering of medication during the last 3 weeks) **(Table 1)**. As such, maintenance efficacy has not been systematically evaluated, so patients who are continued on longer-term treatment should be reassessed frequently for effectiveness and tolerability.

Dosage & administration

CLON-XR is available in tablets of 0.1 and 0.2 mg, and is not scored. In this formulation, CLON is combined with cellulose ethers in a stable matrix which allows the release of CLON over a 12-h period [6]. The medication should be swallowed whole and never cut, crushed or chewed, any of which would eliminate its XR capability. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired efficacy is achieved or tolerability problems arise (not to exceed maximum dose of 0.4 mg/day) **(Table 2)**. Doses should be taken twice a day, with either an equal or higher split dosage given at bedtime. It is not recommended to directly substitute

Table 1. Summary of randomized, placebo-controlled studies.

	CLON-XR for pediatric patients with ADHD	CLON-XR as an add-on therapy to psychostimulants in children and adolescents with ADHD
Number of subjects (intent to treat)	228	197
Dosing	Fixed, 0.2 or 0.4 mg/day, divided b.i.d.	Flexible dosing, up to 0.4 mg/day, divided b.i.d.
Study duration	8 weeks (5-week titration and 3-week taper)	8 weeks (5-week titration and 3-week taper)
Mean (SD) baseline ADHD-RS-IV total scores	45 for PBO 43.8 for 0.2 mg/day 44.6 for 0.4 mg/day	39.0 for PBO + stimulant 38.9 for CLON-XR + stimulant
Mean changes (SD) in ADHD-RS-IV scores for inattention (LOCF)	-3.4 for PBO -7.7 for 0.2 mg/day -7.7 for 0.4 mg/day	-5.8 for PBO + stimulant -7.8 for CLON-XR + stimulant
Mean changes (SD) in ADHD-RS-IV scores for hyperactivity (LOCF)	-4.1 for PBO -7.9 for 0.2 mg/day -8.8 for 0.4 mg/day	-5.8 for PBO + stimulant -7.9 for CLON-XR + stimulant
Mean changes (SD) in ADHD-RS-IV total scores (LOCF)	-7.5 for PBO -15.6 for 0.2 mg/day -16.5 for 0.4 mg/day	-11.5 for PBO + stimulant -15.7 for CLON-XR + stimulant

ADHD-RS-IV: ADHD Rating Scale-IV; b.i.d.: Twice weekly; CLON: Clonidine; LOCF: Last observation carried forward; PBO: Placebo; SD: Standard deviation; XR: Extended release.
Adapted from [6,11].

Table 2. Dosing guidance for clonidine extended release.

Total daily dose (mg)	Morning dose (mg)	Bedtime dose (mg)
0.1		0.1
0.2	0.1	0.1
0.3	0.1	0.2
0.4	0.2	0.2

When initiating, dosage should be adjusted in increments of 0.1 mg/day at weekly intervals.
When tapering, dosage should decrease in decrements of no more than 0.1 mg every 3–7 days.
Data taken from [7].

the XR oral form for other CLON products on a mg-per-mg basis, because of differing pharmacokinetic profiles between the extended- and immediate-release versions. When discontinuing the medication, the dose should be tapered in decrements of no more than 0.1 mg every 3–7 days.

Clinical pharmacology

CLON is a central acting α-2 adrenergic agonist. It stimulates all three subtypes of α-2 receptors in the brain. CLON reduces sympathetic outflow from the CNS and decreases peripheral resistance, renal vascular resistance, heart rate and blood pressure [7]. The exact mechanism of action of CLON in ADHD is unknown.

CLON-XR has different pharmacokinetics than immediate-release CLON. It is suggested that the C_{max} is 50% lower for CLON-XR and occurs approximately 5 h later, compared with immediate-release CLON. The total systemic bioavailability of CLON-XR is approximately 89% of that for immediate-release CLON. The two formulations have similar elimination half-lives of approximately 12–16 h. Although studies with CLON-XR have not yet evaluated CLON excretion or the effects of renal impairment, the results are likely to be similar to immediate-release CLON. For immediate-release CLON, the half-life can be as long as 41 h in those persons with severe renal impairment and 40–60% of the absorbed dose is excreted, unchanged in the urine. For both medications, food has no effect on plasma concentration, bioavailability or elimination half-life.

Clinical evidence

■ Immediate-release CLON

Results of early acute pharmacotherapy treatment studies suggested that immediate-release CLON may be used most effectively in ADHD as part of a combination of treatments, such as when added to stable stimulant treatment. In treatment recommendations from the AACAP, published prior to approval of the XR preparation, immediate-release CLON was suggested for off-label use, as an adjunct to enhance stimulant treatment or to treat comorbid symptoms such as impulsivity, tics or insomnia [2]. A 1999 meta-analysis assessed 11 studies which enrolled patients with or without various comorbid conditions and calculated an effect size of 0.58 for immediate-release CLON [8].

One well-controlled study on the use of immediate-release CLON in 136 children aged 7–12 years with ADHD and comorbid Tourette's syndrome randomly assigned subjects to take one of four treatments: immediate-release CLON, immediate-release methylphenidate, CLON plus methylphenidate, or placebo for 12–16 weeks. CLON dosages averaged 0.25 mg/day for the CLON-alone group and 0.28 mg/day for the CLON plus methylphenidate group. Methylphenidate dosages averaged 25.7 mg/day for the methylphenidate-alone group and 26.1 mg/day for the CLON plus methylphenidate group. Both medications were dosed two- to three-times daily. All active treatments were superior to placebo in improving ADHD as well as tic symptoms, while the combination treatment resulted in the greatest benefit for both disorders. The investigators suggested that immediate-release CLON was helpful for aggression, impulsivity and sleep problems [9]. Last, the active treatments were well tolerated, including absence of any evident cardiac toxicity or drug–drug interactions.

Another controlled study enrolled 122 children aged 6–12 years with ADHD and no other comorbidities. Subjects also received one of four treatments: immediate-release CLON, immediate-release methylphenidate, CLON plus methylphenidate, or placebo. In this study, CLON was dosed three- to four-times daily. The mean daily doses of medication were 0.24 mg for the CLON-alone group and 30.2 mg for the methylphenidate-alone group.

For subjects receiving combination treatment, the mean daily doses were 0.23 mg for CLON and 25.4 mg for methylphenidate. CLON alone, in this study, was not statistically different from placebo, however, the combination treatment provided a better response for reducing ADHD symptoms [10].

CLON-XR

In September 2010, an XR preparation of CLON was approved for use in pediatric ADHD. This approval was based on two randomized, placebo-controlled studies (Table 1). The first study was a multicenter, randomized, double-blind, placebo-controlled study of two fixed doses (0.2 or 0.4 mg/day, divided dosing) of CLON-XR in subjects aged 6–17 years with ADHD. Patients were titrated to their fixed dose increasing by 0.1 mg/day each week. The primary efficacy measure was the change in total ADHD Rating Scale-IV (ADHD-RS-IV) score from baseline to week 5. A significant effect was observed as early as week 2 and was maintained throughout the study period. The effect sizes were 0.713 for the 0.2-mg/day group and 0.766 for the 0.4-mg/day group [6]. Somnolence was the most common treatment-emergent adverse event and occurred more frequently during the weeks of dose escalation than during dose maintenance or dose tapering. In this study, the most common treatment-emergent adverse events leading to discontinuation were from somnolence/sedation (0% in placebo, 4% in the 0.2-mg/day group and 6% in the 0.4-mg/day group) and fatigue (0% in placebo, 3% in the 0.2-mg/day group and 5% in the 0.4-mg/day group). In approximately 1% of the patients on 0.4 mg/day, formication, constipation, vomiting, prolonged QT interval or rash led to discontinuation [6].

The second study was a multicenter, randomized, double-blind, placebo-controlled trial of a flexible dose of CLON-XR as adjunctive therapy to a psychostimulant in subjects aged 6–17 years with ADHD [11]. Patients with ADHD who had an inadequate response to their psychostimulant, defined as a total score ≥26 on the ADHD-RS-IV questionnaire after a minimum of 4 weeks on a stable stimulant regimen (i.e., ≤10% variation in dose), were randomized to CLON-XR or placebo in addition to their stimulant treatment for a total treatment period of 8 weeks. In the placebo plus stimulant group, 62% of patients were on a methylphenidate stimulant and 38% were on an amphetamine. In the CLON-XR plus stimulant arm, 58% were administered a methylphenidate stimulant, and 42% were administered an amphetamine. CLON-XR was initiated at 0.1 mg/day and titrated up to a maximum of 0.4 mg/day (divided dosing, twice daily) over a 3-week period. Up until week 5, the dose of CLON-XR could be adjusted to account for maximal efficacy and tolerability. After week 5 the dose was tapered, at a rate of 0.1 mg/week, until reaching the lowest possible dose (i.e., 0.1 mg/day) at week 8.

Of the CLON-XR subjects, 76% were titrated up to the maximum dose of 0.4 mg/day. The primary outcome measure was the total change in ADHD-RS-IV score from baseline to week 5. The improvement in this score was statistically significant in the CLON-XR plus stimulant group compared with the placebo plus stimulant group beginning in the first week of study treatment (week 2) and was maintained through week 8 [11]. No statistically significant effect versus placebo was observed between the CLON-XR plus methylphenidate and the CLON-XR plus amphetamine groups. By allowing the stimulant medication regimen to vary on the basis of the response of individual patients (i.e., methylphenidate or amphetamine), it was impossible to determine whether specific combinations of stimulant treatment with CLON-XR were more effective than others. It is therefore unknown if the combination of CLON with one specific stimulant would be better than another, or what the effects of CLON-XR would have been if a formal dose optimization phase had been used.

For all groups, the occurrence of treatment-emergent adverse effects was higher during weeks 0–3 when the study drug was initiated and titrated compared with all other weeks, even in the placebo plus stimulant arm. In the placebo plus stimulant group, 3% discontinued treatment owing to increased heart rate (n = 1), aggression (n = 1) and somnolence (n = 1). In the CLON-XR plus stimulant group, 1% discontinued owing to slowed thought processes (n = 1). More patients who received CLON-XR plus stimulant reported somnolence/sedation and fatigue. Throughout the study, changes in cardiovascular parameters as a result of treatment with CLON-XR were consistent with known effects of the drug (i.e., decreased heart rate and blood pressure) but were not clinically significant. From baseline to week 5, patients in the placebo plus stimulant group had a mean

increase in heart rate of 0.9 beats/min, a mean increase in systolic blood pressure of 0.4 mmHg, and a mean decrease in diastolic blood pressure of 0.1 mmHg. In the CLON-XR plus stimulant group there was a mean decrease in heart rate of 4.7 beats/min, a mean decrease in systolic blood pressure of 3.5 mmHg, and a mean decrease in diastolic blood pressure of 0.7 mmHg. The cardiac parameters were similar between the subjects on CLON versus placebo during the discontinuation period.

Adverse reactions

The most common adverse reactions experienced with CLON-XR monotherapy include somnolence, fatigue and irritability **(Table 3)** [7]. The most common side effects experienced when combined with stimulant medication include somnolence, fatigue, headache, nasal congestion and upper abdominal pain [11]. Somnolence and fatigue are generally worse during titration phases and occurred less than the immediate-release form [12]. In one study, 14–21% of patients reported moderate somnolence with CLON-XR compared with reports of moderate-to-severe sedation/drowsiness in 42–55% of patients with immediate-release CLON [12]. As an α-2 adrenergic agonist, CLON-XR has the potential to decrease blood pressure and heart rate. The study by Jain *et al.* demonstrated mean changes in systolic and diastolic measures of up to -8.8 mmHg and -7.3 mmHg, respectively, and up to -7.7 beats/min in heart rate on the 0.4-mg/day dose [6]. When combined with psychostimulant medication, effects are similar [11]. Alterations in electrocardiographic readings reflect the known pharmacology of CLON. In the study by Jain *et al.*, the percentages of patients with prolonged QTc interval (QTc ≥450) were 14% in the placebo group and CLON-XR 0.4-mg/day group and 11% in the 0.2-mg/day group [6]. No patients had a QTc

Table 3. Summary of adverse events†.

Study: CLON-XR for pediatric patients with ADHD			
Adverse event	**Placebo (%)**	**CLON-XR 0.2 mg/day (%)**	**CLON-XR 0.4 mg/day (%)**
Somnolence	6.6	39.5	30.8
Fatigue	1.3	15.8	12.8
Irritability	3.9	9.2	7.7
Pharyngolaryngeal pain	3.9	7.9	7.7
Increase in body temperature	2.6	5.3	2.6
Insomnia	1.3	5.3	6.4
Ear pain	1.3	5.3	0
Emotional disorder	1.3	3.9	5.1
Nightmare	0	3.9	9.0
Constipation	0	1.3	6.4
Dry mouth	1.3	0	5.1
Study: CLON-XR as add-on therapy to psychostimulants in children and adolescents with ADHD			
Adverse event	**Placebo + stimulant**	**CLON-XR + stimulant**	
Somnolence	8	20	
Headache	21	19	
Fatigue	4	16	
Upper abdominal pain	8	12	
Nasal congestion	6	9	
Pharyngolaryngeal pain	4	8	
Cough	8	6	
Irritability	9	5	
Insomnia	3	5	
Increased body temperature	2	5	
Dizziness	2	5	

†Adverse events with 5% or greater incidence in any active treatment group and at least twice the incidence of placebo.
CLON: Clonidine; XR: Extended release.
Data taken from [6,11].

reading ≥500 at any time during the study. As an adjunctive therapy to psychostimulant medications, no clinically significant change in QTc has been found [11].

CLON-XR should be used with caution in patients with a history of hypotension, bradycardia, heart block, cardiovascular disease or who are at risk for syncope. Blood pressure and heart rate should be obtained at baseline, following any dose changes, and periodically while on stable treatment [7]. Clinicians should monitor for any episodes of syncope or feeling faint after exertion, which may suggest an inadequate cardiovascular response to exercise challenge which may be induced by CLON.

Abrupt cessation of CLON-XR has not been studied in children and adolescents. When tapering, the dose of CLON-XR should be reduced in decrements of no more than 0.1 mg every 3–7 days. In hypertensive adults, abrupt discontinuation has resulted in symptoms of anxiety, brief light-headedness, tightness in the chest, headache, flushing, nausea and tachycardia. There are no known risks for abuse or dependence [7].

Drug interactions

Drug interaction studies with CLON-XR in children have not been conducted. However, reported interactions with oral immediate-release formulations include the possibility of potentiated CNS-depressive effects with other sedating medications, and bradycardia and atrioventricular block with agents that affect sinus node function or AV nodal conduction such as calcium channel blockers, β-blockers and digitalis. Other possible interactions include potentiated antihypertensive effects with antihypertensives and other CLON-containing medications [7].

Use in specific populations

Pregnancy

CLON-XR has a Category C pregnancy rating and is not recommended for use in pregnancy unless clearly needed [7].

Nursing mothers

Caution is advised for nursing mothers as CLON-XR is expressed in breast milk [7].

Adults

CLON-XR has not been studied in the treatment of ADHD in the adult population.

Preschool

CLON-XR has not been studied in children with ADHD less than 6 years of age. Rat studies revealed no drug effects on fertility, sexual or neurobehavioral development in young rats exposed to approximately three-times the maximum recommended dose [7].

Renal impairment

The pharmacokinetic impact that renal impairment has on CLON has not been studied in children. Patients with renal impairment should receive doses dependent on their level of impairment with cautious titration and frequent monitoring of blood pressure and heart rate [7].

Conclusion & future perspective

Although stimulants are effective and generally well-tolerated in the treatment of ADHD, some patients clearly need nonstimulant alternatives. Based on the two recent studies discussed in this article, CLON-XR is efficacious and relatively well-tolerated on a short-term basis for monotherapy or adjunctive therapy in the treatment of ADHD in children and adolescents. Long-term follow-up is needed to help delineate the role of CLON-XR in the long-term treatment of ADHD symptoms in children and adolescents.

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