Clonidine Extended-Release Tablets for Pediatric Patients With Attention-Deficit/Hyperactivity Disorder

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Objective: This study examined the efficacy and safety of clonidine hydrochloride extended-release tablets (CLON-XR) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). **Method:** This 8-week, placebo-controlled, fixed-dose trial, including 3 weeks of dose escalation, of patients 6 to 17 years old with ADHD evaluated the efficacy and safety of CLON-XR 0.2 mg/day or CLON-XR 0.4 mg/day versus placebo in three separate treatment arms. Primary endpoint was mean change in ADHD Rating Scale–IV (ADHD-RS-IV) total score from baseline to week 5 versus placebo using a last observation carried forward method. Secondary endpoints were improvement in ADHD-RS-IV inattention and hyperactivity/impulsivity subscales, Conners Parent Rating Scale–Revised: Long Form, Clinical Global Impression of Severity, Clinical Global Impression of Improvement, and Parent Global Assessment from baseline to week 5. **Results:** Patients (N = 236) were randomized to receive placebo (n = 78), CLON-XR 0.2 mg/day (n = 78), or CLON-XR 0.4 mg/day (n = 80). Improvement from baseline in ADHD-RS-IV total score was significantly greater in both CLON-XR groups versus placebo at week 5. A significant improvement in ADHD-RS-IV total score occurred between groups as soon as week 2 and was maintained throughout the treatment period. In addition, improvement in ADHD-RS-IV inattention and hyperactivity/impulsivity subscales, Conners Parent Rating Scale–Revised: Long Form, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, and Parent Global Assessment, occurred in both treatment groups versus placebo. The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on electrocardiogram were minor and reflected the known pharmacology of clonidine. **Conclusions:** Clonidine hydrochloride extended-release tablets were generally well tolerated by patients in the study and significantly improved ADHD symptoms in this pediatric population. Clinical trials registry information—Study Evaluating the Safety and Efficacy of Clonicel to Treat Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD), URL: *http://www.clinicaltrials.gov*, unique identifier: NCT00556959. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(2):171–179. **Key Words:** α_2-adrenergic agonist, attention-deficit/hyperactivity disorder, clonidine hydrochloride extended-release tablets

Attention-deficit/hyperactivity disorder (ADHD) is a neurobiological syndrome that results in inattention,[1] hyperactivity,[2] decreased performance of daily activities (e.g., school),[3] and increased health care use.[4] The etiology of ADHD remains elusive, but genetics[5] and environmental factors[6] may play a role. The disorder affects 1.5% to 15.8% of children and adolescents in the Western population.[7-10]

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ADHD is often comorbid with a range of psychological disturbances, including oppositional defiant disorder, autism, anxiety, and substance abuse.[11,12]

Although treatment guidelines for ADHD recommend stimulants (i.e., medications in the methylphenidate and amphetamine classes) as first-line therapies,[13] as many as 15% of patients are unresponsive to these medications.[14] In addition, adverse events (AEs), such as decreased appetite[15] and decreases in growth rate, have been reported.[16] There is a clear, unmet need for well-tolerated, nonstimulant therapies for some patients with ADHD.

Clonidine is a centrally acting α_2-adrenergic agonist that has been used successfully alone or in combination with stimulants to treat patients with hyperactivity disorders, conduct disorders, and ADHD.[17-25] In adults, clonidine is rapidly absorbed after oral administration,[26] thus dictating frequent dosing and producing AEs (i.e., sedation during peak concentrations) that have limited its use in the treatment of ADHD. A transdermal formulation of clonidine was developed to deliver the drug at a constant rate, thereby decreasing the peak-and-trough pharmacokinetics (PK) of the oral tablets[27]; however, adverse skin reactions have prevented its widespread use.[28]

To overcome the fluctuating PK of oral, immediate-release clonidine and to avoid the limitations of the transdermal patch, an extended-release formulation of clonidine (clonidine hydrochloride extended-release tablets [CLON-XR]) was developed. This formulation contains clonidine combined with cellulose ethers, such as hydroxypropyl methyl cellulose in a stable matrix, which allows the release of clonidine over a 12-hour period. A PK study of clonidine 0.1 mg in healthy adults showed that the maximum plasma concentration of CLON-XR occurred approximately 7 hours after dosing versus approximately 2 hours with the traditional immediate-release clonidine formulation.[29] The objective of the present study was to determine the efficacy and safety of CLON-XR (KAPVAY; Shionogi Inc., Florham Park, NJ) compared with placebo for the treatment of children and adolescents with ADHD.

METHOD

Patient Population

Patients 6 to 17 years of age with a diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtype according to criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and each patient's clinical research physician and a minimum score of 26 on the ADHD Rating Scale–IV (ADHD-RS-IV) were eligible to participate in the study. Patients were required to be in good health, be able to swallow tablets, be mentally competent, and have a body mass index of at least the fifth percentile for the patients' age group. Patients with a concomitant diagnosis of tics or oppositional defiant disorder were eligible for study inclusion. Assessment of ADHD and comorbid psychiatric disorders relied on the clinical assessment of the clinical research physician and the result of the Kiddie-Sads-Present and Lifetime Version questionnaire (version 1.0, 1996, Kaufman, Birmaher, Brent, Rao, and Ryan).

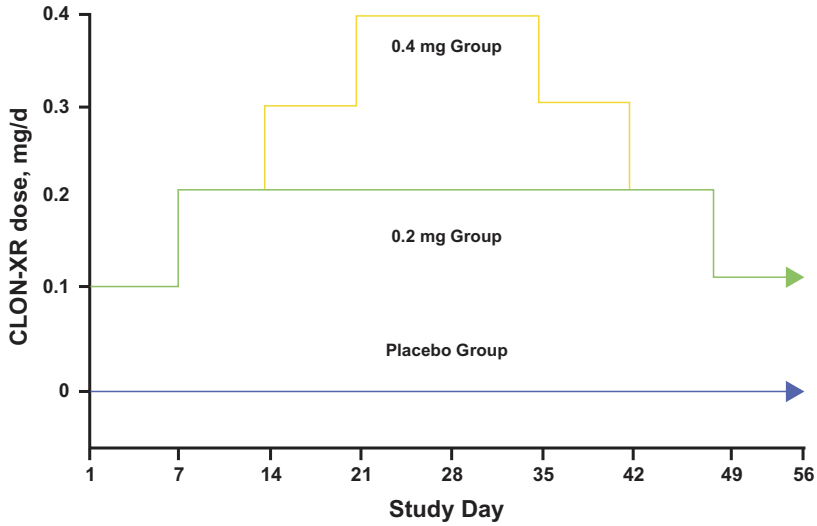
Female patients of childbearing age who were pregnant or lactating or who refused to use birth control were excluded from the study. Patients were also excluded if they had a clinically significant illness or abnormality that would increase the safety risk of clonidine or if they had a clinically significant abnormality on electrocardiographic readings that were interpreted by a single entity. Patients with a concomitant diagnosis or history of a psychiatric disorder that required psychotropic medication and patients with a severe concomitant Axis I or II disorder that could interfere with assessment of clonidine safety and efficacy were also excluded. In addition, patients with a history of conduct disorders, syncopal episodes, or seizures (except for febrile seizure before 2 years of age) were not enrolled. Patients with known drug abuse, a history of drug abuse, or a history of clonidine intolerance, including dermatologic reaction to transdermal clonidine, were excluded. Patients were also not enrolled if they had used any investigational drug within 30 days of the study initiation or had a positive drug test result for any medications other than those used for the treatment of ADHD.

The study protocol, all protocol amendments, and the informed consent form were approved by the Quorum Review Board, Seattle, WA. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice requirements described in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines. Written informed consent was obtained from all patients' legal guardians before enrollment; separate written assent forms were completed by all patients before study initiation.

Study Design

This 8-week, parallel-group, randomized, double-blind, placebo-controlled study was conducted at 13 centers in the United States from October 2007 to August 2008. The study was initiated with a screening period to determine eligibility followed by baseline safety and efficacy assessments and a 1- to 2-week washout period, during which all current ADHD medications were discontinued. Patients who completed the screening and washout periods were assigned to the treatment group of the next available randomization number at the study site. Patients were randomly assigned to receive placebo, CLON-XR 0.2 mg/day, or CLON-XR 0.4 mg/day in divided doses in a 1:1:1 ratio. Matching clonidine and placebo tablets were provided in weekly prepackaged blister sachets according to the randomization schedule. A forced dose-escalating titration schedule of 0.1 mg/day per week was used to achieve the target dose for the patient (i.e., 0.2 mg/day at week 2 or 0.4 mg/day at week 4), followed by dose tapering in 0.1-mg/day/week intervals until cessation of treatment at the end of week 8 (Figure 1). Patients who experienced AEs warranting dose reduction were discontinued from the

FIGURE 1 Study design showing dose escalation and tapering schematic. Note: A forced dose-escalating titration schedule of 0.1 mg/day per week was used to achieve the target dose for the patient (i.e., 0.2 mg/day at week 2 or 0.4 mg/day at week 4), followed by dose tapering in 0.1-mg/day/week intervals until cessation of treatment at the end of week 8. CLON-XR = clonidine hydrochloride extended-release tablets.



study. Safety and efficacy were determined at weekly visits, and a final safety assessment was performed 1 week after cessation of the study medication (i.e., week 9).

Study Assessments

Efficacy. The ADHD-RS-IV was completed by the investigator at screening, baseline, and weeks 1 through 8. The primary efficacy measurement was change in ADHD-RS-IV total score from baseline to week 5 using a last observation carried forward (LOCF) method to account for discontinuations that occurred sooner than week 5.

Secondary outcome measurements included ADHD-RS-IV hyperactivity/impulsivity and inattention subscales, the Clinical Global Impression of Severity (CGI-S) scale, Clinical Global Impression of Improvement (CGI-I) scale, Conners Parent Rating Scale–Revised: Long Form (CPRS-R), and Parent Global Assessment (PGA) scale. The CGI-S was completed by the investigator at baseline and at each weekly visit to assess the severity of a patient's condition. The CGI-S scale ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill). The CGI-I scale was also completed by the investigator at all weekly visits using a scale of 1 (very much improved) to 7 (very much worse). The CPRS-R and PGA were completed by parents/guardians. The CPRS-R, a general rating scale to assess hyperactivity and inattentiveness that consists of 80 items scored from 0 (not true at all) to 3 (very much true), was administered at baseline and at weeks 1, 3, 5, and 8. The PGA, a variation of the CGI-S and CGI-I with a scale ranging from 1 (very much improved) to 7 (very much worse), was completed at weekly visits. For each of these scales, the endpoint examined was the change from baseline to week 5 compared with placebo using a LOCF method. Additional secondary endpoints examined but not included in the present report were the Sleep Self Report questionnaire (Child's Form) and the Horacek Adrenergic Dysregulation Scale; these data will be presented elsewhere.

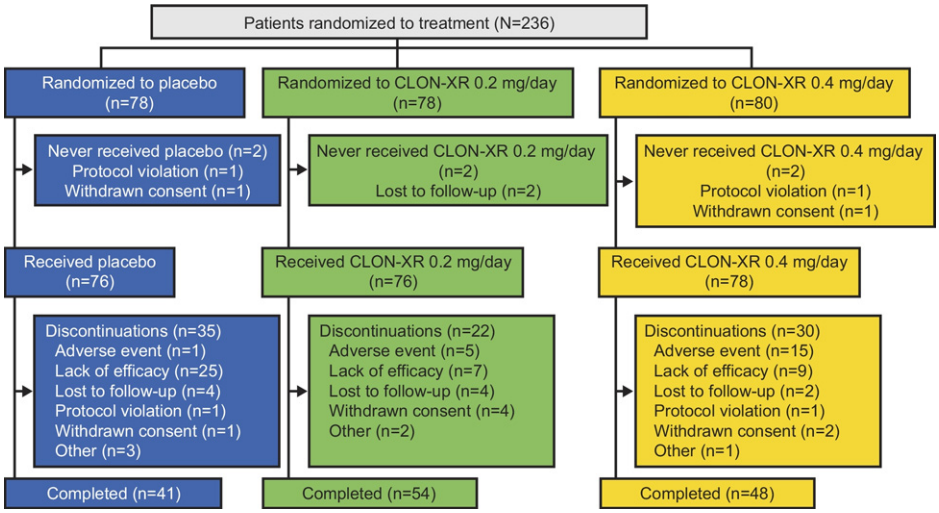
Safety. Safety assessments included evaluations of AEs by patient report in response to a general question on health (e.g., "How are you feeling?") and investigator assessment at all weekly visits. AEs were defined as any untoward medical occurrence in patients receiving an investigational treatment, including any unfavorable and unintended sign, symptom, or disease associated with use of the study medication. Vital sign measurements (i.e., blood pressure, heart rate, and body temperature) were evaluated at baseline and during all weekly visits. Twelve-lead electrocardiograms were obtained at baseline and at weeks 1, 2, 4, 6, 8, and 9. Vital sign measurements and electrocardiographic results were evaluated by a central laboratory. Laboratory assessments, including hematology and blood chemistry, were performed at screening and cessation of treatment.

Statistical Analyses

Sample Size. Sample size calculation using Student *t* tests to detect an effect size of 0.53 (i.e., mean change in ADHD-RS-IV total score of 8 points with an assumed standard deviation of 15) between the treatment groups and the placebo group at 90% power and a 2-sided α level of 0.05 was performed. This calculation indicated that 75 patients per treatment group would be required to achieve statistical significance in pairwise comparisons.

Efficacy Analyses. The intent-to-treat population was defined as all patients who were randomized to treat-

FIGURE 2 Patient recruitment and disposition. Note: CLON-XR = clonidine hydrochloride extended-release tablets.



ment, took at least one dose of study medication, and provided at least one efficacy assessment after baseline. The safety population consisted of all patients who received at least one dose of study medication.

All predefined primary statistical analyses were conducted for the intent-to-treat population. Primary efficacy was evaluated by comparing the change in ADHD-RS-IV total score from baseline to week 5 using an analysis of covariance model with terms for baseline ADHD-RS-IV total score, study site, and treatment. A LOCF method was used to account for patients who discontinued from the study before week 5. The p values were derived from two-sided tests, which were compared with the α level of 0.05 for statistical significance without adjusting for multiple group comparisons. As a sensitivity analysis, the analysis of covariance was applied to all patients who completed 5 weeks of treatment (observed case [OC] method). An additional sensitivity analysis of change in ADHD-RS-IV total score from baseline to weeks 1 through 5 was conducted post hoc at the request of the U.S. Food and Drug Administration using a mixed model for repeated measures method that included baseline ADHD-RS-IV total score as a fixed covariate and treatment group, study site, week, and treatment-by-week interaction as fixed factors. The degree of freedom of the denominator was approximated by the Kenward-Roger method, and the method of estimation was the restricted maximum likelihood (REML).[30] Secondary outcome measurements were analyzed using procedures similar to those used to evaluate ADHD-RS-IV total score. Effect size was calculated post hoc by treatment dose based on the observed mean differences between the groups and observed standard deviations using the unbiased version of the Hedges g. Safety data (i.e., AEs, vital signs, laboratory assessments, electrocardiograms) were collected from the defined safety population and were presented by treatment dose as descriptive statistics.

RESULTS

Patient Demographics and Disposition

In total 236 patients were randomized, of whom 230 received treatment: placebo (n = 76), CLON-XR 0.2 mg/day (n = 76), or CLON-XR 0.4 mg/day (n = 78; Figure 2). Two patients in the CLON-XR 0.2-mg/day group received study medication but did not complete any assessment after baseline (one withdrew consent and one was lost to follow-up) and were therefore excluded from the intent-to-treat population. Mean ADHD-RS-IV total score was similar among all groups at baseline (Table 1). The most commonly used class of concomitant medications was cough and cold preparations (11.4%), which were more commonly used in the CLON-XR 0.2-mg/day group (16%) than in the placebo (10%) and CLON-XR 0.4-mg/day (8%) groups. Patients in the CLON-XR 0.2-mg/day group also had greater use of systemic antibacterial agents, anti-inflammatory products, and antirheumatic products than the placebo or CLON-XR 0.4-mg/day groups. All other patient demographics were similar across all groups. Study completion was obtained in 53% of patients in the placebo group, 69% of patients in the CLON-XR 0.2-mg/day group, and 60% of patients in the CLON-XR 0.4-mg/day group (Figure 2). Discontinuations because of lack of efficacy were observed in 32%

TABLE 1 Patient Demographics and Characteristics (Intent-to-Treat Population)

Parameter	Placebo (n = 76)	CLON-XR 0.2 mg/day (n = 74)	CLON-XR 0.4 mg/day (n = 78)
Age (y), mean (range)	9.4 (6–16)	9.6 (6–17)	9.4 (6–17)
Age category, n (%)			
6–12 y	62 (81.6)	61 (82.4)	65 (83.3)
>12–17 y	14 (18.4)	13 (17.6)	13 (16.7)
Gender, n (%)			
Male	52 (68.4)	58 (78.4)	55 (70.5)
Female	24 (31.6)	16 (21.6)	23 (29.5)
Race, n (%)			
White	44 (57.9)	45 (60.8)	46 (59.0)
Black/African-American	23 (30.3)	19 (25.7)	20 (25.6)
Hispanic/Latino	6 (7.9)	6 (8.1)	7 (9.0)
Other	3 (3.9)	4 (5.4)	5 (6.4)
Weight (kg), mean (range)	42.3 (20.4–90.9)	40.8 (20.8–128.7)	40.1 (17.0–106.1)
ADHD-RS-IV total score, mean (range)	45.0 (15–54)	43.8 (27–54)	44.6 (27–54)

Note: ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale–IV; CLON-XR = clonidine hydrochloride extended-release tablets.

of patients who received placebo and in 9% and 11% of patients who received CLON-XR 0.2 mg/day and CLON-XR 0.4 mg/day, respectively. Medication compliance as assessed by tablet counts was similar between groups.

Efficacy

Mean improvement in ADHD-RS-IV total score from baseline to week 5 was significantly greater in both active treatment groups than in the placebo group as determined by the LOCF, OC, and mixed model for repeated measures methods[30] ($p < .0001$; Table 2). Mean change in ADHD-RS-IV total score in the two treatment groups was significantly different from placebo beginning at week 1 for the CLON-XR 0.2-mg/day group ($p = .02$) and week 2 for the CLON-XR 0.4-mg/day group ($p < .0001$) and continued throughout the treatment period (Figure 3). Results of the OC and mixed model for repeated measures methods[30] were similar to those of the LOCF method. The ADHD-RS-IV treatment effect size by dose was 0.713 (95% confidence interval 0.38–1.04) for the CLON-XR 0.2-mg/day group and 0.766 (95% confidence interval 0.44–1.09) for the CLON-XR 0.4-mg/day group.

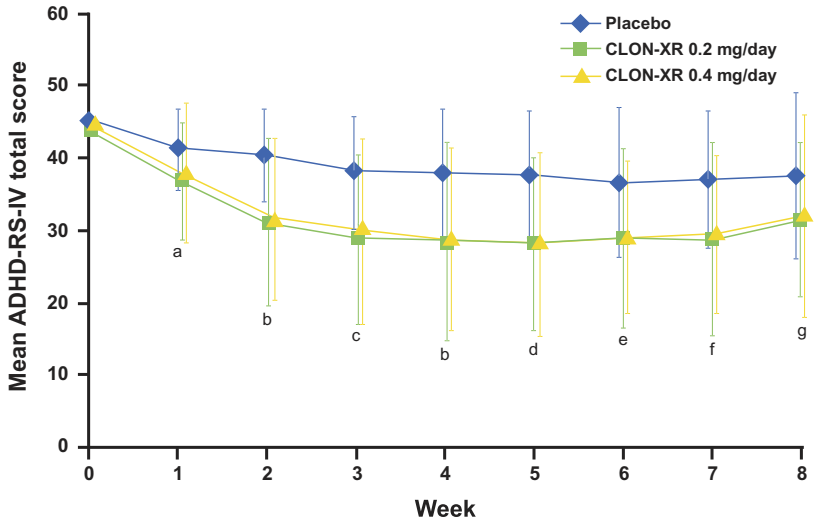
TABLE 2 Mean Change in Attention-Deficit/Hyperactivity Disorder Rating Scale–IV (ADHD-RS-IV) Total Score, Hyperactivity Subscale Score, and Inattention Subscale Score from Baseline to Week 5 (Intent-to-Treat Population)

ADHD-RS-IV Parameter	Placebo (n = 76)	CLON-XR 0.2 mg/day (n = 74)	CLON-XR 0.4 mg/day (n = 78)
LOCF method			
Total score, mean (SD)	−7.5 (9.41)	−15.6 (12.96)[§]	−16.5 (13.54)[§]
Hyperactivity, mean (range)	−4.1 (5–27)	−7.9 (0–27)[§§]	−8.8 (1–27)[§§§]
Inattention, mean (range)	−3.4 (1–27)	−7.7 (2–27)[#]	−7.7 (1–27)[††]
OC method			
Total score, mean (SD)	−8.0 (9.16)	−16.5 (12.08)[§]	−19.4 (12.75)[§]
Hyperactivity, mean (range)	−4.5 (5–27)	−8.3 (0–27)[†††]	−10.1 (1–27)[§]
Inattention, mean (range)	−3.5 (1–27)	−8.2 (2–27)[‡]	−9.3 (1–27)[§]
MMRM method[30]			
Total score, mean	−8.0	−16.5[§]	−19.4[§]

Note: CLON-XR = clonidine hydrochloride extended-release tablets; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; OC = observed case; SD = standard deviation.

[§]p < .0001, [§§]p = .0012, [§§§]p = .0002, [#]p = .0011, [††]p = .0006, [†††]p = .0017, [‡]p = .0003 versus placebo.

FIGURE 3 Mean Attention-Deficit/Hyperactivity Disorder Rating Scale–IV (ADHD-RS-IV) total score from baseline to week 5 using a last observation carried forward method. Note: ADHD-RS-IV total score was significantly improved at week 1 for the CLON-XR 0.2-mg/day group. Significant improvement was achieved in both CLON-XR groups beginning at week 2 and continued through study termination. Error bars represent standard deviations. Adjustment for multiplicity across visits was not performed. CLON-XR = clonidine hydrochloride extended-release tablets; [a] $p = .0219$ for CLON-XR 0.2 mg/day. [b] $p < .0001$ for both groups. [c] $p < .0003$ for both groups. [d] $p = .0005$ for both groups. [e] $p < .0054$ for both groups. [f] $p < .0074$ for both groups. [g] $p \leq .0288$ for both groups.



Using a LOCF method, patients who received CLON-XR had significantly greater improvement in ADHD-RS-IV inattention and hyperactivity/impulsivity subscale scores from baseline to week 5 than patients who received placebo. Mean change in ADHD-RS-IV inattention subscale score at week 5 versus baseline was −7.7 for both CLON-XR groups versus −3.4 for the placebo group ($p = .0011$ for CLON-XR 0.2 mg/day and $p = .0006$ for CLON-XR 0.4 mg/day). Improvements from baseline to week 5 in ADHD-RS-IV hyperactivity/impulsivity subscale score were −4.1 in the placebo group, −7.9 in the CLON-XR 0.2-mg/day group, and −8.8 in the CLON-XR 0.4-mg/day group ($p < .0012$). With respect to the inattention and hyperactivity/impulsivity subscale scores, a significant improvement in scores from baseline was observed by week 2 in both CLON-XR groups versus the placebo group ($p \leq .0002$ for inattention and $p < .0001$ for hyperactivity/impulsivity). Patients receiving CLON-XR also had significant improvements in other secondary endpoints throughout the study period. Change from baseline to week 5 versus placebo was significantly greater for CPRS-R total score, CGI-S, CGI-I, and PGA assessment. Mean improvement in CPRS-R total score was significantly greater than placebo in both CLON-XR groups ($p \leq .0122$) at weeks 3 and 5. In addition, improvement in CGI-S and CGI-I from baseline to week 5 was significantly greater in both treatment groups versus placebo ($p \leq .0001$ for CGI-S and $p \leq .0032$ for CGI-I). Significant improvement in PGA score from baseline in both treatment groups versus placebo was also observed as soon as week 2 ($p < .0001$) and was maintained through week 7 ($p \leq .0227$) in the CLON-XR 0.2-mg/day group and through week 5 in the CLON-XR 0.4-mg/day group ($p \leq .0099$). Results for all secondary endpoints using the OC method were similar to those obtained using the LOCF method.

Safety

Overall, 83% and 72% of patients who received CLON-XR or placebo, respectively, reported an AE. AEs that led to discontinuation occurred in 1% of patients in the placebo group, 7% of patients in the CLON-XR 0.2-mg/day group, and 19% of patients in the CLON-XR 0.4-mg/day group. The most common reasons for discontinuation were somnolence (0%, 4%, and 6% of patients in the placebo, CLON-XR 0.2-mg/day, and CLON-XR 0.4-mg/day groups, respectively) and fatigue (0%, 3%, 5% of patients in the placebo, CLON-XR 0.2-

TABLE 3 Treatment-Emergent Adverse Events (TEAEs) That Occurred in ≥5% of Treatment Groups and Had at Least Twice the Incidence of Placebo (Safety Population)

TEAE	Placebo, n (%) (n = 76)	CLON-XR 0.2 mg/day, n (%) (n = 76)	CLON-XR 0.4 mg/day, n (%) (n = 78)
Somnolence	5 (6.6)	30 (39.5)	24 (30.8)
Fatigue	1 (1.3)	12 (15.8)	10 (12.8)
Irritability	3 (3.9)	7 (9.2)	6 (7.7)
Pharyngolaryngeal pain	3 (3.9)	6 (7.9)	6 (7.7)
Increase in body temperature	2 (2.6)	4 (5.3)	2 (2.6)
Insomnia	1 (1.3)	4 (5.3)	5 (6.4)
Ear pain	1 (1.3)	4 (5.3)	0 (0)
Emotional disorder	1 (1.3)	3 (3.9)	4 (5.1)
Nightmare	0 (0)	3 (3.9)	7 (9.0)
Constipation	0 (0)	1 (1.3)	5 (6.4)
Dry mouth	1 (1.3)	0 (0)	4 (5.1)

Note: CLON-XR = clonidine hydrochloride extended-release tablets.

mg/day, and CLON-XR 0.4-mg/day groups, respectively). Other reasons for discontinuation in the CLON-XR 0.4-mg/day group included formication (1%), constipation (1%), vomiting (1%), prolonged QT interval corrected for heart rate (QTc; 1%), and rash (1%). No discontinuations for reasons other than somnolence or fatigue were noted in the CLON-XR 0.2-mg/day group.

No deaths or serious AEs occurred during the study. The percentages of treatment-emergent AEs (TEAEs) thought by the investigator to be related to treatment were 45% in the placebo group, 70% in the CLON-XR 0.2-mg/day group, and 62% in patients in the CLON-XR 0.4-mg/day group. The most common TEAEs with an incidence of ≥5% are listed in Table 3. Most TEAEs were mild or moderate. Mild somnolence was reported in 18% of patients who received CLON-XR 0.2 mg/day and in 10% of patients who received CLON-XR 0.4 mg/day. Moderate somnolence occurred in 21% of patients in the CLON-XR 0.2-mg/day group and in 14% of patients in the CLON-XR 0.4-mg/day group. Mild fatigue occurred in 13% and 4% of patients in the CLON-XR 0.2-mg/day and 0.4-mg/day groups, respectively. Moderate fatigue was reported by a larger percentage of patients in the CLON-XR 0.4-mg/day group (8%) than in the CLON-XR 0.2-mg/day group (1%). Six percent of patients experienced a severe TEAE. Severe fatigue was the only TEAE reported in the CLON-XR 0.2-mg/day group (1 of 76 patients; 1%). Patients in the CLON-XR 0.4-mg/day group reported severe somnolence (5 of 78 patients; 6%), infection (4 of 78 patients; 5%), aggression (1 of 78 patients; 1%), fatigue (1 of 78 patients; 1%), and constipation (1 of 78 patients; 1%). In all groups, the median time to onset of somnolence or fatigue occurred on days 8 to 9. The median duration of somnolence or fatigue was 19 to 25 days for all groups.

Minor dose-related changes in blood pressure and heart rate were observed. Mean systolic and diastolic blood pressures increased in the placebo group, increased and decreased in the CLON-XR 0.2-mg/day group, and decreased in the CLON-XR 0.4-mg/day group during the first period of the study (i.e., weeks 2 to 5). Heart rate was lower in both CLON-XR groups and alternately increased and decreased in the placebo group. Only one patient (CLON-XR 0.4-mg/day group) discontinued medication because of an increased heart rate. Laboratory assessments revealed no drug-related safety concerns, and no meaningful changes in body temperature were observed in any of the groups.

The incidence of sinus bradycardia (heart rate <55 beats/min for patients 6–11 years old and <50 beats/min for those 12–17 years old) increased from baseline in 5% to 6% of patients in the placebo and CLON-XR 0.2-mg/day groups and in 21% of patients in the CLON-XR 0.4-mg/day group. Changes from baseline in QT, QRS, and PR intervals were minimal and reflected the known pharmacology of clonidine. The percentages of patients with prolonged QTc interval during therapy (i.e., QTc ≥450 ms) were 14% in the placebo and CLON-XR 0.4-mg/day groups and 11% in the CLON-XR 0.2-mg/day group. An increase from baseline of QTc interval >60 ms was observed in zero patients in the placebo group, two patients in the CLON-XR 0.2-mg/day group, and one patient in the CLON-XR 0.4-mg/day group. No patients had a QTc reading ≥500 ms at any time during the study.

DISCUSSION

Although stimulants are the mainstay of therapy for patients with ADHD, safety concerns and lack of response may limit their use in some patients. Nonstimulant medications such as the α_2-adrenergic agonists clonidine[17-22,24] and guanfacine[31-33] have been evaluated for the treatment of ADHD with successful results; however, immediate-release formulations of these two medications elicit untoward effects, including somnolence,[20] sedation,[24] and drowsiness.[21] Both drugs also display a

relatively short half-life, requiring frequent dosing that may contribute to increased side effect burden and noncompliance. Extended-release formulations of guanfacine (guanfacine extended release [GXR]) and clonidine (i.e., CLON-XR) have been developed to overcome the AEs associated with the fluctuating PK of the immediate-release formulations. This study evaluated the efficacy of two doses of CLON-XR (0.2 and 0.4 mg/day) in decreasing ADHD symptoms in pediatric patients with ADHD.

Improvement in ADHD-RS-IV total score in this study was similar to that reported for GXR[31] and other emerging nonstimulants (i.e., atomoxetine and modafinil).[34-37] A significant effect of CLON-XR was observed early in treatment (i.e., week 1 for the CLON-XR 0.2-mg/day group and week 2 for the CLON-XR 0.4-mg/day group) and was maintained throughout the study period. The treatment effect sizes were 0.713 for the CLON-XR 0.2-mg/day group and 0.766 for the CLON-XR 0.4-mg/day group. These effect sizes are similar to those reported for other nonstimulant ADHD therapies, including atomoxetine (0.71),[35,36] modafinil (0.69),[34] and GXR (0.53[38] for GXR 1 mg/day, 0.43[38] to 0.64[31] for GXR 2 mg/day, 0.58[38] to 0.66[31] for GXR 3 mg/day, and 0.62[38] to 0.86[31] for GXR 4 mg/day). Clinical improvement in both clonidine groups was seen from baseline to week 5 by clinicians (i.e., improvement in CGI-S and CGI-I scores) and parents (i.e., improvement in CPRS-R and PGA scores) and was statistically significant compared with patients receiving placebo. Similar improvements in CGI-I and PGA scores have been reported for GXR.[31]

Clonidine hydrochloride extended-release tablets were generally well tolerated, with most TEAEs being mild to moderate. As with immediate-release clonidine[20,21,24] and guanfacine,[31] somnolence was the most common TEAE. This TEAE occurred more frequently in the first study period (i.e., weeks of dose escalation) than in the second (i.e., dose maintenance) and third (i.e., dose tapering) periods. One of the most common TEAEs (i.e., somnolence) was less severe in patients who received CLON-XR than in those treated with the traditional clonidine formulation; 14% to 21% of patients reported moderate somnolence with CLON-XR compared with the previously reported occurrence of moderate to severe sedation/drowsiness in 42% to 55% of patients who received flexible dosing (up to 0.6 mg/day) of traditional clonidine.[25] The clinical impact of CLON-XR on blood pressure and heart rate did not cause discontinuation in most patients, and alterations in electrocardiographic readings reflected the known pharmacology of clonidine.

These results should be interpreted in the context of the study design of fixed-dose escalation. This study design was chosen to ensure that sufficient numbers of patients were included in all dose groups to adequately power efficacy and safety assessments. Unfortunately, this design did not give clinicians the ability to adjust the dose based on a patient's weight or age; therefore, the results of this study may overestimate the safety concerns associated with CLON-XR in clinical practice. Nevertheless, CLON-XR significantly improved symptoms of ADHD, including hyperactivity and inattention, in children and adolescents with hyperactive-subtype or combined inattentive/hyperactive-subtype ADHD. Long-term follow-up and additional trials are necessary to more fully assess the efficacy of CLON-XR, especially in pediatric patients with comorbid psychiatric disorders (e.g., tics and oppositional defiant disorder) and in patients with inattentive-subtype ADHD. &

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