Clonidine for Attention-Deficit/Hyperactivity Disorder: II. ECG Changes and Adverse Events Analysis

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ABSTRACT

Objective: To examine the safety and tolerability of clonidine used alone or with methylphenidate in children with attention-deficit/hyperactivity disorder (ADHD). **Method:** In a 16-week multicenter, double-blind trial, 122 children with ADHD were randomly assigned to clonidine ($n = 31$), methylphenidate ($n = 29$), clonidine and methylphenidate ($n = 32$), or placebo ($n = 30$). Doses were flexibly titrated up to 0.6 mg/day for clonidine and 60 mg/day for methylphenidate (both with divided dosing). Groups were compared regarding adverse events and changes from baseline to week 16 in electrocardiograms and vital signs. **Results:** There were more incidents of bradycardia in subjects treated with clonidine compared with those not treated with clonidine (17.5% versus 3.4%; $p = .02$), but no other significant group differences regarding electrocardiogram and other cardiovascular outcomes. There were no suggestions of interactions between clonidine and methylphenidate regarding cardiovascular outcomes. Moderate or severe adverse events were more common in subjects on clonidine (79.4% versus 49.2%; $p = .0006$) but not associated with higher rates of early study withdrawal. Drowsiness was common on clonidine, but generally resolved by 6 to 8 weeks. **Conclusions:** Clonidine, used alone or with methylphenidate, appears safe and well tolerated in childhood ADHD. Physicians prescribing clonidine should monitor for bradycardia and advise patients about the high likelihood of initial drowsiness. *J. Am. Acad. Child Adolesc. Psychiatry,* 2008;47(2):189–198. **Key Words:** clonidine, electrocardiogram, tolerability, methylphenidate. Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00031395.

Clonidine, an α_2-agonist, has been demonstrated efficacious for youths with attention-deficit/hyperactivity disorder (ADHD) in previous studies.[1–3] Likewise, clonidine has demonstrated efficacy for tic disorders[4] and has been reported effective, in combination with stimulants such as methylphenidate, for tics and other problems commonly associated with stimulant treatments of ADHD, including rebound ADHD symptoms occurring later in the day and insomnia at bedtime.[1,5–7] Clonidine continues to be widely used in children despite the relatively small number of empirical studies demonstrating its safety, especially in combination with stimulant medications.[8,9]

Particular concerns about the safety of clonidine have arisen after case reports of sudden deaths in children treated with clonidine.[10] One patient was a 9-year-old boy treated with clonidine, promethazine, methylphenidate, and fluoxetine who experienced seizures and high levels of promethazine and fluoxetine attributed to

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an overdose. The second was a 9-year-old girl taking clonidine and methylphenidate who died 1 week after having general anesthesia and had no detectable blood levels of clonidine or methylphenidate at autopsy. A third was a 7-year-old boy also taking clonidine and methylphenidate whose medical history was remarkable for premature birth and on autopsy had fibrotic scarring of the left ventricle and papillary muscle attributed to perinatal hypoxia. A fourth patient taking clonidine and methylphenidate was noted on autopsy to have congenital heart malformations thought to have caused a fatal arrhythmia.

These cases have fueled an ongoing debate about the cardiovascular safety of clonidine, when used alone or with a stimulant.[11,12] Consistent with previous reports in adults,[13,14] some investigators have reported cases of bradycardia in children treated with clonidine.[10,15] From an estimated 60 children treated with clonidine, Chandran[15] reported three cases of bradycardia along with varying combinations of supraventricular premature complexes, nonspecific intraventricular conduction delays, anterior ischemic changes, and T wave abnormalities. However, all three children were taking concomitant medications with known effects on cardiac rhythms. In contrast, a chart review of pre- and posttreatment electrocardiograms (ECGs) in 42 consecutive children prescribed clonidine (alone or with stimulants) reported no systematic effects regarding heart rate (HR), PR intervals, or QTc intervals and noted that subjects' posttreatment ECGs were as likely to normalize on clonidine as to show new abnormalities.[16]

To date, there have been three published randomized controlled trials that systematically measured ECGs in a total of 107 children and adolescents prescribed clonidine. The first study involved both children and adults and reported no significant changes in ECGs in 24 subjects assigned to clonidine.[4] In contrast, a second study noted that two of eight children taking clonidine alone and four of eight children taking clonidine and concomitant methylphenidate developed new cases of bradycardia.[17] Only one of these cases was symptomatic, with the child experiencing fatigue and lethargy along with a resting junctional escape rhythm on the ECG. This same study also reported that subjects taking clonidine and methylphenidate had a significantly greater lengthening of PR intervals than subjects on clonidine monotherapy, although no child had a PR prolongation that was clinically significant or met criterion for a first-degree atrioventricular block. Most recently, a placebo-controlled trial in youths with ADHD and comorbid tics treated with clonidine alone (n = 34), methylphenidate alone (n = 37), and clonidine combined with methylphenidate (n = 33) noted no evidence of cardiac toxicity based on ECG changes, but reported one case of asymptomatic isorhythmic dissociation on clonidine alone.[3] In summary, data from these randomized controlled trials of clonidine have been contradictory regarding the cardiac effects of this medication in children. Both sides of the clonidine safety debate agree that more empirical study is needed.

Although the potential cardiac effects of clonidine have received more attention, other adverse events have also been reported. The most common adverse events associated with clonidine in pediatric clinical trials have included sedation, irritability, sleep disturbance, hypotension, dry mouth, and dizziness.[1] Such adverse events reportedly lessen over time or can be managed by dividing or lowering doses. Patients may also experience rebound hypertension and other physical complaints if doses are missed.[18,19] Such missed doses may have been a factor in at least one case of sudden death on clonidine.[10,12]

Given the continuing controversy about clonidine in children with mental health problems, further empirical study regarding its safety is needed to help clinicians and parents make more informed choices about its use. With this in mind, we conducted a multicenter, double-blind study of clonidine, randomly assigning children with ADHD to one of four groups: clonidine only (CLON), methylphenidate only (MPH), the combination of both drugs (COMB), or placebo (PBO). Another article reports findings regarding the efficacy of these treatments.[20] The present article examines changes from baseline cardiovascular and ECG measures, along with adverse events (AEs) based both on spontaneous reports and on parent and teacher side effect rating scales. The study was designed to compare subjects treated with clonidine (CLON or COMB groups) to subjects not treated with clonidine (MPH or PBO groups). Given the recent concerns raised about cardiovascular safety in children prescribed methylphenidate or other stimulants alone[21] and continuing questions regarding the safety of clonidine when used with stimulants, however, we also did an exploratory analyses to compare safety and tolerability across all four treatment groups and to identify possible interactions between clonidine and methylphenidate.

METHOD

From October 2000 to April 2004, a total of 201 subjects were screened as being eligible for this study. Of these, 122 children, 7 to 12 years of age, with a confirmed *DSM-IV* diagnosis of ADHD were randomly assigned to CLON (n = 31), MPH (n = 29), COMB (n = 32), or PBO (n = 30) in a 2 × 2 factorial design. Exclusion criteria included tic disorder, major depression, pervasive developmental disorder, autism, psychosis, mental retardation, anorexia nervosa, bulimia, a serious cardiovascular (e.g., significant hypotension, congenital heart disease) or other medical disorder that would preclude the safe use of methylphenidate or clonidine, impaired renal function (a routine urinalysis was performed), or pregnancy (a urine pregnancy test was performed on all adolescent girls). The following cardiac features were also considered exclusions for enrollment: prolonged QTc interval (>440 milliseconds), high-grade ventricular ectopy, atrioventricular block beyond first degree, bundle-branch block, intraventricular conduction block (>100 milliseconds), pacemaker rhythm or HR <60 bpm on the ECG, significant hypotension, cardiomyopathy, congenital heart disease, aortic or pulmonary stenosis, history of syncope, blood pressure at least 2 SDs above or below the age- and 2 sex-adjusted mean, and family history of cardiovascular problems (e.g., long QT syndrome, cardiomyopathy, premature death at younger than 45 years of age). The study's inclusion and exclusion criteria, randomization procedures, and other methods are detailed in a companion article.[20]

Subjects underwent a 16-week double-blind treatment period and were flexibly titrated on either clonidine or matching placebo over the first 4 weeks. methylphenidate or matching placebo was added and titrated over the next 4 weeks, followed by an 8-week dose maintenance period. Medication doses were adjusted to optimize tolerability and clinical response up until the last 2 weeks of the 16-week study period. The maximum allowed dose of clonidine was 0.6 mg/day (divided no more than four times daily, with first dose given as early as first thing in the morning and last dose generally given within an hour of bedtime). The maximum allowed dose of methylphenidate was 60 mg/day (divided no more than three times daily, given in the morning and at noon, with the same or a lower third dose prescribed at 4 P.M.).

Safety and tolerability were evaluated in part by spontaneous self-reports of AEs, either provided during study visits (weeks 4, 8, 12, and 16) or by telephone calls conducted between visits. AEs reported by participants were rated by the investigators as ''mild,'' ''moderate,'' or ''severe.'' AEs were also monitored at each visit by having parents and teachers complete the Pittsburgh Side Effects Rating Scale, a 20-item measure modified from the original 13-item measure to include potential side effects associated with clonidine.[22] With this, the parent or teacher rates each potential side effect on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Additional safety monitoring included serial checks of weight and supine and standing blood pressures and pulses for orthostatic changes (tilt) at each visit. An ECG was also obtained at each visit, although times elapsing between doses of study medication and ECGs were not controlled. Only changes from baseline to the final visit in vital signs and ECGs are reported here, including changes in HR, QRS, PR, and QTc intervals. The QTc interval was digitally determined as an averaged QTc. Any questionable QTc intervals were subsequently verified by the study's cardiologist (P.H.) as averaged intervals, calculated by hand. All of the safety and tolerability data were reviewed twice yearly by an independent safety monitoring committee and an National Institute of Neurological Disorders and Stroke–appointed Data and Safety Monitoring Board to rule out trends that would suggest that subjects were being exposed to intolerable risks through their participation in this study.

Rates of AEs and ECG abnormalities were compared among the treatment groups using Fisher exact tests. The primary comparisons focused on the main effects of clonidine (CLON + COMB versus MPH + PBO) and methylphenidate (MPH + COMB versus CLON + PBO), but comparisons among the four groups were also performed. Analysis of covariance was used to compare mean changes from baseline to week 16 in continuous outcomes (ECG results and vital signs) among the treatment groups, adjusting for the baseline value of the outcome variable. As above, the primary comparisons focused on the main effects of clonidine and methylphenidate. The analyses were performed according to the intention-to-treat principle and included all randomized subjects. For continuous outcomes, if a subject was missing a response at a particular visit, then the last available observation for that subject was carried forward and imputed for that visit. To determine the impact of subject withdrawal, the analyses were repeated including only subjects who had complete data for the response variable of interest, but the results differed only slightly from those of the above analyses and hence are not reported here. Values are presented as mean ± SD unless noted otherwise. p Values <.05 were considered statistically significant.

RESULTS

Details of subject flow and subjects' baseline characteristics are provided in the companion article[20] but summarized here. Subjects were 24 girls (20%) and 98 boys (80%) with a mean age 9.5 ± 1.6 years. Ninety-five subjects were white (78%), 13 African American (11%), 8 Hispanic (7%), and 6 "other" (4%). There were no important differences among the treatment groups regarding demographic and clinical variables. Mean doses of clonidine and methylphenidate are shown in Table 1 and frequencies of doses per day are shown in Table 2 for subjects assigned to active treatments.

Table 3 includes information on vital signs, ECG results, and AEs by treatment combination as well as by clonidine (yes/no) and methylphenidate (yes/no) status.

TABLE 1
Prescribed Doses of Clonidine and Methylphenidate in the Active Treatment Groups

	Mean Daily Dose of Clonidine, mg/day		Mean Daily Dose of Methylphenidate, mg/day	
Week	CLON	COMB	MPH	COMB
4	0.24 ± 0.10	0.24 ± 0.11		
8	0.23 ± 0.11	0.24 ± 0.13	26.5 ± 14.8	21.9 ± 14.3
16	0.24 ± 0.11	0.23 ± 0.13	30.2 ± 18.9	25.4 ± 18.2

Note: Values are means ± SDs. CLON = clonidine alone, MPH = methylphenidate alone, COMB = methylphenidate and clonidine combined.

TABLE 2
Prescribed Dosing of Clonidine and Methylphenidate in the Active Treatment Groups

Dosing administrations of clonidine			
Week	No. of Doses/Day	CLON, %	COMB, %
4	0	0.0	3.2
	1	3.2	3.2
	2	16.1	16.1
	3	51.6	54.8
	4	29.0	22.6
8	0	0.0	3.2
	1	9.7	9.7
	2	6.4	16.1
	3	51.6	48.4
	4	32.3	22.6
16	0	0.0	3.2
	1	10.0	12.9
	2	6.7	12.9
	3	50.0	48.4
	4	33.3	22.6
Dosing administrations of methylphenidate			
Week	No. of Doses/Day	MPH, %	COMB, %
8	0	8.7	6.9
	1	4.3	13.8
	2	26.1	27.6
	3	60.9	51.7
16	0	8.7	6.9
	1	4.3	13.8
	2	26.1	17.2
	3	60.9	62.1

Note: CLON = clonidine alone, MPH = methylphenidate alone, COMB = methylphenidate and clonidine combined.

The rate of bradycardia on ECG, defined as HR <60 bpm, was significantly higher in subjects treated with clonidine than in subjects not treated with clonidine (p = .02). Subjects taking clonidine alone experienced a trend toward a greater mean decrease in HR from the baseline to the final visit than subjects in the other groups, as measured by the ECG. There were otherwise no significant differences among the treatment groups regarding changes in ECG outcomes.

Subjects in either group treated with methylphenidate experienced a mean increase in sitting pulses relative to the other groups. No other mean changes differed significantly among the groups, except that subjects treated with clonidine experienced a greater orthostatic increase in systolic blood pressures (tilt), determined by comparing each subject's supine and standing blood pressures. All four groups had mean weight gains during the 16-week study period, but these gains were significantly less for subjects taking methylphenidate than for subjects not taking methylphenidate. No interactions were noted between clonidine and methylphenidate with respect to the continuous outcome variables, either based on ECG outcomes or vital signs.

Also shown in Table 3 are rates of the most common AEs reported spontaneously at any time during the 16 week follow-up period, including complaints of at least moderate severity that occurred in >5% of the sample. These included nervousness, somnolence, apathy, depression, dyspepsia, insomnia, fatigue, and headache. The incidence of AEs rated at least moderate in severity differed significantly among the four treatment groups, with the highest rates noted in subjects treated with clonidine. The four treatment groups differed significantly regarding rates of somnolence, with subjects treated with clonidine experiencing a higher rate than subjects not treated with clonidine (p < .0001). Fatigue was also significantly more common in subjects treated with clonidine (p = .03) as was nervousness (p = .04).

Additional analyses compared incidences of new AEs reported at least moderate in severity on the Pittsburgh Side Effects Ratings Scale by parents (Table 4) or teachers (Table 4). These findings were consistent with spontaneously reported AEs summarized above. Once again, subjects treated with clonidine differed significantly from subjects not treated with clonidine in having a higher rate of being "dull/tired/listless" and having "drowsiness/sedation," both on parent and teacher ratings (p < .0001 for all). Moreover, subjects treated with clonidine had a higher rate of "dry mouth" as reported by parents (p = .01), but not by teachers. Subjects taking methylphenidate had a lower rate of being worried/anxious as reported by parents (p = .03) but not by teachers (p = .15).

Because many subjects treated with clonidine experienced drowsiness, we examined rates of drowsiness over time as reported by parents on the Pittsburgh Side Effects Rating Scale, categorizing symptom reports as positive if they were rated at least mild. As summarized in Figure 1, many youths in either group treated with clonidine experienced initial drowsiness relative to others not treated with clonidine. However, the relative frequency of drowsiness lessened over time to levels equivalent to those in subjects not taking clonidine. Similar findings were apparent in subjects taking clonidine from teachers' reports on the Pittsburgh Side Effects Rating scale. These reports of drowsiness did not

TABLE 3
Changes in Vital Signs, ECGs, and AEs by Treatment Group

					Taking Clonidine?			Taking Methylphenidate?		
	PBO (n = 30)	MPH (n = 29)	CLON (n= 31)	COMB (n= 32)	Yes (n = 63)	No (n= 59)	p	Yes (n = 61)	No (n = 61)	p
Examination changes										
Weight, kg	1.4 ± 1.6[a]	0.3 ± 2.3[a,b]	2.0 ± 2.9[b,c]	0.6 ± 2.3[c]	1.3 ± 2.7	0.9 ± 2.0		0.4 ± 2.3	1.7 ± 2.3	.0007
Supine SBP	−2.0 ± 7.1[a]	−1.1 ± 7.6	−0.9 ± 10.0	2.8 ± 11.6[a]	1.0 ± 10.9	−1.5 ± 7.3		1.0 ± 10.0	−1.5 ± 8.6	.05
Supine DBP	−1.3 ± 7.1	−2.1 ± 7.7	−1.2 ± 8.8	1.0 ± 8.8	−0.1 ± 8.8	−1.7 ± 7.4		−0.5 ± 8.4	−1.2 ± 8.0	
Supine HR	−2.1 ± 11.0	3.1 ± 10.7	−2.5 ± 13.6	−0.1 ± 13.6	−1.3 ± 13.6	0.5 ± 11.1		1.4 ± 12.3	−2.3 ± 12.3	.03
Standing SBP	0.1 ± 8.6	−0.5 ± 9.5	−4.5 ± 10.9[a]	2.0 ± 15.5[a]	−1.2 ± 13.7	−0.2 ± 9.0		0.8 ± 12.9	−2.2 ± 10.0	.06
Standing DBP	0.3 ± 6.3	0.1 ± 10.3	−1.7 ± 8.7	−1.4 ± 8.5	−1.5 ± 8.6	0.2 ± 8.4		−0.7 ± 9.4	−0.7 ± 7.6	
Standing HR	−1.9 ± 12.0	4.4 ± 14.2	−0.9 ± 17.0	−2.1 ± 14.8	−1.5 ± 15.8	1.2 ± 13.4		1.0 ± 14.8	−1.4 ± 14.6	
Tilt SBP	−2.1 ± 7.8	−0.6 ± 8.3	3.5 ± 10.9	0.8 ± 12.7	2.1 ± 11.8	−1.4 ± 8.0	.05	0.01 ± 10.8	0.7 ± 9.8	
Tilt DBP	−1.6 ± 7.6	−2.2 ± 11.7	0.5 ± 10.3	2.4 ± 9.1	1.4 ± 9.6	−1.9 ± 9.7	.08	0.2 ± 10.5	−0.5 ± 9.0	
Tilt HR	−0.2 ± 9.4	−1.3 ± 14.3	−1.5 ± 13.6	2.0 ± 9.7	0.3 ± 11.8	−0.8 ± 12.0		0.4 ± 12.1	−0.9 ± 11.6	
ECG changes										
HR, bpm	−1.2 ± 7.3	−0.3 ± 10.3[a]	−6.8 ± 15.4[a]	−1.6 ± 10.8	−4.1 ± 13.4	−0.7 ± 8.8	.09	−1.0 ± 10.5	−4.0 ± 12.4	.10
PR, ms	1.8 ± 13.4	1.7 ± 10.9	0.1 ± 17.1	−0.1 ± 17.1	0.0 ± 16.9	1.7 ± 12.1		0.8 ± 14.4	0.9 ± 15.3	
QRS, ms	0.4 ± 5.1	−1.0 ± 7.6	−0.1 ± 5.7	2.4 ± 9.7	1.2 ± 8.0	−0.3 ± 6.5		0.8 ± 8.9	0.1 ± 5.4	
QTc, ms	2.5 ± 21.9	1.6 ± 23.6	−4.6 ± 23.5	2.4 ± 22.0	−1.0 ± 22.8	2.1 ± 22.6		2.0 ± 22.6	−1.1 ± 22.8	
Abnormal ECG rate, %										
HR <60 bpm	3.3	3.5	22.6	12.5	3.4	17.5	.02	13.1	8.2	
PR >200 ms	0.0	3.5	0.0	0.0	0.0	1.7		1.6	0.0	
QTc >120 ms	0.0	3.5	6.5	0.0	3.2	1.7		1.6	3.3	
AE rate, %										
Nervousness	13.3	17.2	32.3	31.3	31.7	15.3	.04	24.6	23.0	
Somnolence	6.7[a,b]	6.9[c,d]	41.9[a,c]	34.4[b,d]	38.1	6.8	<.0001	21.3	24.6	
Apathy	16.7	13.8	32.3	18.8	25.4	15.3		16.4	24.6	
Depression	20.0	17.2	22.6	12.5	17.5	18.6		14.8	21.3	
Dyspepsia	13.3	24.1	19.4	15.6	17.5	18.6		19.7	16.4	
Insomnia	16.7	3.4	16.1	12.5	14.3	10.2		8.2	16.4	
Fatigue	10.0	0.0[a,b]	22.6[a]	15.6[b]	19.0	5.1	.03	8.2	16.4	
Headache	10.0	3.4	16.1	15.6	15.9	6.8		9.8	13.1	
Any AE, %	40.0[a,b]	58.6[c]	83.9[b,c]	75.0[a]	79.4	49.2	.0006	67.2	62.3	

Note: Examination and ECG changes measured from baseline to week 16 (or last observation carried forward). AE = adverse event rated at least moderate on AEs log. AEs listed only if they occurred in at least 5% within one or more treatment groups. ECG abnormalities and AEs considered present if occurring at any time in the 16-week randomization phase. Superscripts show treatment groups differing significantly (p < .05) in post hoc testing. Only p values ≤.10 reported. ECG = electrocardiogram; AEs = adverse events; PBO = placebo; MPH = methylphendiate only; CLON = CLON only; COMB = combination of clonidine and methylphenidate; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate in bpm; Tilt = change in vital sign from supine to standing position; PR = PR interval; QRS = QRS interval; QTc = corrected QT interval.

lead to early discontinuations of the medication on clonidine with a single exception. One child in the CLON group (taking clonidine 0.20 mg/day) experienced both sedation and social withdrawal and was removed from the study 5 weeks after randomization.

Thirty severe AEs were reported in 10 subjects receiving CLON, 10 in 3 subjects receiving MPH, 39 in 9 subjects receiving COMB, and 9 in 4 subjects receiving PBO. None of the severe AEs involved suicidality or required hospitalization. One subject receiving COMB (0.2 mg/day of clonidine and 5 mg/day of methylphenidate) was withdrawn at week 14 at the recommendation of the study cardiologist after experiencing a prolonged QTc interval (>440 ms) as well as ECG findings suggestive of left ventricular hypertrophy. This child had a normal echocardiogram and never reported physical complaints

TABLE 4
Moderate or Severe Adverse Events on Pittsburgh Side Effect Rating Scale

	PBO (n = 30)	MPH (n = 29)	CLON (n = 31)	COMB (n = 32)	Clonidine Effect? p	Methylphenidate Effect? p
Parent ratings						
Repetitive motor tics	6.7	0.0	0.0	0.0		
Buccal-lingual movements	0.0	0.0	0.0	0.0		
Picking at skin	3.3	10.3	9.7	9.4		
Worried/anxious	10.0	3.4	16.1	0.0		.03
Dull/tired/listless	3.3	6.9	58.1	37.5	<.0001	
Headache	3.3	6.9	19.4	6.3		
Stomachache	16.7	10.3	25.8	12.5		
Crabby/irritable	23.3	31.0	35.5	31.3		
Tearful/sad/depressed	6.7	13.8	19.4	12.5		
Socially withdrawn	3.3	6.9	16.1	6.3		
Hallucinations	0.0	0.0	0.0	3.1		
Trouble sleeping	10.0	20.7	16.1	12.5		
Loss of appetite	10.0	13.8	29.0	9.4		
Dizzy/lightheaded	0.0	3.4	6.5	3.1		
Dry mouth	0.0	0.0	16.1	6.3	0.01	
Palpitations	0.0	3.4	0.0	0.0		
Chest pain	3.3	6.9	0.0	0.0		
Fainting/passing out	0.0	0.0	0.0	0.0		
Skin rash	0.0	0.0	3.2	3.1		
Sedation/drowsiness	3.3	0.0	54.8	28.1	<.0001	.08
Teacher ratings						
Repetitive motor tics	3.3	6.9	0.0	6.3		
Buccal-lingual movements	6.7	6.9	0.0	6.3		
Picking at skin	6.7	10.3	3.2	12.5		
Worried/anxious	20.0	6.9	12.9	6.3		
Dull/tired/listless	13.3	6.9	58.1	31.3	<.0001	
Headache	6.7	6.9	6.5	6.3		
Stomachache	3.3	0.0	6.5	3.1		
Crabby/irritable	16.7	0.0	12.9	15.6		
Tearful/sad/depressed	3.3	6.9	6.5	9.4		
Socially withdrawn	6.7	13.8	16.1	15.6		
Hallucinations	0.0	0.0	0.0	0.0		
Trouble sleeping	3.3	3.4	9.7	0.0		
Loss of appetite	3.3	0.0	3.2	0.0		
Dizzy/lightheaded	0.0	0.0	0.0	6.3		
Dry mouth	3.3	0.0	0.0	0.0		
Palpitations	0.0	0.0	0.0	0.0		
Chest pain	0.0	3.4	0.0	0.0		
Fainting/passing out	0.0	0.0	0.0	0.0		
Skin rash	0.0	0.0	3.2	3.1		
Sedation/drowsiness	0.0	0.0	41.9	21.9	<.0001	

Note: Columns show percentages of subjects with new complaints rated moderate or severe at any point in the 16-week trial. Treatment groups included placebo (PBO), methylphenidate alone (MPH), clonidine alone (CLON), or clonidine and methylphenidate combined (COMB). Only $p < 0.10$ are reported. Because of attrition, fewer subjects in each group had side effects data from every study visit: PBO (n = 9), MPH (n = 17), CLON (n = 26), and COMB (n = 24).

suggestive of cardiovascular problems. A second subject taking methylphenidate 20 mg/day was withdrawn in the last week of the double-blind phase complaining of repeated incidences of tachycardia and heart palpitations. No abnormalities were observed in this subject's vital signs or ECGs.

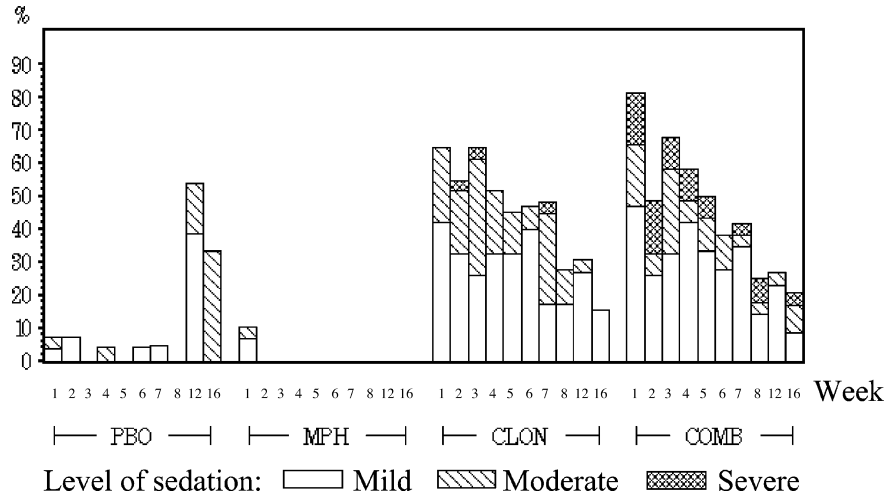

Fig. 1 Shown are rates of sedation/drowsiness across time, as reported on the parent version of the Pittsburgh Side Effects Scale in the four treatment groups: placebo only (PBO), CLON only (CLON), methylphenidate only (MPH), or the combination of both drugs (COMB).

Ratios of those completing the 16-week trial across the four groups were as follows: PBO = 9/30 (30%), MPH = 17/29 (59%), CLON = 26/31 (84%), and COMB = 24/32 (75%). Completion rates were significantly higher in subjects treated with clonidine than not treated with clonidine (79.4% versus 44.1%, $p < .0001$), despite higher reported rates of moderate to severe adverse events in subjects taking clonidine. Moderate to severe AEs were cited as a reason for withdrawal in eight subjects, although not always the primary reason, including five taking COMB, two taking CLON, and one taking MPH. In the COMB group, AEs associated with early withdrawals included irritability ($n = 1$), tearfulness and irritability ($n = 1$), headaches ($n = 1$), itching ($n = 1$), and asymptomatic ECG abnormalities as described above ($n = 1$). In the CLON group, one subject withdrew early complaining of social withdrawal and sedation and another of a 10-pound weight gain. In the MPH group, one subject withdrew early complaining of tachycardia and palpitations, as described above.

DISCUSSION

Amid continuing concerns about the safety and tolerability of clonidine when used alone or in combination with a stimulant in youths, this study conducted a detailed analysis of changes in ECGs, cardiovascular vital signs including orthostatic changes, along with parent and teacher reports of AEs in a large pediatric sample of children with ADHD. All subjects were participating in a randomized placebo-controlled trial of clonidine, with and without methylphenidate. The most notable group difference in ECG outcomes was the higher rate of bradycardia in subjects taking clonidine. Although our definition of bradycardia (HR <60 bpm) and findings are consistent with another study of clonidine in children,[17] the bradycardia experienced by most children in the present study was asymptomatic and of questionable clinical significance. No other consistent patterns were noted comparing ECG changes over time across treatment groups. We observed a greater difference over time in orthostatic increases (tilts) between supine and standing systolic blood pressures in subjects treated with clonidine relative to those not treated with clonidine, but in most cases, these were also asymptomatic.

These findings related to changes in vital signs but not ECGs are largely consistent with findings in a case series of 42 children with ADHD treated with clonidine alone or clonidine combined with a stimulant[16] and in two other randomized controlled trials[3,4] of clonidine. We observed no consistent findings to suggest an increased risk of atrioventricular or intraventricular conduction delays, in contrast to a small randomized controlled trial in children.[17] Of note, one subject in the COMB group experienced a prolonged QTc interval and signs of left ventricular hypertrophy on the ECG and was withdrawn as a precautionary measure, despite no reported cardiac symptoms and a normal echocardiogram.

Subjects in either group treated with clonidine also reported significantly higher rates of moderate or severe

AEs. Somnolence was a commonly reported side effect in subjects taking clonidine (with or without methylphenidate), along with potentially related side effects such as seeming dull, tired, or listless. Curiously, parent-reported somnolence over the 16-week period was significantly more common in subjects treated with COMB than with CLON (evident in Figure 1), yet these rates of somnolence differed between groups even in the first 4 weeks before subjects in the COMB group had received a stimulant, suggesting that they may represent a spurious finding. In contrast, clinician-rated fatigue considered moderate or greater in severity at any time over the 16-week trial was significantly less common in subjects treated with COMB than with CLON. In both COMB and CLON groups, parent-reported somnolence seemed to improve steadily over time, perhaps suggesting tolerance to clonidine. Similar patterns of early but improving somnolence on clonidine have been reported in previous randomized controlled trials.[3,17,23] Although somnolence and other AEs were greater in subjects taking clonidine, these were generally not clinically significant. In fact, early withdrawal from the study occurred significantly less often in subjects treated with clonidine relative to those not treated with clonidine.

Others have suggested that the combination of clonidine and stimulants may increase the risk of cardiovascular side effects.[11] All but one of the previous case reports of sudden death in children involved patients treated with a combination of clonidine and methylphenidate.[10] Curiously, no such cases have been reported more recently despite continued widespread use of this combination. Moreover, the design of the present study allowed us to systematically examine for potential interactions between clonidine and methylphenidate, given subjects' randomization to either or both active treatments or placebo in a 2×2 factorial design. However, in the present study, there was no hint of such interactions between clonidine and methylphenidate with respect to changes in ECGs, blood pressure, pulse, or AEs. Our findings thus echo results of another large randomized trial[3] and suggest that combined use of clonidine and methylphenidate is relatively safe when appropriate precautions are taken.

Concerns have also been raised about the risks with clonidine of rebound hypertension when doses are missed or the drug is abruptly discontinued.[18,19] Abrupt withdrawal of clonidine may have contributed to at least one of the cases of sudden death reported with clonidine.[10] Such rebound symptoms, however, were not observed in the present trial, perhaps because patients likely to be noncompliant were excluded up front, and medication compliance was closely monitored. Clinicians considering a trial of clonidine should remain selective about which patients are prescribed this medication, advise families of the risks of AEs related to noncompliance, and monitor treatment compliance closely.

Our findings should be viewed cautiously in light of the relatively small numbers in each of the four treatment groups, especially given greater rates of attrition in subjects assigned to placebo or methylphenidate alone. The study relied largely on parent and teacher questionnaires to identify possible side effects with medications. However, not all AEs are medication side effects. Such rating scales may overestimate rates of medication side effects because sometimes such complaints reflect other factors such as the underlying condition or comorbid psychopathology. For instance, parents reported that 30% of subjects in the overall sample had at least moderate levels of irritability (including 23% assigned to placebo), whereas teachers reported that 11% had moderate levels of being worried or anxious (including 20% assigned to placebo). Children with certain other psychiatric and medical conditions were excluded from the present study, and consequently our findings may not extend to children with ADHD with these other comorbid psychiatric or medical problems. Finally, it is important to note that rare but important AEs, either cardiovascular or psychiatric, may only be captured in a much larger sample.

Despite these limitations, our study suggests that clonidine, used alone or with methylphenidate, appears safe and well tolerated in children with ADHD without baseline cardiovascular problems, family history of cardiovascular problems, or certain other comorbid mental health problems. Our findings are generally supportive of the latest version of ADHD practice guidelines for patients taking clonidine.[19] Although routine monitoring of ECGs in patients prescribed clonidine and/or methylphenidate is not recommended, the fact that 17% of our sample treated with clonidine experienced asymptomatic bradycardia (defined here as HR <60 bpm) underscores the need for regular monitoring of pulse and blood pressure changes, and

symptoms suggestive of cardiovascular problems (e.g., exercise intolerance, dizziness, syncope). Families should also be advised of the high likelihood of initial somnolence with clonidine, which typically will improve over time. Should bradycardia or other intolerable side effects occur, clinicians may try to lower clonidine doses gradually to see whether these improve, but should avoid abruptly discontinuing clonidine, especially when patients are taking higher doses.

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