Long-Tenn Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in Adults With ADHD

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FOCUS POINTS

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurobehavioral condition that can persist into adulthood.
- Psychostimulants are recommended as first-line pharmacologic agents for ADHD symptom management in children and adults.
- Psychostimulants such as methylphenidate and mixed amphetamine salts exert sympathomimetic effects that can lead to changes in cardiovascular parameters.
- Although psychostimulant-induced cardiovascular changes are generally not clinically significant in pediatric patients, little is known about the cardiovascular effects of such agents in adults.
- In this study, most adults with ADHD (in whom major medical illness and cardiovascular morbidity are absent) given up to 24 months of mixed amphetamine salts extended release (MAS XR) 20-60 mg/day exhibited small and clinically insignificant average changes in cardiovascular parameters.
- The small number of cases with borderline blood pressure or pulse measures at baseline who experienced clinically significant increases in such values with MAS XR therapy highlights the importance of evaluating blood pressure and pulse at baseline and periodically during therapy so that treatment regimen can be adjusted in a timely manner.

ABSTRACT

Objective: To assess long-term cardiovascular effects of mixed amphetamine salts extended release (MAS XR) in adults with attention-deficit/hyperactivity disorder (ADHD) combined subtype.

Methods: 223 otherwise healthy adults (≥18 years of age) with ADHD combined subtype were exposed to s24 months of MAS XR (20—60 mg/day). Resting sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) and pulse were measured at baseline and weekly, then monthly during long-term treatment. Twelve-lead electrocardiograms were obtained at screening/baseline, weekly, then at 3- and 6-month intervals up to 24 months.

Findings: With MAS **XR** 20-60 mg/day, mean changes in DBP (1.3±9.2 mm Hg; P=.O42), SBP (2.3±12.5 mm Hg; P=.006), and pulse (2.1±13.4 bpm; P=,019) were small and not clinically significant. A clinically insignificant increase in QTcB (corrected by Bazett's formula) interval (7.2 msec; Pc.OOl) was observed at 24 months. No subject exhibited QTcB interval >480 msec (QTcF [corrected by Fridericia's formula] >454 msec). Seven subjects discontinued due to a cardiovascular adverse event (hypertension, n=5, palpitation/tachycardia, n=2); none of these events was reported as serious. Few subjects with normal baseline vital signs (using approved parameters at the time of study initiation) exhibited clinically significant abnormalities at end point; several subjects with borderline baseline values exhibited shifts to abnormal values during MAS XR therapy.

Conclusion: Cardiovascular effects of long-term MAS XR (≤60 mg/day) were minimal in otherwise healthy adults with ADHD. Nevertheless, vital signs should be monitored prior to and during treatment with any stimulant.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the more prevalent chronic health conditions encountered in pediatrics,[1,2] with as many as 2% to 18% of community school-age children estimated to be affected.[1] An estimated 30% to 65% of patients continue to experience symptoms into adulthood.[3-5] Awareness of adult ADHD is growing and has raised the need to define effective and well-tolerated treatment options. Currently, psychostimulants such as amphetamines or methylphenidate (MPH) constitute first-line pharmacologic treatment of ADHD in pediatric and adult cases.[6] Efficacy in adults with immediate-release (IR) and extended-release (XR) formulations of MPH and mixed amphetamine salts

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(MAS) appears to be comparable to that seen in children with ADHD.[7,10]

Stimulants have sympathomimetic effects that can result in increases in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate at therapeutic doses. However, such changes with IR amphetamine and MPH formulations in children and adolescents are, in general, clinically unremarkable.[11,12] A scientific statement released by the American Heart Association (AHA) recommended determining heart rate and blood pressure (BP) at baseline and on follow-up visits for children or adolescents receiving IR stimulant medications; however, the guidelines made no specific recommendations for electrocardiographic (ECG) monitoring with stimulant therapy.[13] The potential for harmful cardiovascular effects of stimulant use in children and adults has also been highlighted by recent regulatory actions in the United States and Canada. In 2004, a warning label was placed on MAS XR stating that amphetamine misuse or use by patients with underlying structural cardiac abnormalities may cause sudden death or serious cardiovascular events. During 2005, Health Canada briefly removed then reinstated MAS XR in the Canadian marketplace. The actions of Health Canada prompted a US Food and Drug Administration re-review of the postmarketing data and the FDA panel concluded that the rate of sudden death in 12 pediatric patients treated with MAS XR did not exceed the number that would be expected to occur in children (1-20 years of age) even without amphetamine treatment (~3.3 in 100,000 annually). The FDA panel further found that all of the postmarketing cases in question were marked by underlying structural cardiac abnormalities, preexisting cardiovascular disease, a family history of ventricular tachycardia, or unusual cardiovascular stress, or drug misuse. The panel recommended no further regulatory action; subsequently, in August 2005, Health Canada reinstated the use of MAS XR throughout the Canadian market.

These cases highlight the fact that cardiovascular disease or its history often goes undetected or noted by currently treating physicians; in adults for instance it has been estimated that ~1.7% to 8.8% of cases with evidence of ischemic heart disease go unrecognized.[14] They also highlight the timeliness and importance of the AHA recommendations to obtain careful patient and family histories regarding cardiovascular conditions in patients receiving any type of psychostimulant therapy.

The cardiovascular effects of stimulant therapy in adults with ADHD are less well characterized but appear to be similar in magnitude to those changes seen in pediatric patients.[7,8] While this is encouraging, much more research is required to fully characterize the cardiovascular changes and potential risks of stimulant therapy in adults with ADHD. Such patients may be more vulnerable to changes in BP and pulse not only due to their increasing age (typically between ages 35 and 40), but also due to the potential presence of medical comorbidities, such as essential hypertension and arteriosclerosis, that may go undetected even during careful screening. Very limited research has been conducted on the cardiovascular effects of XR stimulant formulations. In a 1-year study of treatment with a long-acting, osmotic-release formulation of MPH (18-54 mg/day) in children with ADHD, sustained improvements in ADHD symptoms were not accompanied by any clinically meaningful changes in BP or pulse (<4 mm Hg and <4 beats per minute [bpm], respectively).[15] MAS XR has been formulated for once-daily dosing via the inclusion of immediate-release and delayed-release pellets,[16] with therapeutic effects persisting for up to 12 hours.[17] In an earlier report from a short-term, multicenter, double-blind, forced-dose-escalation study in adults with ADHD, MAS XR exhibited a safety profile similar to that reported in pediatric studies.[10] Herein, we present cardiovascular assessments obtained among subjects who participated in the short-term study and a 24-month, open-label extension of that study.

METHODS

The cardiovascular safety of MAS XR in the management of adults with ADHD was examined in two phases: a 4-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group, forced-dose-escalation study of MAS XR 20, 40, and 60 mg/day[10] and a 24-month open-label extension study.

Subjects

Subjects were male orfemale, al 8 years of age, diagnosed with ADHD based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR)[18] criteria for ADHD combined type, and thought to be in good physical health at short-term study entry. Excluded were subjects with a history of or ongoing cardiovascular disease, including history of coronary artery disease, angina pectoris, or other coronary artery disease variant; myocardial infarction; bypass surgery; angioplasty; or any clinically or electrocardiographically significant cardiac or vascular abnormality. A BP consistently >139/89 mm Hg, heart rate consistently <50 or >120 bpm, or

a requirement for concomitant medications that could affect heart rate, BP, or the central nervous system also were exclusionary. It should be noted that the blood pressure and pulse thresholds used for subject selection, while higher than what is considered normal among physicians today, were in line with AHA guidelines when this study was designed and implemented. Subthreshold anxiety or depressive symptoms were not exclusionary, but subjects with comorbid psychiatric diagnoses (eg, psychosis; bipolar disorders; pervasive developmental disorder; severe obsessive-compulsive, depressive, or anxiety disorders; history of suspected substance abuse or dependence disorder [excluding nicotine] according to DSM-IV-TR criteria) were not eligible to participate. To be eligible for the extension study, subjects were required to have completed at least 1 week of double-blind treatment in the short-term study without experiencing any clinically important adverse events that would preclude continued exposure to MAS XR. Institutional review boards at each participating research site approved all study procedures and informed consent forms. All subjects voluntarily signed the informed consent form.

Study Visits and Dosing

The studies were designed to test the safety and efficacy of MAS XR administered once daily at doses ranging from 20 to 60 mg in adults with ADHD. During the initial 4-week study, subjects were randomly assigned to receive MAS XR 20, 40, or 60 mg/day in a forced-dose-escalation manner. Study visits occurred at baseline and weekly during this time. During the open-label extension study, visits occurred weekly for the first 4 weeks to assess safety and tolerance, and to adjust dose levels if necessary. Thereafter, visits occurred at monthly intervals for up to 24 months.

For the first week of the open-label extension study, all subjects initiated MAS XR treatment at 20 mg/day, regardless of final dose in the double-blind study. During the first month of the extension, the study dose could be increased by the investigator in 20-mg increments up to 40 or 60 mg/day at the weekly visits. Doses could be increased by a 20-mg increment at the month 2 visit and increased or decreased by 20-mg increments at subsequent monthly visits based on the investigator's judgment of optimal dose. Optimal dose was determined by the safety (eg, occurrence, severity, relationship of adverse events to MAS XR) and effectiveness (ADHD Rating Scale scores[19]) of the drug.

Cardiovascular Measures

Cardiovascular measures included resting/sitting SBP and DBP and resting/sitting pulse rate. BPs were measured in the same arm by the same study personnel using the same cuff when possible (either manual or automated) after the subject had been seated for at least 3 minutes at every study visit. Measurements were taken at baseline and weekly during the short-term study. During the long-term study, cardiovascular measurements were taken at baseline (the last visit of the short-term study), weekly during the first month, and then monthly up to 24 months. The timing of vital sign assessment relative to medication administration was not standardized; however, most clinic visits were likely to have occurred within 12 hours of the morning MAS XR dose.

ECG measurements were performed using a 12-lead ECG. For the short-term study, ECGs were completed at the screening or baseline visit (baseline ECG), week 2, and again at the final study visit (after 4 weeks of MAS XR treatment or at the final clinic visit if a participant withdrew from the study early). The end point ECG from the short-term study was considered the baseline ECG for the long-term study; repeat ECGs (timed to assess subjects receiving a stable, optimized dose for at least 1 month) were conducted at months 3, 6, 12, 18, and 24 (or upon early termination). A central laboratory was used to evaluate all ECG readings (Covance Central Diagnostics, Reno, NV). If the central laboratory deemed an ECG abnormal, the study investigator evaluated the abnormality for clinically significant changes from baseline. If the investigator considered the ECG abnormality to be clinically significant, it was then reviewed by a cardiologist. The Bazett formula was used to correct QT intervals for heart rate effect (QTcB).[20] BP, pulse, and ECGs were not assessed with respect to time of medication dose administration or in relation to peak blood levels of MAS XR in either study.

Statistical Analyses

Only subjects enrolled in the 4-week double-blind study were eligible to participate in the 24-month open-label extension study. Subject data for this report were summarized by three rollover categories from the short-term double-blind study: (1) subjects who were new to MAS XR (eg, MAS XR naive: all subjects who were randomized to receive placebo in the short-term study); (2) subjects who received uninterrupted MAS XR treatment (eg, MAS XR continuous: all subjects

whose final visit of the short-term study served as their baseline visit for the long-term study); and (3) subjects who received interrupted MAS XR treatment (eg, MAS XR interrupted: all subjects who experienced a disruption in MAS XR treatment for any reason between studies). The safety sample included all subjects who enrolled in the open-label extension study and received at least one dose of MAS XR. All statistical analyses were performed using SAS® for Windows Version 6.12 or higher (SAS Institute, Cary, NC). The baseline visit for the open-label extension study was the last visit of the double-blind treatment phase of the short-term study. Vital sign and ECG data were summarized by descriptive statistics and by rollover category, and mean changes from baseline to each postbaseline visit and end point (defined for any given subject as the last valid postbaseline observation) were analyzed using one-sample paired t tests with a=.O5.

Clinically significant and abnormal laboratory values, vital signs, and ECG data were summarized in addition to the statistical analysis of changes from baseline. A predefined limit al 10 bpm or an increase of >25 bpm relative to baseline was considered clinically significant for individual pulse measurements. Individual BP measurements >=150 mm Hg systolic (or an increase of >20 mm Hg relative to baseline) or 2=100 mm Hg diastolic (or an increase of >10 mm Hg relative to baseline) at any study visit were considered clinically significant. Individual changes in QT, QTcB, or QTcF (corrected by Fridericia's formula) intervals >30 msec relative to baseline values were considered clinically noteworthy.[21] Treatment-emergent adverse events, drug-related adverse events, adverse events leading to study discontinuation, and serious adverse events were summarized using Coding Symbols for the Thesaurus of Adverse Reaction Terms (COSTART) terminology, dose at the onset of the adverse event, and relationship to MAS XR as judged by the investigator.

FINDINGS

Subjects

Subject baseline demographic characteristics are summarized for each of three rollover groups in Table 1. The groups were demographically similar, with mean age ranging from 39.5-42.7 years and slightly more than half of each group being male. No enrolled subject had a history of or current diagnosis of cardiovascular disease. Of the 223 subjects who enrolled, 147 (66%) discontinued the study prior to completing 24 months of therapy with MAS XR. Forty-eight subjects withdrew because of adverse events, 38 withdrew consent, 23 were lost to follow-up, and 22 were withdrawn because of protocol violations (typically noncompliance).

MAS XR Long-term Dosing

All subjects (N = 223) initiated treatment with MAS XR 20 mg/day. After 1 month of treatment, 179 subjects (80.3%) had achieved a dose of 40 or 60 mg/day. This dosing level was also seen during the remainder of the study period. Beginning at month 5 and continuing through month 24, s6% of subjects required further dosage modification during their scheduled monthly clinic visit.

Systolic and Diastolic Blood Pressure

Mean SBP and DBP observed during 24 months of open-label MAS XR treatment are shown in Figure 1. Mean baseline sitting SBP (119.8 mm Hg) was increased beginning at month 8 and occasionally emerged as statistically significant through month 24- At end point, statistically significant, but clinically insignificant, increases in mean baseline SBP (2.3±12.5 mm Hg; P=.006) and DBP (1.3±9.2 mm Hg; P=.O42) were seen. The change in SBP at end point was numerically greater but not statistically different in MAS XR-naive subjects (3.2 mm Hg) or MAS XR-interrupted subjects (3.5 mm Hg) compared with subjects in the MAS XR-continuous group (1.8 mm Hg).

Pulse

Mean change in pulse at end point for each of the rollover groups is illustrated in Figure 2. Changes from baseline pulse at end point were comparably small (^3 bpm) among all of the rollover groups. A clinically insignificant change in mean baseline pulse was seen at end point for the cohort as a whole (2.1 ± 13.4 bpm; P=.O19).

Electrocardiogram Assessments

Change from baseline ECG parameters at end point for each of the rollover groups and the cohort as a whole is summarized in Table 2. Between baseline and end point, the group mean change in the PR interval was statistically significant but not clinically important (-5.9+14.1 msec; I[J]<.001). No statistically significant change occurred in the group mean QRS interval (-0.4±6.8 msec; P=.375) was observed. No clinically meaningful changes in QT interval measurements were observed. Small increases in mean QTcB (7.2±22.O msec; P<.001) and QTcF (2.9±16.6 msec; P=.OO9) intervals were

observed; however, no subject had a QTcB interval >480 msec (QTcF >454 msec). At end point, two subjects demonstrated a change from baseline QT 2:60 msec and three subjects demonstrated a change from baseline QTcB a60 msec, but none of the final values was >472 msec.

Adverse Cardiovascular Events

Seven subjects were withdrawn from the study because of cardiovascular adverse events, two subjects because of palpitations and/or tachycardia (MAS XR dose 40 mg/day in both cases), and five subjects because of hypertension (MAS XR 20 mg/day, n=l; 40 mg/day, n=l; 60 mg/day, n=3). Of the five subjects withdrawn because of hypertension, three had no history of hypertension. Four of the five cases with hypertension exhibited unresolved hypertension during continued follow-up, which suggests the development of primary essential hypertension in these four subjects. An estimated 50 million people in the US have essential hypertension, and the rate observed here (1.8%) appears to be commensurate with the estimated incidence rate of essential hypertension in the general population, as reported in a recent Canadian study.[22] Tachycardia/palpitations resolved in both subjects who discontinued due to this adverse event.

TABLE 1. BASELINE DEMOGRAPHIC CHARACTERISTICS (INTENT-TO-TREAT SAMPLE)

	Rollover From Short-Term Study			
	MAS XR Naive (n=56)	MAS XR Continuous (n=144)	MAS XR Interrupted (n=21)	Total (N=221)
Age (years)				
Mean±SD	39.9±11.4	39.3±11.3	42.6±12.9	39.8±11.5
Range	19-59	18-68	21-76	18-76
Age category (years), n (%)				
18-29	12(21.4)	34 (23.6)	3(14.3)	49 (22.2)
30-39	17 (30.4)	43 (29.9)	6 (28.6)	66 (29.9)
40-49	15 (26.8)	38 (26.4)	5 (23.8)	58 (26.2)
s50	12(21.4)	29 (20.1)	7 (33.3)	48(21.7)
Sex, n (%)				
Male	37 (66.1)	82 (56.9)	12 (57.1)	131 (59.3)
Female	19 (33.9)	62 (43.1)	9 (42.9)	90 (40.7)
Ethnic origin, n (%)				
White	52 (92.9)	129 (89.6)	19 (90.5)	200 (90.5)
Hispanic	2 (3.6)	8 (5.6)	1 (4.8)	11 (5.0)
Black	2 (3.6)	3(2.1)	1 (4.8)	6(2.7)
Other	0(0)	4(2.8)	0(0)	4(1.8)
Baseline ADHD-RS-IV scores, Mean±SD				
Total Score	26.5±12.5	17.9±11.6	19.7±11.5	20.2±12.3
Inattentive subscale	14.8±7.1	10.0±7.2	10.1±6.9	11.3±7.4
Hyperactivity/ impulsivity subscale	11.7±7.2	7.8±5.4	9.6±5	9.0±6.1

MAS XR=mixed amphetamine salts extended release; MAS XR Naïve=subjects new to MAS XR; MAS XR Continuous=subjects who received uninterrupted MAS XR; MAS XR Interrupted=subjects whose MAS XR regimen was interrupted; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale IV; SD=standard deviation.

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Few subjects exhibited shifts from normal values at baseline to clinically significant abnormal measures for vital signs or ECG parameters throughout the study or at end point (end point data shown in Table 3). For the majority of all time points examined, the absolute number of subjects with an abnormal pulse, SBP, or DBP ranged from 0—4, and those with an increase in QTcB &60 msec ranged from 0-3. No apparent relationship was observed between vital sign changes and time or previous MAS XR

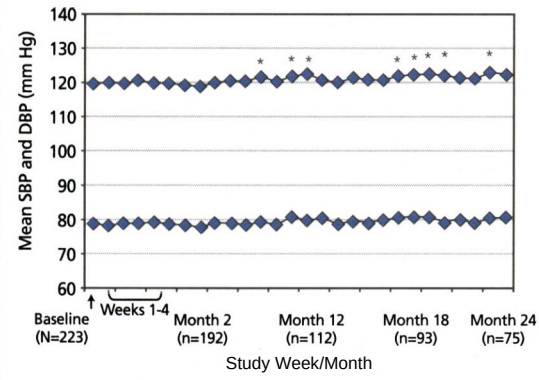

FIGURE 1. Change in mean blood pressure during long-term, open-label MAS XR treatment

* P<.05 compared with mean baseline value by one-sample ttest.
SBP=systolic blood pressure; DBP=diastolic blood pressure;
MAS XR=mixed amphetamine salts extended release.

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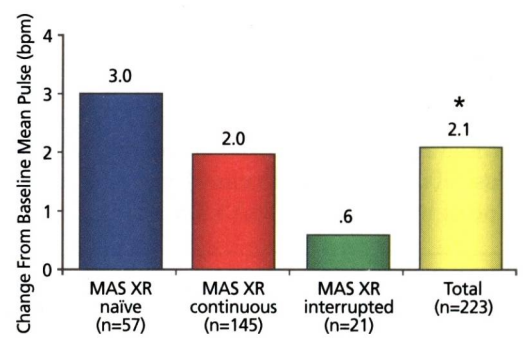

FIGURE 2. Change in mean baseline pulse rate (bpm) at study end

* P<.05 compared with mean baseline value by one-sample ttest.

MAS XR=mixed amphetamine salts extended release; MAS XR Naive=subjects new to MAS XR; MAS XR Continuous=subiects who received uninterrupted MAS XR; MAS XR Interrupted=subjects whose MAS XR regimen was interrupted.

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TABLE 2. ECG PARAMETERS, CHANGE FROM BASELINE WITH MAS XR (ALL ENROLLED SUBJECTS)

ECG Parameter (Mean)	MAS XR Naive (n=57)	MAS XR Continuous (n=145)	MAS XR Interrupted (n=2D	Total (N=223)
Heart Rate (bpm)				
Baseline	64.5	71.8	70.3	69.8
End point	72.3	76.0	70.0	74.5
Change	7.6	4.2	-0.3	4.6
P value*	<.001	<.001	.902	<.001
PR (msec)				
Baseline	156.4	147.9	149.4	150.3
End point	147.7	142.7	146.9	144.4
Change	-8.8	-5.3	-2.6	-5.9
P value	<.001	<.001	.473	<.001
QRS (msec)				
Baseline	90.5	88.8	89.8	89.3
End point	89.2	88.8	89.0	89.0
Change	-1.6	0.1	-0.8	-0.4
P value	.099	.870	.639	.372
QTcB[f] (msec)				
Baseline	386.5	398.9	400.6	395.9
End point	400.1	404.7	402.6	403.4
Change	12.8	5.8	2.0	7.2
P value	<.001	.002	.659	<.001

*P values based on comparison of change from screening using an analysis of covariance model with treatment as a fixed effect and screening as a covariate; statistical significance defined as Pc.05.

t QTcB=QT interval corrected by Bazett's formula [QT (msec) (heart rate/60)^{05}].

ECG=electrocardiogram; MASXR=mixed amphetamine salts extended release; MAS XR Naive=subjects new to MASXR; MAS XR Continuous= subjects who received uninterrupted MAS XR; MAS XR Interrupted=subjects whose MAS XR regimen was interrupted; bpm=beats per minute.

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exposure (ie, MAS XR naive, MAS XR continuous, or MAS XR interrupted). There was no difference between rollover categories in the frequency of such abnormalities. For most subjects with a clinically significant vital sign abnormality at any study visit (pulse >110 bpm, n=18; SBP 2:150 mm Hg, n=17; DBP >100 mm Hg, n=17; QTcB increase 2480 msec, n=0), the abnormality was seen during a single study visit and the subject remained in the study.

The highest pulse measured at any time during the study (137 bpm) was seen in a white 24-year old female at month 4 (MAS XR 40 mg/day). This subject had tachycardia at baseline and several post-baseline study visits, for which she received propranolol; it remained unresolved at the time of her later withdrawal from the study due to weight loss. The highest SBP measured (172 mm Hg) was seen in a 28-year-old Asian male (MAS XR 40 mg/day) who had elevated BP at baseline (152 mm Hg); he later discontinued due to worsening hypertension. The highest DBP measured (118 mm Hg; month 5) was seen in a 39-year-old white male (MAS XR 40 mg/day) who had elevated DBP (112 mm Hg) at week 2 and later discontinued due to noncompliance. The longest QTcB interval observed was 472 msec.

Ten subjects had QTcB change from baseline a60 msec (8 males and 2 females). The highest final QTcB in these subjects was 472 msec. No subjects had QTcF change from baseline 26O msec. Two subjects had a clinically significant abnormal ECG interpretation during at least one clinic visit among the 223 subjects enrolled in this extension study. One subject exhibited an abnormal T-wave and a lengthened QT interval at baseline, both of which resolved during the study. The second subject exhibited clinically significant left anterior hemiblock beginning at month 3 that was ongoing at month 24- Neither subject was withdrawn from the study.

DISCUSSION

This is the first detailed assessment of cardiovascular changes in adults during long-term treatment with an XR stimulant formulation. It also is the largest study examining the long-term effects of a stimulant medication in adults with ADHD. For the majority of adult subjects in this study, the average cardiovascular effects of MAS XR appear to be minimal with up to 24 months of treatment. For the vast majority of subjects, mean changes in pulse, BP, and ECG interval measurements were not clinically significant. A small number of subjects exhibited significant changes from baseline in vital signs and ECG assessments. However, only seven subjects (7/223; 3.1%) were withdrawn from the study because of a cardiovascular event.

The current analysis is significant in that it provides the first substantial evidence demonstrating that long-term stimulant therapy in otherwise healthy adults with ADHD tends to cause minimal changes in BP, pulse, and ECG parameters. This is particularly important given the increasing vulnerability to elevated BP and pulse that is seen with advancing age. In general, the changes in cardiovas-

TABLE 3. INCIDENCE OF QUALITATIVE CHANGE FROM BASELINE IN CARDIOVASCULAR PARAMETERS AT END POINT (LOCF)

Parameter N (%)	MAS XR Naive (n=57)	MAS XR Continuous (n=145)	MAS XR Interrupted (n=21)	Total (N=223)
Pulse				
2:25 bpm	3 (5.3)	9(6.2)	0 (0.0)	12(5.4)
al 10 bpm	1 (1.8)	2(1.4)	0 (0.0)	3(1.3)
SBP				
a20 mm Hg	7 (12.3)	13 (9.0)	3 (14.3)	23 (10.3)
al50 mm Hg	2(3.5)	1 (0.7)	0 (0.0)	3(1.4)
DBP				
alO mm Hg	11 (19.3)	30 (20.7)	4(19.0)	45 (20.2)
al00 mm Hg	0 (0.0)	2(1.4)	1 (4.8)	3(1.4)
QTcB				
a30 msec	10(17.5)	17 (11.7)	3(14.3)	30(13.4)
a500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

LOCF=last observation carried forward; MAS XR=mixed amphetamine salts extended release; MAS XR Naive=subjects new to MAS XR; MAS XR Continuous=subjects who received uninterrupted MAS XR; MAS XR Interrupted=subjects whose MAS XR regimen was interrupted; bpm=beats per minute; SBP=systolic blood pressure; DBP=diastolic blood pressure; QTcB=QT interval corrected by Bazett's formula.

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cular parameters observed here are similar in magnitude to those reported previously with MAS XR among pediatric patients with ADHD.[23] In one previous investigation, adolescents treated with open-label once-daily MAS XR (10-60 mg/day) for up to 6 months exhibited small, clinically insignificant mean increases at end point in baseline SBP (1.7 mm Hg), DBP (0.6 mm Hg), and pulse (4.4 bpm). Similarly, the current findings are in line with a recent report describing changes in heart rate and BP observed in a number of small, short-term clinical trials of stimulant and nonstimulant medications in adults with ADHD.[7 8] In the analysis by Wilens and colleagues,'[8] small changes in SBP, DBP, and pulse were reported and no differences were detected between MPH and amphetamine or any of the other agents examined.[8] Importantly, we observed, as did Wilens and colleagues,[8] that normotensive ADHD adults appear to tolerate the minor cardiovascular effects of stimulant medications well. In most cases here, abnormal vital sign values were observed at a single study visit, resolved spontaneously, and did not require any change in dose or withdrawal from the study. Wilens and colleagues[8] noted that the presence of hypertension at end point was predicted by higher BPs at baseline, suggesting the need to assess vital signs at baseline prior to beginning stimulant therapy. This is also in line with current AHA guidelines for pediatric patients receiving stimulant therapy[13] and constitutes prudent clinical practice. Patients with abnormal cardiovascular indices can be safely excluded from or flagged for close follow-up with stimulant therapy, whereas those with mildly abnormal cardiovascular indices can be more vigilantly monitored.

Frequency or incidence of clinically significant changes and abnormalities seen here was slightly greater than seen previously among adolescents with MAS XR.[21] For any given vital sign or ECG parameter, 10-18 adult subjects met criteria for a clinically significant abnormality at any time during this study. Although such abnormalities may be at least partially due to the stimulant medication under study, it also seems likely to be related to the adult population involved in this investigation. In several cases, cardiovascular abnormalities were observed at baseline of the open-label study. One white female exhibited tachycardia at baseline that remained unresolved during open MAS XR treatment; she later discontinued the study due to weight loss. A second subject, an Asian male, exhibited an elevated SBP at baseline (152 mm Hg); this worsened during open MAS XR therapy (up to 172 mm Hg) and led to his discontinuation from the study at month 3. Similarly, a 29-year-old white man developed elevated DBP at week 2 of open treatment (112 mm Hg), which worsened with continuing treatment (118 mm Hg); he was later discontinued due to noncompliance. Underlying pathology (eg, atherosclerosis, borderline hypertension) may have gone undetected at initial evaluation in some subjects, and these individuals may have been more vulnerable to the sympathomimetic effects of MAS XR. Moreover, increasing age is associated with increased risk of hypertension and cardiovascular events. Given the lack of a placebo-control group in the current open-label investigation, the rate at which cardiovascular abnormalities emerge among adults with ADHD who are not receiving stimulant medication could not be characterized. In a recent study by Wilens and colleagues,[23] hypertension (>140/90 mm Hg) emerged in 8% of subjects during short-term monitoring. Further investigation is required to determine the extent to which the clinically significant events seen here were related to underlying risks versus stimulant therapy. Nevertheless, these cases highlight the importance of evaluating BP and pulse at baseline and the need to monitor vital signs during the early phase of medication dose titration. The findings of this study indicate that patients with borderline BP or pulse values are at risk for developing vital sign abnormalities with stimulant therapy and may require adjustments to their treatment regimen if clinically significant abnormalities should develop.

Limitations

The results presented here are from an analysis of a long-term, open-label extension study that was designed to demonstrate the overall safety and efficacy of MAS XR. Subjects enrolled were required to have normal BP and pulse on study entry, and subjects with hypertension (consistently elevated BP >139/89 mm Hg) or any other cardiovascular disorder were excluded from participation. Because of this criterion, the current findings may not generalize to the broader population of adults with ADHD who present with medical comorbidities, including hypertension. Recent evidence suggests, however, that even adult patients with hypertension that requires management with antihypertensive medication are able to tolerate MAS XR without a significant elevation in BP. This suggests it is safe to co-manage ADHD and hypertension and presents a possible option for patients who exhibit elevated BP at baseline, rather than excluding such patients from stimulant therapy.[24] The effects of short-

or long-term use of MAS XR in patients with significant cardiovascular dysfunction or BP abnormalities are unknown. The study population included adults who were not receiving any other medications that could affect BP or pulse. The addition of XR stimulant formulations to other medications with cardiovascular effects in adults with ADHD has not been assessed. Lack of standardization in the timing of medication administration and assessment of vital signs could have resulted in measurements after the medication effects had worn off, but this is unlikely given that few clinic visits would have occurred >12 hours after dosing.

CONCLUSION

The cardiovascular effects of MAS XR appear minimal in patients with ADHD who are otherwise in good physical health; they are similar to those reported for pediatric patients and with both short - and long-acting amphetamines and methylphenidate, as well as the nonstimulant atomoxetine. While the AHA guidelines regarding the evaluation of heart rate and BP at baseline and during follow-up pertain to children and adolescents, we believe these same guidelines should apply to adults as well. Given the incidence of hypertension and cardiovascular disease seen in adults, routine monitoring of vital signs at baseline and periodically throughout treatment in adults with ADHD is recommended. The FDA and Health Canada have both issued guidelines regarding the use of stimulants in patients thought to have structural cardiac abnormalities. K2ÉÉ]

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