An Open-Label Study of the Tolerability of Mixed Amphetamine Salts in Adults With Attention-Deficit/Hyperactivity Disorder and Treated Primary Essential Hypertension

Timothy E. Wilens, M.D.; Randall M. Zusman, M.D.; Paul G. Hammerness, M.D.; Amy Podolski, B.A.; Julia Whitley, B.S.; Thomas J. Spencer, M.D.; Martin Gignac, M.D.; and Joseph Biederman, M.D.

Objective: To evaluate the short-term tolerability of an extended-release preparation of the stimulant medication mixed amphetamine salts (MAS XR) in adults with attention-deficit/hyperactivity disorder (ADHD) whose hypertension has been successfully treated with antihypertensive medications.

Method: An 8-week, 2-phase, open-label study design was implemented. All adults had ADHD (DSM-IV diagnosis) and essential hypertension and were required to be normotensive (blood pressure < 135/85 mm Hg, treated) for at least 4 weeks at entry into the study. MAS XR was given for a 6-week period, titrated once each week to a target maximum dose of 60 mg/day given once daily in the morning (phase 1), and then discontinued for 2 weeks at the end of the study (phase 2). At baseline, subjects underwent a comprehensive clinical assessment, medical history, vital signs assessment, and electrocardiogram (ECG). Rating scales were used throughout the study to assess response to treatment, and blood pressure was measured manually at each study visit. The primary outcome was the effect of MAS XR on blood pressure and the development of hypertension.

Results: Thirteen subjects receiving antihypertensive therapy were entered and placed on MAS XR treatment and completed the trial. There were no serious adverse events. No sustained elevated blood pressure (> 140/90 mm Hg at 2 consecutive visits) was observed in the subjects treated with MAS XR. Similar rates of single episodes of hypertension were observed in phases 1 and 2. Similarly, there was no group mean increase in systolic or diastolic blood pressure or pulse during treatment with MAS XR. No clinically significant changes in the ECG were observed. During the 6-week medication phase, significant improvement was found on rating scales assessing ADHD symptoms and severity that reversed with discontinuation of MAS XR.

Conclusion: The results of this open study suggest that adults with ADHD and controlled hypertension can be safely treated with MAS XR.

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Corresponding author and reprints: Timothy E. Wilens, M.D., Massachusetts General Hospital, Pediatric Psychopharmacology Unit, YAW 6A, 55 Fruit St., Boston, MA 02114 (e-mail: twilens@partners.org).

There has been increasing recognition of the continuity of pediatric attention-deficit/hyperactivity disorder (ADHD) into adulthood.[1–3] While 6% to 8% of youth are affected,[4,5] longitudinal data coupled with survey and recent epidemiology studies suggest that 4% to 5% of adults in the general population manifest ADHD.[6–8] Furthermore, an overrepresentation of ADHD has been reported in adults with a substance use disorder, generalized anxiety disorder, or depression.[9–11] Controlled studies indicate that, compared to adults without ADHD, adults with ADHD have higher rates of comorbid psychopathology, occupational and/or academic underachievement, and interpersonal difficulties necessitating treatment.[3,12,13] While the effectiveness of various treatment modalities remains unclear in this population, data indicate that pharmacotherapy is an efficacious treatment for the symptoms of the disorder.[14]

Of the available options, stimulant medications are among first-line agents in adults with ADHD,[15–17] with both mixed amphetamine salts (MAS) and D-methylphenidate being specifically U.S. Food and Drug Administration (FDA)-approved for use in adults with ADHD. Both MAS and methylphenidate are the most commonly used stimulant medications in adults, with over 15 published controlled trials demonstrating their efficacy (for review see Wilens[14]). While these medications are highly efficacious in the treatment of adults with ADHD, a number of short-term adverse

effects of stimulants used for ADHD have been described in adults.[18–21] Among reported adverse events, benign vital sign effects associated with ADHD agents in adults have been consistently reported.[18–22] For example, we recently reported minor changes in systolic and diastolic blood pressure (BP) in adults with ADHD and found that these changes were notable in both stimulant and nonstimulant agents.[22] That the agents used for the treatment of ADHD would result in BP and heart rate increases is consistent with their catecholaminergic properties.

We also found that a small group of adults manifest hypertension during treatment with their medication. Hypertension at endpoint was predicted by relatively higher BP or hypertension prior to starting medication (baseline),[22] further emphasizing the need to evaluate BP in ADHD patients prior to initiating treatment.[23] That adults with ADHD presenting for treatment may be at risk for hypertension is not surprising given that 1 in 4 Americans have hypertension[22] and the typical age of presentation for ADHD in adults in clinical trials is from 35 to 40 years, a common time for initial presentation of elevated BP.[18–21,24–26]

Given the existence of hypertension in adults with ADHD, one clinical dilemma that remains is the appropriate treatment strategy for these adults. Given that stimulants may increase BP, and that those at risk for hypertension on ADHD medications are those who start with high baseline BP,[22] it remains to be seen if treating adults for their hypertension prior to initiating treatment will attenuate the change in BP associated with stimulant pharmacotherapy. Unfortunately, a limited literature is available in this area, in part resulting from the exclusion of hypertensive adults with ADHD from clinical trials. Ratey and colleagues[27] reported on the tolerability of β-blockers (nadolol) with stimulants for reducing adverse effects. They found improvement in ADHD symptoms with the use of methylphenidate and a β-blocker. Despite this small case series, no prospective studies are available to guide clinical practice. It remains to be seen if adults with treated hypertension can tolerate stimulants for ADHD in terms of BP and pulse and if adjunct stimulants in treated hypertensive subjects will be effective for treating the core ADHD symptoms.

To this end, we prospectively evaluated adults with ADHD and essential hypertension who were stabilized on a regimen of antihypertensive medications for their elevated BP and were then treated with clinically relevant doses of an extended-release preparation of MAS (MAS XR) to evaluate cardiovascular response and ADHD symptomatology changes over time. To help assess if BP changes were related to MAS XR or were occurring spontaneously, we used a 2-phase study to assess BP changes: 6 weeks on drug treatment (phase 1) followed by 2 weeks off treatment (phase 2). We hypothesized that adults with ADHD and treated hypertension would have predictable, small, but clinically insignificant changes in their BP and pulse and that MAS XR would be effective for treatment of ADHD symptoms.

METHOD

Subjects

Men and women from the ages of 18 to 60 years were recruited at the Massachusetts General Hospital (MGH), Boston, from ongoing clinical trials, from clinical referrals to psychopharmacology clinics, and from patients receiving hypertensive treatment in primary care and cardiology clinics. Potential subjects were screened for ADHD by reviewing the DSM-IV criteria for ADHD.

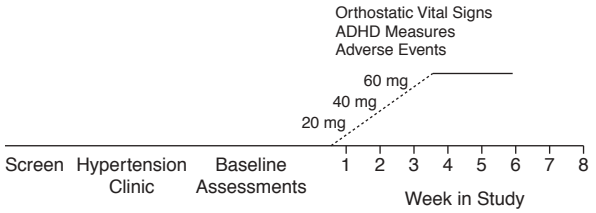
Subjects were eligible if they met diagnostic criteria for any subtype of ADHD based on the DSM-IV and had a history of treated hypertension or manifest hypertension during screening (> 140/90 mm Hg). Subjects were excluded from participation if they had a major physical or sensorimotor deficit (e.g., profound deafness, blindness, or profound disorders of language); organic brain disorders; suspected mental retardation; a lifetime major psychiatric disorder of psychosis, autism, schizophrenia, or bipolar disorder; or a current psychiatric disorder that necessitated intervention or would interfere with the execution of the study. Pregnant or nursing women were excluded, as were subjects with alcohol or substance abuse or dependence within 6 months prior to baseline. Subjects who had a known structural cardiac abnormality, medically unstable history of myocardial infarction or arrhythmia, or a diagnosis of secondary hypertension or isolated systolic hypertension were also excluded.

Prior to entering the medication trial, all subjects were required to be taking at least 1 FDA-approved antihypertensive medication and achieve a stable BP of < 135/85 mm Hg. Antihypertensive medications were prescribed at the discretion of the treating cardiologist (R.M.Z.). Other medications taken by the subjects were not altered during the entire duration of the trial. This study was approved by the institutional review board, and all subjects reviewed and signed a consent form prior to the initiation of any study procedures.

Study Design

This study had an 8-week, 2-phase design (Figure 1). Subjects who were found to be hypertensive during screening were sent for additional stabilization by MGH cardiology (R.M.Z.) and were required to have a stable BP < 135/85 mm Hg for at least 4 weeks prior to entry into the study. At baseline, subjects underwent a clinical assessment including a psychiatric evaluation, structured diagnostic interview, cognitive testing, medical history, an electrocardiogram (ECG), orthostatic vital signs, and a pregnancy test (for women of childbearing age). The Structured Clinical Interview for DSM-IV[28] was used to

Figure 1. Study Design[a]



[a]All subjects (N = 13) were screened and if found to have elevated blood pressure were referred for evaluation and management of their hypertension. Subjects with treated hypertension with blood pressure < 135/85 mm Hg were entered into the trial and treated with extended-release mixed amphetamine salts (MAS XR) at 20 mg weekly titrated upward in 20-mg increments to a maximum of 60 mg/day. All subjects (N = 13) underwent discontinuation of MAS XR treatment at the end of week 6 and were followed for an additional 2 weeks.

assess adult psychiatric and substance use disorders. ADHD was diagnosed using both current symptom criteria by DSM-IV and the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E), which was used to confirm the childhood onset of ADHD.[29]

In phase 1, subjects were given MAS XR for a 6-week period. Study medication was initiated at 20 mg/day and titrated at 20 mg each week to a target maximum dose of 60 mg/day, given once daily in the morning. The upper limit of dosing was established based on a large, multisite study of MAS XR demonstrating efficacy and safety to 60 mg/day.[30,31] Subjects were instructed to take medication at 7:00 a.m. Measurement of adherence for both the antihypertensive medication and MAS XR was accomplished through use of daily medication diaries. At each study visit, MAS XR was counted to ensure that pill counts were consistent with the protocol. Vital signs were completed at each weekly visit at the same time (± 1 hour) throughout the study. Subjects were generally seen between 3:00 p.m. and 5:00 p.m.

In phase 2, MAS XR was discontinued, and subjects remained on their antihypertensive regimen. Subjects were monitored during 1 study visit over this 2-week period.

Study Measures

Orthostatic vital signs were taken in a sitting and a standing position by a clinician who received additional training in reliably assessing manual blood pressures. Blood pressure was measured manually following 5 minutes of rest, once while subjects were seated in a chair with their back supported and their arms bared and supported at heart level, and again after 3 minutes. These 2 readings separated by 3 minutes were averaged. However, if they differed by more than 5 mm Hg in systolic and/or diastolic readings, 1 additional reading in that position was obtained and the 3 values were then averaged. A standard 12-lead ECG was also completed at baseline and week 6 with electronic and manual interpretation by a board-certified cardiologist.

Response to treatment was assessed weekly from information elicited from the subject using the physician-rated Adult ADHD Investigator Symptom Checklist Severity Scale (AISRS) capturing DSM-III-R and DSM-IV symptoms.[32] This checklist assessed each of the individual symptoms of ADHD (0–3 on a scale of severity; 0 = minimum score, 54 = maximum score). In addition, the Clinical Global Impressions scale (CGI),[33] which includes the following scale ratings: Global Severity (1 = not ill to 7 = extremely ill) and Global Improvement (1 = very much improved to 7 = very much worse) was used. The 24-item Hamilton Rating Scale for Depression (HAM-D)[34] was completed by the study clinician initially and at the end of treatment (week 6 or end of study visit, if this occurred sooner) to evaluate depressive symptoms. The 14-item Hamilton Rating Scale for Anxiety (HAM-A)[35] was completed by the study clinician initially and at the end of treatment (week 6 or end of study visit, if this occurred sooner) to evaluate symptoms of anxiety.

Safety and Tolerability Assessment

The specific type and dose of antihypertensive medication remained constant throughout the study unless mandated by the protocol. Elevated BP was defined as BP > 140/90 mm Hg. All cases of elevated BP were managed by the treating physician who consulted with the study cardiologist. A priori options for elevated BP (> 140/90 mm Hg)[36] were (1) observation if minor elevation (e.g., ≤ 145/95 mm Hg) with no increase in MAS XR dosing for that week, (2) upward titration of their existing antihypertensive medication for more elevated BP (> 145/95 mm Hg), (3) addition of another antihypertensive medication (if only taking 1 currently), (4) having their dose of MAS XR adjusted downward, or (5) withdrawing from the study.

Adverse events were systematically recorded at each visit. The relationship of each adverse event to the study drug (MAS XR) was determined as being not related, possibly related, or related. The medical assessment of intensity was determined as mild, moderate, or severe.

Statistical Methods

All adults were evaluated for their BP and pulse at baseline, while on MAS XR treatment (6 weeks), and after a period of 2 weeks after discontinuation of the treatment. The primary outcome was the effect of MAS XR on BP and the development of hypertension.

To evaluate whether MAS XR resulted in statistically and clinically significant BP and pulse changes in adults with ADHD and concurrent well-controlled hypertension, we used random regression models with the main effect of time (baseline through the 8-week visit). We also

estimated the change in BP over time as a function of MAS XR dose. We further evaluated the incidence of isolated hypertension (> 140/90 mm Hg). To evaluate the effect of MAS XR on ADHD symptoms, we analyzed the difference in AISRS and CGI ADHD severity scores between baseline and week 6. All analyses were intent to treat with the last observation carried forward (LOCF). The secondary outcome was the effect of MAS XR on ADHD symptoms.

Because we assessed our sample over time, the assumption that each observation is independent of all other observations is violated in these data. To account for correlation within individuals, we used robust estimates of variance so that p values would not be underestimated.[37] Statistical models were fit with the statistical software package STATA.[38] Generalized estimating equation models with the identity link and Gaussian family specification were used to perform linear regression models to predict dimensional outcomes. The statistical significance of each regression model was determined by Wald χ^2 test. We used 2-tailed tests with an alpha of 0.05. All data are presented as mean ± SD unless otherwise stated.

RESULTS

Demographic and Baseline Characteristics

Twenty-eight subjects were enrolled in the study. Fifteen of these subjects dropped out prior to exposure to MAS XR because they were not interested in receiving treatment for their BP or lost interest in the study. Of the 13 subjects enrolled and exposed to at least 1 dose of MAS XR, all completed the 8-week trial.

The mean age of subjects was 44.2 ± 8.0 years, and the majority of subjects were male (77% [N = 10]) (Table 1). The majority of subjects had lifetime comorbid psychiatric disorders, with substance use disorder as the most common comorbid diagnosis. These adults had substantial impairment in functioning as indicated by their Global Assessment of Functioning scores for both lifetime (52 ± 4.6) and current functioning (past month: 59 ± 5.4).

The majority of adults (54% [N = 7]) were taking angiotensin converting enzyme inhibitors, 38% (N = 5) were taking thiazide diuretics, 31% (N = 4) β-blockers, and 23% (N = 3) calcium channel blockers. Sixty-two percent (N = 8) of subjects were taking 1 antihypertensive medication, 23% (N = 3) were taking 2 antihypertensive medications, and 15% (N = 2) were taking 3 or more antihypertensive medications for control of their BP.

Dose of MAS XR

At the end of the study (LOCF), the mean dose of MAS XR was 48.5 mg. Of the 13 subjects who received medication, 7 were taking the maximum dose of 60 mg of MAS XR at week 6 (end week). Of the 6 subjects who did not complete the study at maximum dose, 2 attempted 60-mg doses but experienced non–BP-related adverse events including insomnia, appetite loss, jittery feeling, and dry mouth; 3 subjects experienced non–BP-related adverse events at lower doses, therefore their dosage was not titrated upward; and 1 subject experienced complete alleviation of symptoms at 20 mg. No subjects had their MAS XR dose titrated downward due to BP elevation.

Table 1. Demographic Characteristics of Adult Patients With Attention-Deficit/Hyperactivity Disorder and Treated Hypertension

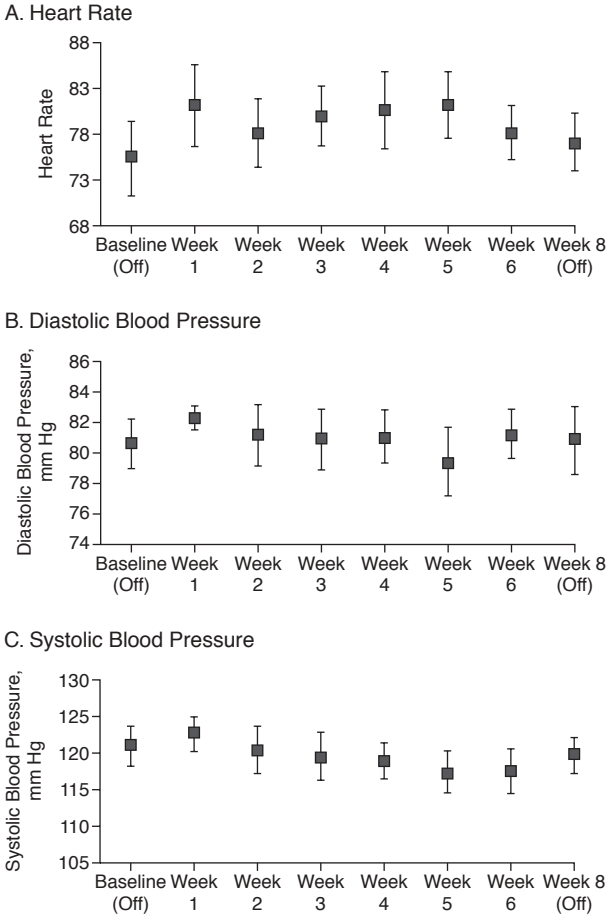
Characteristic	All Groups (N = 13)
Age, mean, y	44
Sex, male, N (%)	10 (77)
Race, %	
White	75
African American	25
Global Assessment of Functioning score, mean	
Past	52
Current	59
Lifetime psychiatric comorbidities, N (%)	
Major depressive disorder (severe)	1 (8)
Anxiety disorder	1 (8)
Antisocial personality disorder	2 (15)
Substance use disorders	10 (77)

Outcome

Cardiovascular outcome. Figure 2 shows cardiovascular measures at each week, and Table 2 shows the main dependent variables at baseline and weeks 6 and 8. There were no significant differences between all weeks of treatment versus baseline (week 0) on measures of mean diastolic BP (p = .63), which increased 0.7% (0.60 mm Hg) from baseline to week 6. Likewise, no significant differences were found between weeks on measures of mean systolic BP (p = .18), which decreased 2.9% (3.47 mm Hg) from baseline to week 6. There was a trend toward higher mean heart rate associated with treatment (p = .06) between all weeks including baseline, with a 3.6% increase at endpoint (vs. baseline). There was no significant difference between week 0 (baseline) and end of week 8 (off MAS XR treatment).

While none of the subjects experienced 2 consecutive episodes of hypertension, 3 subjects experienced single episodes of systolic and/or diastolic hypertension while taking the study medication. During week 2, the first subject was taking 20 mg of MAS XR and had a combined BP of 145/93 mm Hg. The second subject was receiving 40 mg of MAS XR in week 3 and had a BP of 146/98 mm Hg. The third subject displayed an elevated systolic reading at week 5 of 137/92 mm Hg. Hence, according to study protocol, the MAS XR dosage was not increased the following week for any of these subjects. Blood pressure measures in these 3 subjects were < 140/90 mm Hg during the following week, so protocol titration was resumed with no further elevation of BP found. No subjects re-

Figure 2. Heart Rate (A), Diastolic Blood Pressure (B), and Systolic Blood Pressure (C) During the Course of the Study (N = 13)[a,b]



[a]Values are expressed as median with range.
[b]There were no significant differences between any treatment timepoint and baseline for any of the measures shown.

Table 2. Main Psychiatric and Cardiovascular Outcomes of 13 Adult Patients With Attention-Deficit/Hyperactivity Disorder and Treated Hypertension Receiving Extended-Release Mixed Amphetamine Salts (MAS XR)[a]

Outcome Measure	Baseline	Week 6 (on MAS XR treatment)	Week 8 (off MAS XR treatment)
Psychiatric rating scale			
AISRS	30.6 ± 8.1	8.2 ± 9.2**	25.6 ± 9.6**
CGI-S	4.4 ± 5.1	2.2 ± 1.2**	4.2 ± 0.55
HAM-A	4.6 ± 3.9	3.2 ± 3.5	NA
HAM-D	3.8 ± 3.5	2.9 ± 2.8	NA
BP/heart rate measure			
Heart rate	75.2 ± 14.4	78.0 ± 11.0	76.9 ± 11.5
Systolic BP	120.6 ± 9.9	117.1 ± 11.1	119.4 ± 8.8
Diastolic BP	80.5 ± 5.6	81.1 ± 5.9	80.7 ± 7.8
ECG interval, msec			
PR	162 ± 31.6	152.2 ± 18.3	
QRS	97.3 ± 16.9	98.9 ± 14.9	
QT	403.2 ± 27.8	379.9 ± 28.7*	
QTc	419.0 ± 20.3	413.4 ± 14.9	

[a]Values shown as mean ± SD.
*p < .05 compared to baseline.
**p < .001.
Abbreviations: AISRS = Adult ADHD Investigator Symptom Checklist Severity Scale, BP = blood pressure, CGI-S = Clinical Global Impressions scale, ECG = electrocardiogram, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NA = not assessed.

quired adjustments in their antihypertensive or MAS XR regimen during the study. At week 8 (off MAS XR treatment for 2 weeks), 2 subjects each experienced an isolated episode of systolic hypertension, with readings of 137/92 and 127/92 mm Hg.

To test the effect of dose on cardiovascular measures, we estimated a model with these measures as the dependent variable and dose as the independent variable, using data collected at week 6. We restricted the analysis to week 6 data because all subjects began the study at the same dose and were titrated upward similarly. Thus, variability in dose was achieved only at the end of the trial. In these models, dose was not a significant predictor of heart rate, systolic BP, or diastolic BP (all p values > .05).

There were no significant ECG changes associated with MAS XR on PR, QRS, or QTc measures when comparing end of week 6 to baseline. The only significant difference found on MAS XR compared to baseline was a 17% decrease in the QT interval (p < .002).

Efficacy outcome. Regarding improvements in ADHD symptoms, significant differences were found in AISRS scores between baseline and week 6 (–74%; p < .001). Mean CGI ADHD severity scores also decreased significantly between baseline and week 6 (p < .001) and then increased significantly between week 6 and week 8 (p < .001) when study medication was stopped. No significant differences were found between baseline and week 6 for either the HAM-A (p = .12) or HAM-D (p = .29).

Adverse Effects

There were no serious adverse events in this study. The most common adverse effects reported were headache (N = 6) and dry mouth (N = 5). There were no suspected drug interactions with the antihypertensive medications.

Despite the discontinuation of MAS XR at week 6, there was no evidence of worsening of BP or ADHD symptom changes at week 7 or 8 compared to baseline measures. Likewise, no reported subjective adverse events emerged that were indicative of any withdrawal symptoms.

DISCUSSION

Our short-term trial in a small number of treated hypertensive adults with ADHD showed generally good cardiovascular tolerability with MAS XR. These data suggest,

despite the small sample size, that patients who are taking a stable regimen of antihypertensive medication can be placed on treatment with stimulants for ADHD without becoming clinically hypertensive. These data also suggest that the ADHD response of MAS XR is maintained when combined with antihypertensives.

To our knowledge, no other studies of this type have been conducted; however, the use of stimulant medications for ADHD with antihypertensive medications has been previously described in the literature. Ratey et al.[27] added β-blockers to accentuate the response of stimulant medications in adults with ADHD. In this report, β-blockers were found to reduce the adverse effects of the stimulant, and the combination was well tolerated by the adults. No indication of changes in BP were noted in the study. Of interest, β-blockers have been used to offset some of the stimulant-induced adverse events in adults with ADHD.[17,39]

In our current study, 2 subjects developed transient elevations in their BP. By the open nature of the study, we are unable to determine if these elevations were related to the stimulant or the underlying hypertension. Of interest, both subjects became normotensive spontaneously without alteration in their regimen, and 2 other subjects had isolated hypertension during phase 2 of the study (off MAS XR treatment). Given the apparent lack of tolerance, short term, to the pressor effects of the stimulants[22,40,41] and the later outcome of hypertension in 2 other subjects, we suspect that the 2 subjects had spontaneous changes in their BP unrelated to the medication.

Our current overall data show a lack of clinically significant BP increases with use of stimulant medication in a population that is particularly vulnerable to elevations of BP. Albeit limited by a small sample size, the current data suggest the tolerability of using stimulants in adults with appropriately treated hypertension. Despite a substantial literature that demonstrates an increase of BP with stimulant treatment,[22,40] our current data suggest that coadministration of an antihypertensive may attenuate BP increases.

The choices of antihypertensives used in this study are indicative of use in the general population.[36] The small sample size does not allow for differentiation of results between the medications; however, the lack of an overall effect demonstrates, in general, the success in regulating BP with antihypertensives as a class when treating subjects with stimulant medication.

In this trial, treatment with MAS XR was also associated with significant improvement in ADHD. These data are similar to those from a number of open and controlled trials with MAS XR[30] and suggest that coadministration of those antihypertensives used in the current study does not attenuate the effects of MAS XR.

That MAS XR, and probably other stimulants by nature of their similar chemical properties, can be administered to adults with well-controlled hypertension is of clinical interest. Recent analyses indicate that 10% of adults receiving ADHD medications had hypertension with treatment[22] and that the biggest predictor of having hypertension at endpoint was having the highest BP at baseline. The aggregate data punctuate the need to obtain baseline BP/pulse in adults prior to initiating treatment. The management of adults with hypertension requiring treatment for ADHD suggests that treatment of the hypertension should be initiated prior to that for ADHD. Isolated hypertension should be observed with the understanding that the underlying hypertension, the ADHD medication, or the combination may be related to the elevation. Sustained hypertension during treatment with ADHD medications necessitates consideration of lowered ADHD medication dose, alternative ADHD medications, or a change in the antihypertensive regimen.

The results of this study should be viewed in light of several important limitations. The small sample size and short-term nature of the study may limit the generalizability of the current findings. Moreover, due to the small sample size and short duration of the study, the results cannot certainly guarantee absolute safety for individuals with hypertension. The results were also restricted by the small variance in the time of BP measurements, lack of 24-hour ambulatory BP monitoring, variability in antihypertensives used, and inability to control for dietary influences (e.g., caffeine, nicotine) on BP. The open conditions of this trial provide potential for observer bias. However, all BP and heart rate readings were objectively completed by trained clinicians. While we attempted to be very inclusive in the study, subjects in these studies were screened and could not have unstable cardiac disease (e.g., recent myocardial infarction, angina, malignant hypertension) and were without concurrent medical or substance abuse conditions. Hence, the generalization of these data to other groups of less screened, more medically compromised adults is unclear. As a result of the target-dose design of the individual studies, there was no ability to evaluate for a dose-response relationship. Because these studies were of relatively short duration, we were unable to evaluate the longer-term effects of ADHD therapy on BP and heart rate.

Despite these limitations, there was a relative paucity of BP or heart rate increases found with coadministration of antihypertensives and MAS XR up to 60 mg. This medication treatment was well tolerated among subjects and resulted in clinically significant resolution of ADHD symptoms. Data from this small, open-label study support that individuals with ADHD who are adequately treated for hypertension can be treated successfully with MAS XR and probably other stimulants and nonstimulants that may have mild pressor effects. Larger placebo-controlled trials of longer duration are necessary to enhance our knowledge of cardiovascular safety of using medications in treated hypertensives with ADHD.

Drug names: methylphenidate (Ritalin, Metadate, and others), mixed amphetamine salts (Adderall and others), nadolol (Corgard and others).

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REFERENCES

1. Biederman J. Attention-deficit/hyperactivity disorder: a life-span perspective. J Clin Psychiatry 1998;59(suppl 7):4–16
2. Weiss G, Hechtman L, Milroy T, et al. Psychiatric status of hyperactives as adults: a controlled prospective 15 year followup of 63 hyperactive children. J Am Acad Child Psychiatry 1985;24:211–220
3. Wilens T, Faraone SV, Biederman J. Attention-deficit/hyperactivity disorder in adults. JAMA 2004;292:619–623
4. Bauermeister JJ, Canino G, Bird H. Epidemiology of disruptive behavior disorders. Child Adolesc Psychiatr Clin N Am 1994;3:177–194
5. Faraone SV, Sergeant J, Gillberg C, et al. The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2003;2:104–113
6. Murphy K, Barkley RA. Prevalence of DSM-IV symptoms of ADHD in adult licensed drivers: implications for clinical diagnosis. J Atten Disord 1996;1:147–161
7. Barkley RA, Fischer M, Smallish L, et al. Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 2004;45:195–211
8. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602
9. Alpert J, Maddocks A, Nierenberg A, et al. Attention deficit hyperactivity disorder in childhood among adults with major depression. Psychiatry Res 1996;62:213–219
10. Levin FR, Evans SM, Kleber HD. Practical guidelines for the treatment of substance abusers with adult attention-deficit hyperactivity disorder. Psychiatr Serv 1999;50:1001–1003
11. Wilens TE. Attention-deficit/hyperactivity disorder and the substance use disorders: the nature of the relationship, subtypes at risk and treatment issues. Psychiatr Clin North Am 2004;27:283–301
12. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993;150:1792–1798
13. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 2004;161:1948–1956
14. Wilens T. Drug therapy for adults with attention-deficit hyperactivity disorder. Drugs 2003;63:2395–2411
15. Goldman L, Genel M, Bezman RJ, et al. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. JAMA 1998;279:1100–1107
16. Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002;41(suppl 2):26S–49S
17. Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry 2004;65:1301–1313
18. Wender PH, Reimherr FW, Wood DR. Attention deficit disorder ("minimal brain dysfunction") in adults: a replication study of diagnosis and drug treatment. Arch Gen Psychiatry 1981;38:449–456
19. Spencer T, Wilens TE, Biederman J, et al. A double blind, crossover comparison of methylphenidate and placebo in adults with childhood onset attention deficit hyperactivity disorder. Arch Gen Psychiatry 1995;52:434–443
20. Spencer T, Biederman J, Wilens T, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2001;58:775–782
21. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. Am J Psychiatry 2001;158:282–288
22. Wilens T, Hammerness P, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2005;66:253–259
23. Gutgesell H, Atkins D, Barst R, et al. AHA scientific statement: cardiovascular monitoring of children and adolescents receiving psychotropic drugs. J Am Acad Child Adolesc Psychiatry 1999;38:1047–1050
24. Wilens T, Biederman J, Prince J, et al. Six-week, double blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. Am J Psychiatry 1996;153:1147–1153
25. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry 2003;53:112–120
26. National Institutes of Health. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Bethesda, Md: National Heart, Lung, and Blood Institute; 1997
27. Ratey JJ, Greenberg MS, Lindem KJ. Combination of treatments for attention deficit hyperactivity disorder in adults. J Nerv Ment Dis 1991;179:699–701
28. First M, Spitzer R, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders. Washington, DC: American Psychiatric Press; 1997
29. Ambrosini PJ. Historical development and present status of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). J Am Acad Child Adolesc Psychiatry 2000;39:49–58
30. Weisler RH, Biederman J, Chrisman AK, et al. Long-term safety and efficacy of once-daily Adderall-XR in adults with ADHD. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif. 242:NR647
31. Weisler RH. Safety, efficacy and extended duration of action of mixed amphetamine salts extended-release capsules for the treatment of ADHD. Expert Opin Pharmacother 2005;6:1003–1018
32. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:187–202
33. National Institute of Mental Health. Clinical Global Impression (CGI). Psychopharmacol Bull 1985;21:839–844
34. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
35. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
36. Magill MK, Gunning K, Saffel-Shrier S, et al. New developments in the management of hypertension. Am Fam Physician 2003;68:853–858
37. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22
38. Stata Corporation. Stata User's Guide, Release 7.0. College Station, Tex: Stata Corporation; 2001
39. Wilens TE, Spencer T. The stimulants revisited. Child Adolesc Psychiatr Clin N Am 2000;9:573–603
40. Safer DJ. The relative cardiovascular safety of psychostimulants used to treat attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 1992;2:279–290
41. Wilens TE, Biederman J, Lerner M, et al. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2004;24:36–41

