Blood Pressure Changes Associated With Medication Treatment of Adults With Attention-Deficit/Hyperactivity Disorder

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Objective: To evaluate the effects of medications used in the treatment of adults with attention-deficit/hyperactivity disorder (ADHD) on blood pressure and pulse.

Method: Subjects were those with DSM-III-R–/DSM-IV–diagnosed ADHD enrolled in placebo-controlled studies of 5 different medications for ADHD. Cardiovascular data from these studies of both stimulants (methylphenidate, amphetamine compounds, pemoline) and nonstimulants (bupropion, desipramine) were reanalyzed for baseline-to-endpoint active-treatment or placebo effects on blood pressure and heart rate.

Results: There were 125 subjects with a mean ± SD age of 39 ± 9 years. In general, active drug treatment for ADHD compared to baseline was associated with several statistically significant changes in systolic blood pressure (bupropion: +5.9 mm Hg, $p < .05$ by paired t test; amphetamine: +5.4 mm Hg, $p < .05$), diastolic blood pressure (desipramine: +7.1 mm Hg, $p < .05$), and heart rate (bupropion: +6.9 mm Hg, $p < .05$; amphetamine: +7.3 mm Hg, $p < .05$; methylphenidate: +4.5 mm Hg, $p < .05$). New-onset cases of systolic or diastolic hypertension (blood pressure ≥ 140/90) were recorded in 8% (7/89) of placebo-treated subjects and 10% (9/89) of subjects receiving active medication, regardless of the class (stimulant, nonstimulant).

Conclusion: Both stimulant and nonstimulant catecholaminergic medications used in adults with ADHD are associated with minor, but statistically significant, changes in heart rate and blood pressure that were often observed in those receiving placebo. Given the minor pressor and chronotropic effect of these medications, adults with ADHD should have their blood pressure and heart rate checked at baseline and periodically during treatment.

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The continuity of pediatric attention-deficit/hyperactivity disorder (ADHD) into adulthood has been increasingly recognized.[1–3] While 3% to 9% of youth are affected,[4,5] longitudinal data coupled with survey and recent epidemiology studies suggest that 4% of adults in the general population manifest ADHD.[6–10] Data also suggest that approximately 20% of adults with a substance use disorder, generalized anxiety disorder, or depression have comorbid ADHD.[11–13] Compared to non-ADHD adults, controlled studies indicate that adults with ADHD have higher rates of comorbid psychopathology, occupational and/or academic underachievement, and interpersonal difficulties necessitating treatment.[14,15] 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.[16]

An emerging literature suggests that the stimulant and nonstimulant agents used for ADHD in children also have efficacy in adults with ADHD.[17] Stimulant medications are among the first-line agents in adults with ADHD, which is similar to guidelines in youth.[5,16,18] Methylphenidate and amphetamine are the most commonly used stimulant medications in adults, with over 15 published controlled trials of their efficacy (for review see reference 16). Alternatively, as part of 2 large multisite studies, atomoxetine has been shown to be effective (and is U.S. Food and Drug Administration–approved) for ADHD in adults.[19] Second-line agents for ADHD in adults that were also demonstrated to be effective under controlled conditions include pemoline, bupropion, and desipramine.[16]

While short-term adverse effects of the medications used for ADHD have been well described in youth,[18,20,21] a paucity of information exists in adults. For example, despite data suggesting benign vital sign effects associated with ADHD agents in children,[22–25] little is available in adults receiving these medications for ADHD. No data exist on similarities and differences among the various sympathomimetic agents employed in the treatment of ADHD in adults. This dearth of research is noteworthy in that adults receiving medications for ADHD may be particularly vulnerable to changes in blood pressure and pulse due to underlying medical comorbidities, such as essential hypertension or arteriosclerosis, that may be unrecognized during evaluation. This is not surprising given that the typical age at presentation for ADHD in adults in clinical trials is between 35 to 40 years,[19,26–30] which is a common time for initial presentation of elevated blood pressure.[31]

The delineation of vital sign changes in pharmacologically treated adults with ADHD is of high clinical and public health value. Delineating predictable vital sign changes and patients at risk for hypertension with treatment can inform clinicians of high-risk groups of patients receiving treatment. Determining differences between various classes of agents used in ADHD can assist clinicians in choosing medications with more benign cardiovascular profiles. From a public health perspective, converging data indicate an elevated risk for both cardiovascular and noncardiac medical complications due to elevations in vital signs.[31] Hence, understanding blood pressure and pulse changes associated with specific agents for ADHD can provide valuable information to guide appropriate use of these medications chronically.

To this end, we evaluated data on the effects of stimulant and nonstimulant agents on vital signs in adults with ADHD, derived from 5 medication trials completed at our site. Because of methodological issues related to regression to the mean, only placebo-controlled trials were included. Based on the limited literature and our clinical experience, we hypothesized that stimulant and nonstimulant medications would be associated with predictable mild increases in blood pressure and heart rate in adults with ADHD.

METHOD

Subjects

Subjects were outpatient adults with ADHD between 18 and 60 years of age, recruited from advertisements and clinical referrals to a clinical psychopharmacology clinic. Cardiovascular data of this population of adults were examined. These adults had participated in 5 previously published placebo-controlled trials of stimulant and nonstimulant medication treatment of ADHD.[27–30,32] Consent forms, study protocol, and any advertisements for subjects were reviewed and approved by the institutional review board of participating centers prior to initiation of each study.

We excluded potential subjects if they had clinically significant chronic medical conditions, a history of cardiac arrhythmias, seizures, mental retardation (IQ < 80), organic brain disorders, clinically unstable psychiatric conditions, bipolar disorder, psychosis, or drug or alcohol abuse or dependence within the 6 months preceding the study; were currently using psychotropics; had sensorimotor deficits that would impede the testing process (profound deafness, blindness, or language disorders); or were pregnant or nursing women. Patients with a blood pressure of > 160/100 mm Hg or a heart rate of > 110 beats per minute were also excluded from the studies.

Assessment Measures

Subjects underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, a medical history, and an electrocardiogram. The structured diagnostic interview was the Structured Clinical Interview for DSM-III-R or DSM-IV (SCID),[33] supplemented for childhood disorders by unmodified modules from the Schedule for Affective Disorders and Schizophrenia for School Age Children-Epidemiologic Version.[34,35] To obtain a full diagnosis of adult ADHD, the subject (a) met full DSM-III-R or DSM-IV criteria for a diagnosis of ADHD by the age of 7 as well as currently (within the past month), (b) described a chronic course of ADHD symptomatology from childhood to adulthood, and (c) endorsed a moderate or severe level of impairment attributed to the ADHD symptoms. Diagnostic reliability between raters and board-certified psychiatrists was excellent. A kappa of 1.0 was obtained for ADHD. Socioeconomic status (SES) was measured by the Hollingshead Four Factor Index of Social Status,[36] in which low values indicate high SES.

Study Design

Detailed study methodology for the pharmacotherapeutic trials can be found in the original reports.[27–30,32] Briefly, all trials were randomized, placebo-controlled (50:50 randomization), target dose studies of varying length from 6 to 10 weeks (Table 1). Three trials[27,28,32] were completed in a crossover design with a 1- to 2-week washout between treatments. Two trials were parallel design.[29,30] Since there was no order effect for blood pressure or pulse (active drug vs. placebo; placebo vs. active drug; baseline 1 or baseline 2), cardiovascular data from crossover trials included the first baseline prior to the first phase (baseline 1 only) and end of each active phase (endpoint 1 and endpoint 2); the total number of cases was equivalent in each treatment group. Cardiovascular

Table 1. Previous Trials of Adults Treated for ADHD (N = 125)

Drug	Study Design*	Mean Endpoint Dose, mg/d
Methylphenidate, 1995[27]	Crossover RCT, 7 wk, 1 wk washout	65
Bupropion, 2001[30]	Parallel RCT, 6 wk	362
Desipramine, 1996[29]	Parallel RCT, 6 wk	147
Pemoline, 1999[32]	Crossover RCT, 10 wk, 2 wk washout	148
Amphetamine compounds, 2001[28]	Crossover RCT, 7 wk, 1 wk washout	54

*All studies compared drug vs. dose-matched placebo.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, RCT = randomized controlled trial.

data not reliably ascertained or recorded were not included in these analyses.

Measurement of Vital Signs

Following medication-free baseline measurements, blood pressure and pulse were taken at weekly intervals. In the 2 earlier trials,[27,29] the physician rater measured blood pressure. The patient was in the sitting position, with the assessed arm at approximately heart level. A standard sphygmomanometer cuff was used to externally compress the brachial artery by raising pressure to a level that occluded blood flow. The rater then determined the systolic pressure to be at the point when the pulse is heard, as pressure was gradually released. Auscultation continued during the release of pressure until the pulse sound completely disappeared (Korotkoff's phase V), which is the standard definition of diastolic pressure. Rate of cuff deflation was approximately 2 to 4 mm Hg per heartbeat.

In the subsequent trials,[28,30,32] blood pressure and heart rate were taken in the sitting position using DINAMAP XL blood pressure monitors.[37] Vital signs were taken in the afternoon while the anti-ADHD effects of shorter acting stimulants were still evident. Any subject who developed persistent systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 100 mm Hg, or persistent heart rate > 100 beats per minute measured twice at the same visit 30 minutes apart were discontinued from the respective studies.

Statistical Analyses

Analyses were completed by comparing endpoint to baseline blood pressure and heart rate assessments, using last-observation-carried-forward endpoints.

Overall, there were 166 subjects in all 5 drug studies, of whom 125 subjects had baseline and on-drug/placebo data and had a baseline blood pressure of < 140/90 mm Hg. Because some studies were parallel design and others were crossover design, there were 178 datapoints derived from these 125 subjects. Paired t tests (2-tailed) were used to investigate change over time. Two-sample t tests were used to compare change scores (endpoint to baseline) between active medication and placebo groups, and between stimulant and nonstimulant medications; 1-sample analyses of variance were used to investigate differences in change scores between study medications. Logistic regression was used to predict factors associated with the new onset of hypertension. All statistical tests were performed using Stata.[38] We set statistical significance at the .05 level. Data are expressed as mean ± SD unless otherwise specified.

Table 2. Demographic Characteristics of Adults in Trials for Treatment of ADHD (N = 125)

Characteristic	Value
Age, mean ± SD, y	39 ± 9
Range	19–55
Socioeconomic scale score, mean ± SD*	1.8 ± 0.9
Male, N (%)	56 (45)

*Hollingshead Four Factor Index.[36]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder.

RESULTS

The mean age of subjects in the combined sample was 39 ± 9 years, with a range of 37 years (Table 2). There was a balanced sex distribution (45% male), and the sample was largely middle class (mean socioeconomic score was 1.8 ± 0.9). Since these were target-dosing studies, subjects were receiving relatively high doses of medication at endpoint (Table 1).

Baseline values for systolic blood pressure, diastolic blood pressure, and heart rate among the various groups (by study and by active drug/placebo status) were not significantly different. In general, active drug treatment for ADHD was associated with several statistically significant changes in systolic blood pressure, diastolic blood pressure, and heart rate at endpoint (Table 3). Compared to baseline, endpoint active-medication vital signs were significantly different for bupropion (systolic blood pressure and heart rate), desipramine (diastolic blood pressure), amphetamine compounds (systolic blood pressure and heart rate), and methylphenidate (heart rate). Of interest, compared to baseline, placebo was associated with significant differences for desipramine (diastolic blood pressure). In comparison to corresponding placebo values, significant increases in mean systolic blood pressure (from baseline to endpoint) with active medication were observed for bupropion and amphetamine; additionally, significant mean heart rate changes were observed for active medication versus placebo with amphetamine compounds.

Vital sign changes between class of medication (stimulant vs. nonstimulant) were not significantly different for systolic blood pressure ($t = -1.3$, $p = .2$), diastolic blood pressure ($t = .3$, $p = .7$), or heart rate ($t = .3$, $p = .7$). Like-

Table 3. Vital Sign Measurements in Adults Treated for ADHD

		Mean Value						Mean Change Value[a]					
		Systolic BP, mm Hg		Diastolic BP, mm Hg		Heart Rate, bpm		Systolic BP		Diastolic BP		Heart Rate	
Study Drug	N	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	mm Hg	p Value	mm Hg	p Value	bpm	p Value
Bupropion	Drug = 16	122.9	128.8†	71.4	74.1	71.9	78.8†	+5.9	.01	+2.7	.3	+6.9	.1
	Placebo = 13	130.9	125.4	75.0	72.3	73.0	73.2	–5.0		–2.7		+0.2	
Desipramine	Drug = 6	122.7	120.7	73.2	80.3†	NA	NA	–2.0	.9	+7.2	.6	NA	NA
	Placebo = 12	125.1	122.3	75.2	80.6†	NA	NA	–2.3		+5.4		NA	
Pemoline	Drug = 23	125.6	128.1	74.8	68.8†	73.1	74.1	+2.6	.6	+6.0	.02	+1.0	.9
	Placebo = 22	127.1	128.0	72.8	73.7	73.5	73.4	+0.9		–0.9		–0.1	
Amphetamine	Drug = 26	121.4	126.8†	72.9	76.9	71.6	78.9†	+5.3	.02	+4.0	.5	+7.3	.05
compounds	Placebo = 25	122.8	121.8	69.5	71.5	70.4	71.3	–1.0		+2.0		+0.9	
Methylphenidate	Drug = 18	116.6	119.0	76.6	76.4	73.8	78.3†	+2.4	.9	–0.2	.7	+4.5	.4
	Placebo = 17	117.2	119.4	76.2	75.2	74.5	76.7	+2.2		–1.1		+2.2	

[a]Change scores obtained from endpoint values minus baseline values; p values are from t tests of mean vital sign change values for drug vs. placebo.
†Paired t tests (endpoint vs. baseline) significant at the $p < .05$ level.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP = blood pressure, bpm = beats per minute, NA = not available.

Table 4. Mean Blood Pressure Measurements for Adults Treated for ADHD

Blood		Hypertension			Mean Change Value[c]		
Pressure (BP)	Drug Status	Status at Endpoint[a]	Baseline BP, mm Hg	Endpoint BP, mm Hg	p Value[b]	mm Hg	p Value[d]
Systolic	Active	Yes (N = 6)	130.7	149.3	.01	+18.7	< .0001
		No (N = 83)	121.2	123.8	.002	+2.5	
	Placebo	Yes (N = 5)	128.6	147.2	.005	+18.6	< .0001
		No (N = 84)	123.3	121.5	.09	–1.8	
Diastolic	Active	Yes (N = 6)	78.3	85.8	.002	+7.5	.4
		No (N = 83)	71.9	75.3	.006	+3.4	
	Placebo	Yes (N = 5)	78.4	86.6	.04	+8.2	.03
		No (N = 84)	73.1	73.1	.97	+0.04	

[a]Systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg.
[b]Paired t test, baseline vs. endpoint measurements.
[c]Endpoint minus baseline measurements.
[d]t Test comparing change values between hypertension status (yes/no) groups.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

wise, there were no significant differences among the specific types of medications for change scores in systolic blood pressure ($F = .7$, $p = .6$), diastolic blood pressure ($F = 1.9$, $p = .12$), and heart rate ($F = .6$, $p = .6$).

We then investigated the rates of new-onset hypertension (blood pressure ≥ 140/90) in our sample. Systolic or diastolic hypertension was noted in 8% (N = 7) of placebo-treated and 10% (N = 9) of active medication–treated cases (Table 4).

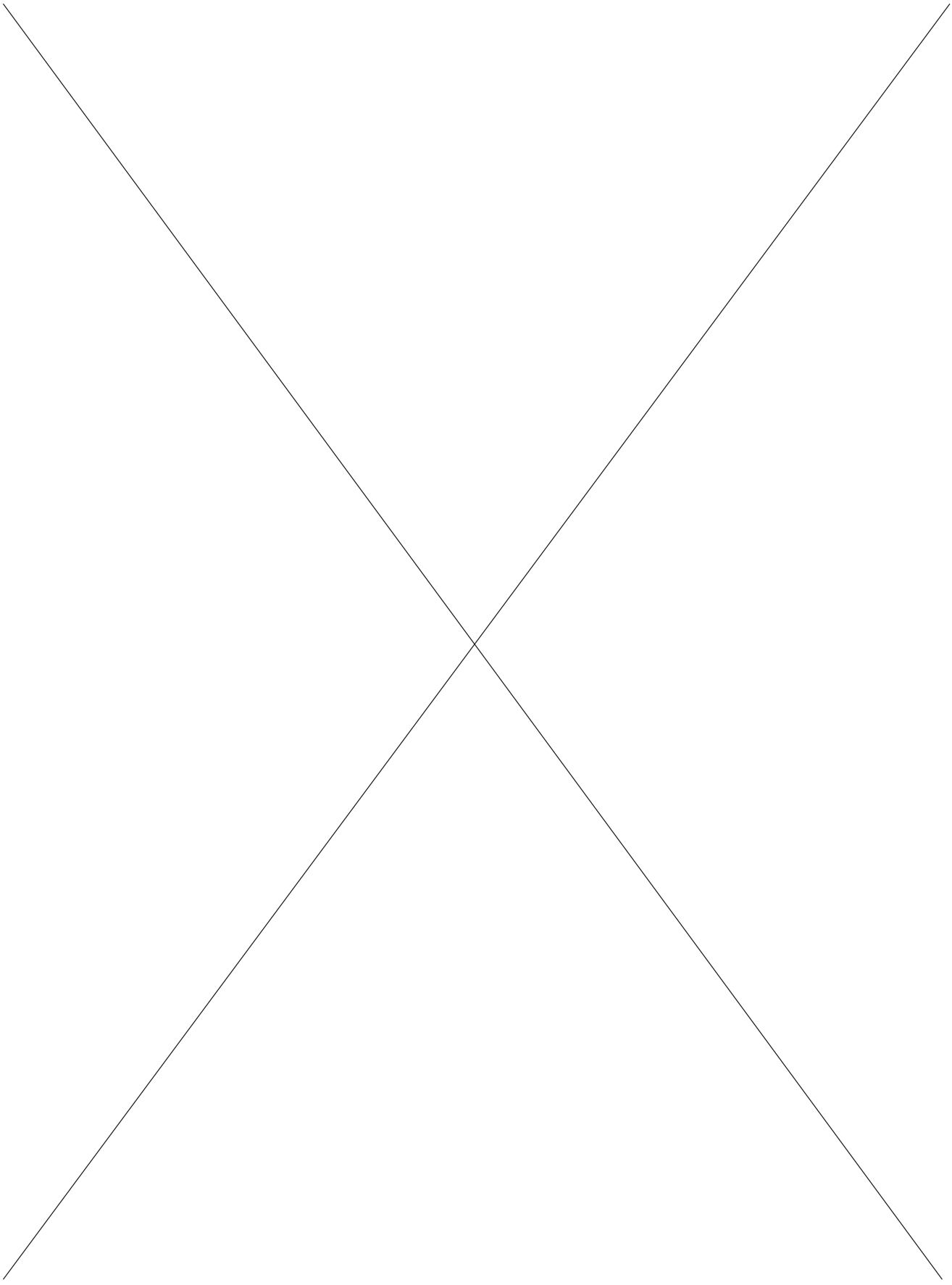
We further evaluated the effects of baseline vital signs on vital signs at endpoint (Table 3). As expected, subjects with higher baseline systolic and diastolic blood pressure had higher corresponding systolic and diastolic blood pressure at endpoint. Significant mean increases in systolic blood pressure were noted with active medication treatment as well as during placebo administration, while significant increases in diastolic blood pressure were noted with placebo administration.

In further analysis, no baseline clinical characteristic (age: $\chi^2 = 2.6$, $df = 1$, $p = .1$; sex: $\chi^2 = .6$, $df = 1$, $p = .5$; SES: $\chi^2 = 0.8$, $df = 1$, $p = .4$), class (stimulant/nonstimulant: $\chi^2 = .6$, $df = 1$, $p = .4$), or specific type of medication (pemoline: $\chi^2 = .6$, $df = 1$, $p = .4$; bupropion: $\chi^2 = 1.0$, $df = 1$, $p = .3$; desipramine: $\chi^2 = .01$, $df = 1$, $p = .9$; amphetamine: $\chi^2 = .6$, $df = 1$, $p = .4$; methylphenidate: $\chi^2 = .8$, $df = 1$, $p = .4$) was associated with an increased risk for developing hypertension. Drug status did not have an effect on the rate of developing hypertension or the change scores for patients with endpoint hypertension (t test of change scores for endpoint hypertensives by drug status, $t = –.02$, $p = .98$ and $t = .3$, $p = .8$, for systolic and diastolic pressures, respectively).

DISCUSSION

The medications used in the treatment of adults with ADHD, both stimulant and nonstimulant (antidepressant class) agents, resulted in statistically significant but minor changes in vital signs that were often noted in those receiving placebo. With active treatment, hypertension at endpoint was predicted by higher blood pressures at baseline. Given the minor elevation in vital signs associated with pharmacotherapeutics for ADHD in adults, patients should have their vital signs checked at baseline and periodically during treatment and be informed of the minor pressor and chronotropic effects of these medications.

The medications for ADHD in adults were associated with mild increases in both systolic and diastolic blood



pressure and heart rate (Table 3). That the agents used for the treatment of ADHD would result in blood pressure and heart rate increases is not surprising by nature of their catecholaminergic properties. Such indirectly acting sympathomimetic amines have both pressor and chronotropic effects on the cardiovascular system,[39] resulting in mild elevations in both blood pressure and heart rate.

In particular, the stimulants have been shown in adult studies of depression[22,40] and pediatric studies of ADHD[22,41] to result in transient elevations of blood pressure and pulse at therapeutic doses. No apparent differences emerged between methylphenidate and amphetamine in the current data set, which is consistent with pediatric literature.[22,41–43]

While these data are limited by statistical power, nonstimulants appear to have a similar magnitude of effect on blood pressure and pulse at dosing that is therapeutic in ADHD. For example, adult studies with tricyclic antidepressants have demonstrated significant increases in vital signs with treatment.[44–46] Similarly, limited data with bupropion have shown elevations in blood pressure and have cautioned of using this compound in the context of unstable hypertension,[47,48] although recent work with a once-daily preparation does not appear to result in significant blood pressure changes in normotensive adults with ADHD.[49] Atomoxetine, a noradrenergic agent shown to be effective in adults with ADHD,[19,50] also results in minor, statistically significant changes of the same magnitude in blood pressure and pulse in short term trials as those observed in the current analyses.

One clinical concern is the risk of inadvertently treating a hypertensive adult with medication for their ADHD. Evaluating the data continuously, while confounded by regression to the mean, we find an inverse relationship between baseline blood pressure or heart rate and change in the indices, suggesting that, in general, adults with relatively higher blood pressures do not automatically manifest worsening of their blood pressure/heart rate with pharmacotherapy. In contrast, adults with relatively lower indices at baseline manifest the most change with treatment. While these findings may reflect resampling bias, they also suggest that adults with normal blood pressure/heart rate may be more susceptible to minor cardiovascular changes by sympathomimetics than those with elevated vital signs. Hence, even normotensive adults with blood pressures clearly within age-specific norms may manifest elevated blood pressures with medication, necessitating the importance of blood pressure monitoring of ADHD adults prior to commencing pharmacotherapy and periodically thereafter during treatment.

Of equal concern is the 10% of cases receiving medications who had systolic hypertension, diastolic hypertension, or the combination with treatment. Despite the confound of inclusion criteria in these clinical studies, the current data highlight the importance of utilizing placebo-controlled clinical trials to evaluate vital sign changes with treatment. We found that individuals in both placebo and active phases tended to have changes in their blood pressures associated with their baseline blood pressure. Moreover, while 10% of subjects receiving active medication had hypertension at endpoint, a number of placebo-treated adults (8%) also developed hypertension at endpoint. The biggest predictor of who developed hypertension at endpoint was who had the highest blood pressure at baseline. In other words, those who started with the highest blood pressure at baseline, despite less change during treatment, were still more often hypertensive at endpoint compared to those who started with lower blood pressure at baseline. These data further punctuate the need to obtain baseline blood pressure/pulse in adults prior to commencing therapy. Clearly, studies of blood pressure and heart rate during psychotropic treatment not only need to consider baseline values but also would benefit from placebo comparators.

The current data are limited to short-term clinical trials; hence, it remains to be seen if the effects of the catecholaminergic agents attenuate over time. For example, data from children receiving stimulant medications indicate a small, but statistically significant increase in blood pressure (but not pulse) that does not attenuate over 1 year.[22,25] In contrast, recently reported data in adults with ADHD receiving open-label atomoxetine suggest a very minor attenuation in blood pressure and pulse associated with treatment at week 10 compared to week 97 (diastolic blood pressure change: acute = 1.8 ± 8.5, longer-term = 1.2 ± 8.9; systolic blood pressure change: acute = 2.9 ± 10.8, longer-term = 1.8 ± 11.4).[51] Given the need to treat ADHD chronically in adults,[51–53] the longer term effects of pharmacotherapy on blood pressure/pulse need to be delineated.

Clinical Recommendations

These findings have relevance to guiding clinicians' medication management and to enhancing discussions with patients regarding the tolerability and potential risks in treatment. While there continues to be debate as to the utility and need to monitor blood pressures in youth with ADHD,[22,25] existing data in adults would suggest the need for baseline and ongoing periodic monitoring of their vital signs with treatment. Adults found to manifest blood pressure ≥ 140/90 should be considered for evaluation and treatment of the elevated blood pressure.[31] Therapeutic options for those adults treated for their ADHD who manifest elevated vital signs include, based on clinical response and need, a reduction or discontinuation in their anti-ADHD regimen or adjunct treatment with an antihypertensive agent. While case reports suggest that the coadministration of antihypertensives and stimulants may accentuate ADHD responsivity,[54] systematic data are lacking on the tolerability

and effectiveness of combined therapies for adults with ADHD.

There are a number of limitations in the current report. The results of these analyses are derived from the pooling of data across 5 separate trials that varied in design (crossover vs. parallel design), were completed at separate times, and were of varying length. Despite using a calibrated instrument, there may have been substantial variability in the measurement of blood pressure and pulse. Moreover, further variability existed as to the exact times at which patients were seen, while blood pressure/heart rate assessments may have been confounded relative to the peak/trough levels of the respective medications. The vital signs represented only a cross-sectional timepoint and no ambulatory vital sign measurements were available.

The relatively small number of subjects and the missing data points in each condition for which reliable data were available severely limited our power to detect differences between active agents. Further data derived from large multisite studies using standardized measurements of blood pressure/pulse are necessary to more fully explore this important issue. Subjects in these studies were screened for inclusion in a clinical trial, did not manifest malignant hypertension, and were without concurrent medical or substance abuse conditions. Hence, the generalization of these data to other groups of less screened adults is unclear. Because 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 not able to evaluate the longer-term effects of ADHD therapy on blood pressure and heart rate.

In conclusion, agents used in adults with ADHD, including both stimulants and nonstimulants, resulted in small, statistically significant changes in vital signs. The development of hypertension was predicted by higher blood pressures at baseline. Given the modest elevation in vital signs associated with the pharmacotherapy for adult ADHD, patients should have their vital signs checked at baseline and periodically during treatment.

Drug names: amphetamine compounds (Adderall, Dexedrine, and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), desipramine (Norpramin and others), methylphenidate (Metadate, Ritalin, and others), pemoline (Cylert and others).

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