Article

Blood Pressure and Heart Rate Over 10 Years in the Multimodal Treatment Study of Children With ADHD

Benedetto Vitiello, M.D.
Glen R. Elliott, M.D., Ph.D.
James M. Swanson, Ph.D.
L. Eugene Arnold, M.D.
Lily Hechtman, M.D.
Howard Abikoff, Ph.D.
Brooke S.G. Molina, Ph.D.
Karen Wells, Ph.D.
Timothy Wigal, Ph.D.
Peter S. Jensen, M.D.
Laurence L. Greenhill, M.D.
Jonathan R. Kaltman, M.D.
Joanne B. Severe, M.S.
Carol Odbert, B.S.
Kwan Hur, Ph.D.
Robert Gibbons, Ph.D.

Objective: It is unknown whether prolonged childhood exposure to stimulant medication for the treatment of attention deficit hyperactivity disorder (ADHD) increases the risk for developing abnormalities in blood pressure or heart rate. The authors examined the association between stimulant medication and blood pressure and heart rate over 10 years.

Method: A total of 579 children, ages 7–9, were randomly assigned to 14 months of medication treatment, behavioral therapy, the combination of the two, or usual community treatment. The controlled trial was followed by naturalistic treatment with periodic assessments. Blood pressure and heart rate data were first analyzed with linear regression models based on an intent-to-treat approach, using raw data and the blood pressure categories of prehypertension and hypertension. Currently medicated patients were then compared with never or previously medicated patients. Associations between cumulative stimulant exposure and blood pressure or heart rate were assessed.

Results: No treatment effect on either systolic or diastolic blood pressure could be detected. Children who were treated with stimulants had a higher heart rate (mean=84.2 bpm [SD=12.4] on medication alone and mean=84.6 bpm [SD=12.2] on medication plus behavioral therapy) than those who were treated with behavioral therapy alone (mean=79.1 bpm [SD=12.0]) or those who received usual community treatment (mean=78.9 bpm [SD=12.9]) at the end of the 14-month controlled trial, but not thereafter. Stimulant medication did not increase the risk for tachycardia, but greater cumulative stimulant exposure was associated with a higher heart rate at years 3 and 8.

Conclusions: Stimulant treatment did not increase the risk for prehypertension or hypertension over the 10-year period of observation. However, stimulants had a persistent adrenergic effect on heart rate during treatment.

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Methylphenidate and amphetamines are commonly used in the treatment of attention deficit hyperactivity disorder (ADHD). By increasing noradrenergic and dopaminergic transmission, these agents exhibit sympathomimetic activity that is associated with cardiovascular effects (1). Several placebo-controlled investigations have documented a statistically significant increase in heart rate and blood pressure with therapeutic doses of stimulants in both children and adults (2–6). In children, average increases of 6–8 bpm in heart rate, 3–6 mm Hg in systolic blood pressure, and 3–4 mm Hg in diastolic blood pressure relative to placebo have been reported after methylphenidate or amphetamine administration (2, 3, 5). Some studies found a positive correlation between stimulant dosage and cardiovascular changes (7). Reports have not been consistent, however, and some adequately powered studies did not find differences between stimulant treatment and placebo after acute treatment (8). Studies for up to 2 years of stimulant treatment suggest that attenuation of acute effects occurs with chronic treatment, but without development of full tolerance (4, 9, 10).

Although the magnitude of the cardiovascular changes during stimulant treatment has been dismissed by some as clinically insignificant (3, 4, 8, 10, 11), even modest increases in blood pressure or heart rate, when sustained over time, may have an effect, since the risk for cardiovascular disease increases monotonically with rising blood pressure values in young adults (12). Available reports are limited to a few weeks of controlled stimulant administration and up to 2 years of uncontrolled treatment. It remains unclear whether stimulant treatment in childhood increases the risk for hypertension or for persistently, though modestly, elevated cardiovascular parameters in future years (13).

To clarify the possible clinical significance of stimulant-induced cardiovascular effects, we analyzed data from

This article is featured in this month's AJP Audio, is discussed in an Editorial by Dr. Kratochvil (p. 112), is the subject of a CME course (p. 237), and is an article that provides Clinical Guidance (p. 185)

the Multimodal Treatment Study of Children With ADHD (MTA), a 14-month randomized controlled clinical trial in 7- to 9-year-old children that was followed by naturalistic treatment with periodic assessment for up to 10 years after randomized assignment. We examined whether exposure to stimulant medication was associated with increased heart rate, systolic or diastolic blood pressure, or blood pressure values in the prehypertension or hypertension range over the 10-year period.

Method

Study Design and Participants

The data we analyzed were collected as part of the MTA, a publicly funded multisite randomized controlled trial that compared the effectiveness of different treatment interventions for children with ADHD. The design, methods, and main clinical outcomes of the MTA have been reported in detail (14–18). A total of 579 children 7–9 years of age (mean=8.5 years; 80% male, 61% white, 20% African American, and 8% Hispanic) with a DSM-IV diagnosis of combined type ADHD were randomly assigned to 14 months of treatment with stimulant medication (7 days a week, with no interruptions for summer holidays), behavioral therapy, a combination of medication and behavioral therapy, or usual community treatment. To be enrolled in the study, children had to be medically healthy, without evidence of cardiovascular disease by history or physical examination. After the 14-month controlled trial, all patients received naturalistic community treatment and were assessed at specified time points (2, 3, 6, 8, and 10 years after randomization). Intent-to-treat analyses based on treatment group identified statistically significant differential treatment effects on ADHD symptoms at the end of the controlled study and up to 10 months afterward (year 2), but not at subsequent assessments (15, 18, 19).

Starting with year 2, a local normative comparison group was added to the follow-up study. This group consisted of 289 children who were randomly selected from the same schools and grades and in the same sex proportion as the MTA patients and the same entry criteria except for ADHD diagnosis (but ADHD was not a reason for exclusion). Their blood pressure and heart rate were assessed in the same manner as in the MTA patients.

The data were collected between 1994 and 2006 at the following clinical sites: University of California, Berkley/University of California, San Francisco; Duke University Medical Center; University of California, Irvine; Long Island Jewish Medical Center and New York University; McGill University/Montreal Children's Hospital; University of Pittsburgh; and Columbia University/New York State Psychiatric Institute and Mount Sinai Medical Center, New York.

Stimulant Medication

A total of 289 children were randomly assigned to receive medication treatment, either alone or in combination with behavioral therapy. Immediate-release methylphenidate was the first-step treatment. Patients who did not respond were given D-amphetamine and, in case of further nonresponse, other agents. Methylphenidate accounted for 85% of stimulant use in the first 14 months. Medication was given in two or three daily doses, 7 days a week, for 14 months. Of the children assigned to usual community treatment, 92 (63.07%) received stimulant medication and five others received nonstimulant medication for ADHD. Some children (N=32) in the behavioral therapy group reported treatment with stimulant medication through their private pediatrician during the 14-month trial. This nonstudy use was accounted for in the analyses by controlling for current use. At the end of the 14 months, the mean daily dose of stimulant was 22.6 mg of methylphenidate equivalents in the usual community treatment group, 31.1 mg in the combined medication and behavioral therapy group, and 38.1 mg in the medication only group (20). After month 14, medication use was naturalistically determined and gradually decreased over time. Across all treatment groups, the numbers of children currently taking stimulant medication were 316, 280, 257, 169, 91, and 18 at month 14, at year 2, at year 3, at year 6, at year 8, and at year 10, respectively. Most (69.0%) of the youths medicated at year 10 had been medicated at month 14, indicating continuity of treatment for medicated patients. Consistent with body growth and with previous reports (18), the average daily dose increased with time and was 54.3 mg of methylphenidate equivalents at year 10. About 4% of the MTA sample received, at some point during the 10-year period, other, nonstimulant psychotropic medications, mainly antidepressants and mood stabilizers. For seven of the 289 children in the normative comparison group, there were reports of use of some psychotropic medication (antidepressants in six cases, and atomoxetine in one case).

Blood Pressure and Heart Rate Measurement

The procedure for assessing heart rate and blood pressure was as follows. After the participant had been sitting for 5 minutes, the heart rate was obtained with an automatic monitor or manually counted for at least 30 seconds. Immediately afterward, the blood pressure was measured in the right arm using a cuff of adequate size for the participant's arm. If any of the measurements were above normal range (>100 bpm for heart rate, >120 mm Hg for systolic blood pressure, and >80 for diastolic blood pressure), the measurement was repeated after the participant had been sitting for an additional 5 minutes, and the lower reading was recorded. There were some site differences in the procedure, but at each site all four treatment groups were assessed in the same way. At one of the sites, three recordings were obtained from each participant at each visit; the first reading was automatically discarded, and the average of the latter two was recorded. At four sites, blood pressure and heart rate were measured using an automatic blood pressure and heart rate monitor, and at the other three sites, blood pressure was measured with manual sphygmomanometry with auscultatory method, and the heart rate with manual measurement at the radial artery at the wrist. At each visit, body height and weight were also measured, and the youths and their families were queried about the occurrence of significant medical problems, hospitalizations, and other medical services. Time of the assessment varied during the day, as did the time since the last medication dose. Clinicians collecting these measurements were not blind to treatment assignment.

Data Analysis

The database was centrally managed and quality-assured at the National Institute of Mental Health, Bethesda, Md. Statistical analyses were conducted at the Center for Health Statistics, University of Illinois at Chicago.

Blood pressure data were analyzed both as absolute values and after classification into the categories of normal, prehypertension, hypertension stage 1, and hypertension stage 2, according to age-, sex-, and height-adjusted percentiles from U.S. population norms for children and adolescents through age 17 (21). Height percentiles were computed according to the 2002 U.S. Centers for Disease Control and Prevention population norms (22). Blood pressure status was classified as normal if both systolic and diastolic blood pressure were below the 90th percentile; prehypertension if the systolic or diastolic blood pressure was at or above the 90th percentile but below the 95th percentile; hypertension stage 1 if the systolic or diastolic blood pressure was at or above the 95th percentile but below the 99th percentile; and

hypertension stage 2 if the systolic or diastolic blood pressure was at or above the 99th percentile (21).

For participants older than age 17, adult criteria for blood pressure were used, according to which normal is a systolic blood pressure <120 mm Hg and a diastolic blood pressure <80 mm Hg; prehypertension is a systolic blood pressure of 120–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg; hypertension stage 1 is a systolic blood pressure of 140–159 mm Hg or a diastolic blood pressure of 90–99 mm Hg; and hypertension stage 2 is a systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥100 mm Hg (23).

The heart rate data were analyzed as absolute values and after categorization into normal or tachycardia based on population norms through age 18 (24). Tachycardia was defined as a heart rate above the 95th percentile, based on age and sex. For example, at age 16, the cutoff was 100 bpm for girls and 95 bpm for boys.

For the intent-to-treat analyses, linear regression models were applied to the blood pressure and heart rate data, testing for treatment effects from the randomly assigned treatment conditions. In addition, multinomial logistic regression models (under the assumption of proportional odds) were applied to the blood pressure data categorized into normal, prehypertension, hypertension stage 1, and hypertension stage 2, and to the heart rate data classified as normal or abnormal. All models included baseline values, site, and race (African American compared with non-African American, given the higher risk for hypertension among African Americans) as covariates and body mass index (BMI) and current medication dosage as time-varying covariates.

To further account for stimulant use beyond the controlled phase of the study, at each assessment point in the naturalistic follow-up, participants were classified as "never medicated," "currently medicated," or "previously medicated" (but not currently on medication), and analyses of blood pressure categories were conducted with these groups.

For analyses testing for possible associations between cumulative dose exposure and blood pressure or heart rate regardless of treatment assignment, multinomial logistic regression models were applied. For each participant, the cumulative dose of methylphenidate received up to each point of assessment was computed. Information about the dose was obtained by interviewing the participants and their parents. Amphetamine doses were multiplied by 2 for conversion into methylphenidate equivalents (25). Overall cumulative exposure over the 10-year assessment period ranged from 0 to 328,976 mg, with the 25th percentile being 7,898 mg and the 75th percentile 43,460 mg. At each assessment point, based on the cumulative dose received thus far, each participant was assigned to one of four exposure categories: no medication (0 mg), low exposure (cumulative dose, 1–7,898 mg), medium exposure (cumulative dose, 7,899–43,460 mg), or high exposure (cumulative dose >43,460 mg). Analyses included baseline values, site, and race (African American compared with non-African American) as covariates and BMI and current medication dose as time-varying covariates.

A number of other sensitivity and complementary analyses were conducted:

1. A logistic regression model was fitted at each assessment point using the continuous cumulative stimulant dose variable after log transformation.

2. Similar multinomial logistic regression models were conducted after combining the four blood pressure categories into three (normal, prehypertension, and hypertension) or two categories (normal and prehypertension/hypertension).

3. Generalized estimating equation methods were used to fit a multinomial logistic regression model simultaneously to all repeated measurements.

4. The analyses described above were repeated using the average daily dose of stimulant medication received for at least 15 days during the 30 days preceding the assessment and categorized into no medication (0 mg/day), low doses (1–24 mg/day), medium doses (25–40 mg/day), or high doses (>40 mg/day), in lieu of the cumulative dose percentile method described above.

5. The possible effect of actual medication use on the same day of the assessment was examined in a multinomial logistic regression model with cumulative exposure and in a longitudinal analysis using a generalized estimating equation.

6. The effect of medication use on the same day of the assessment was examined in the models with average daily dose, described in item 4 above.

7. Stimulant exposure was defined based on the percentage of time spent on stimulant medication, as consistent with other analyses of this database that focused on clinical outcomes and physical growth (17). Based on this approach, being medicated was defined as having been treated with a stimulant at least 50% of the days since the previous assessment point, and the patients were classified as always, sometimes, or never/seldom medicated based on the status at each assessment point. Blood pressure and heart rate data were reanalyzed using these categories of exposure and the normative comparison group by fitting mixed-effects models that included site, race, and time-varying BMI and stimulant use as covariates.

The relationship between heart rate and cumulative dose, average daily dose, or current medication use was examined based on multiple regression analyses adjusted for age, race (African American compared with others), study site, and baseline heart rate, using the same approach described for blood pressure. Logistic regression models were not used to analyze abnormally elevated heart rate because very few participants (<1.8%) had a heart rate above the upper normal range at each assessment point.

For all the analyses, the threshold for statistical significance was set at 0.05 (two-tailed), despite multiple tests, to prevent type II error.

Results

Sample Retention

Of the 579 patients randomly assigned to treatment groups, data on blood pressure and heart rate were available for 506 (87.4%) at month 14, for 505 (87.2%) at year 2, for 455 (78.6%) at year 3, for 419 (72.4%) at year 6, for 376 (64.9%) at year 8, and for 346 (59.8%) at year 10. A comparison of patients who were retained through year 10 (N=346) and those who were not (N=233) showed a lower proportion of males in the retained group (76.0% compared with 86.7%) but no significant differences in age, race, baseline systolic or diastolic blood pressure, heart rate, or distribution among the four assigned treatment groups.

During the controlled trial (first 14 months), no cardiovascular adverse effects leading to drug discontinuation or decrease in drug dosage occurred. During the subsequent naturalistic treatment phase, no cardiovascular event leading to emergency evaluation or hospitalization was reported, nor was any episode of stimulant discontinuation due to cardiovascular adverse events. Three deaths were recorded among the ADHD participants during the 10 years of observation: a suicide at age 14 (the patient was on methylphenidate), a fatal car accident at age 17 (the patient was the driver and was on methylphenidate), and a sudden unexplained death at age 17 (the patient

TABLE 1. Blood Pressure and Heart Rate Over 10 Years in Youths With ADHD Randomly Assigned to 14 Months of Stimulant Medication, Behavioral Therapy, Combined Treatment, or Usual Community Treatment[a]

Treatment Group and Assessment Time (Months)	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)			Heart Rate (bpm)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Combined medication and behavioral therapy									
0	143	99.5	10.3	143	66.1	8.1	145	84.6	10.9
14	132	102.6	10.2	132	66.5	10.4	135	84.6	12.2
24	134	104.0	11.5	134	67.4	11.0	135	80.4	12.1
36	118	107.3	13.4	118	67.0	10.7	119	80.2	12.2
72	109	116.8	13.7	109	67.1	9.7	113	71.3	10.6
96	101	120.1	15.5	101	65.4	9.0	102	69.8	11.0
120	93	119.6	12.8	93	67.7	9.9	93	69.0	12.5
Medication only									
0	142	101.0	9.8	142	66.0	7.9	143	83.4	11.1
14	125	102.4	9.7	125	67.6	9.6	128	84.2	12.4
24	115	104.4	11.6	113	67.6	11.0	117	81.6	12.2
36	106	107.8	12.3	106	65.0	9.4	108	76.6	12.2
72	96	116.4	12.7	96	66.9	8.4	96	72.2	11.5
96	89	119.8	15.6	89	66.8	11.0	91	71.0	12.6
120	77	122.2	14.8	77	67.6	9.8	78	69.9	11.2
Behavioral therapy only									
0	140	99.4	10.1	140	65.6	9.0	142	85.3	13.3
14	121	103.2	10.3	121	68.9	9.1	125	79.1	12.0
24	128	104.4	10.9	128	67.9	11.6	131	79.1	12.4
36	113	108.4	11.2	113	66.3	11.6	116	76.3	12.7
72	109	114.3	12.9	109	66.3	9.0	110	71.3	13.3
96	97	119.1	14.0	97	67.1	9.6	98	70.5	11.0
120	92	119.1	15.0	92	68.6	11.0	92	68.6	12.4
Usual community treatment									
0	142	99.0	9.9	142	64.4	8.2	143	84.5	11.4
14	115	104.1	10.6	115	67.8	8.8	118	78.9	12.9
24	120	102.7	11.0	120	65.7	10.4	122	78.8	12.1
36	109	106.8	12.7	108	64.0	10.6	112	77.8	11.6
72	96	116.7	12.4	96	64.6	8.3	100	71.3	11.7
96	85	119.0	13.5	85	66.8	8.9	85	70.6	13.7
120	81	119.4	11.7	81	68.3	8.8	83	72.4	12.1

[a] Linear regression models were conducted with site and race (African American compared with non-African American) as covariates and current body mass index (BMI) and stimulant dose (in methylphenidate equivalents) as time-varying covariates. For systolic blood pressure, significant effects were observed for time ($p<0.001$), site ($p<0.001$), BMI ($p<0.001$), and stimulant dosage ($p=0.02$), but none were observed for race, treatment group, or treatment group by time. For diastolic blood pressure, significant effects were observed for time ($p<0.001$), site ($p<0.001$), and BMI ($p<0.001$), but none were observed for race, stimulant dose, treatment group, or treatment group by time. For heart rate, significant effects were observed for time ($p<0.001$), site ($p<0.001$), BMI ($p<0.001$), race ($p<0.01$), stimulant dosage ($p<0.001$), and treatment group by time ($p=0.02$), but none were observed for treatment group. A total of 42 pairwise comparisons were run. Significant pairwise comparisons were as follows: at month 14, medication only > behavioral therapy ($p=0.05$), medication only > usual community treatment ($p=0.01$), combined treatment > behavioral therapy ($p=0.01$), and combined treatment > usual community treatment ($p<0.01$); at month 36, combined treatment > medication only ($p=0.01$); and at month 120, community treatment > behavioral therapy ($p<0.01$) (p values not corrected for multiple comparisons).

was found dead in bed; no specific cause of death could be determined; he had been previously treated with methylphenidate and had been off medication for more than 1 year when he died).

Intent-to-Treat Analyses of Randomized Treatment Groups

Intent-to-treat analyses of raw systolic and diastolic blood pressure data or of the hypertension categories did not identify any statistically significant treatment-related effects on any of these measures, either at the end of the controlled trial at month 14 or afterward (Tables 1 and 2 and Figure 1). There was a significant time effect, consistent with a physiological increase of blood pressure with age, and significant effects of site due to differences in blood pressure measurement procedures, but no significant site-by-treatment effects.

At 14 months, there was a significant treatment-by-time effect ($p=0.02$) on heart rate, with the groups assigned to medication treatment having higher mean heart rates (medication only group, mean=84.2 bpm [SD=12.4]; combined medication plus behavioral therapy group, mean=84.6 bpm [SD=12.0]) than the behavioral therapy only group (mean=79.1 bpm [SD=12.0]) or the usual com-

TABLE 2. Blood Pressure Categories Over 10 Years in Youths With ADHD Randomly Assigned to 14 Months of Stimulant Medication, Behavioral Therapy, Combined Treatment, or Usual Community Treatment[a]

Treatment Group and Assessment Time (Months)	Normal		Prehypertension		Hypertension Stage 1		Hypertension Stage 2		
	N	%	N	%	N	%	N	%	Total N
Combined medication and behavioral therapy									
0	97	67.8	23	16.1	22	15.4	1	0.7	143
14	87	65.9	16	12.1	28	21.2	1	0.8	132
24	85	63.4	18	13.4	28	20.9	3	2.2	134
36	77	65.3	15	12.7	21	17.8	5	4.2	118
72	70	64.2	20	18.3	11	10.1	8	7.3	109
96	53	52.5	25	24.8	17	16.8	6	5.9	101
120	54	58.1	31	33.3	8	8.6	0	0.0	93
Medication only									
0	97	68.3	24	16.9	20	14.1	1	0.7	142
14	90	72.0	14	11.2	19	15.2	2	1.6	125
24	79	69.9	12	10.6	17	15.0	5	4.4	113
36	74	69.8	10	9.4	20	18.9	2	1.9	106
72	64	66.7	11	11.5	17	17.7	4	4.2	96
96	52	58.4	19	21.3	14	15.7	4	4.5	89
120	35	45.5	35	45.5	5	6.5	2	2.6	77
Behavioral therapy only									
0	107	76.4	11	7.9	20	14.3	2	1.4	140
14	74	61.2	21	17.4	25	20.7	1	0.8	121
24	85	66.4	16	12.5	25	19.5	2	1.6	128
36	81	71.7	10	8.8	19	16.8	3	2.7	113
72	72	66.1	17	15.6	17	15.6	3	2.8	109
96	67	69.1	12	12.4	14	14.4	4	4.1	97
120	56	60.9	22	23.9	12	13.0	2	2.2	92
Usual community treatment									
0	110	77.5	15	10.6	17	12.0	0	0.0	142
14	75	65.2	19	16.5	18	15.7	3	2.6	115
24	86	71.7	9	7.5	24	20.0	1	0.8	120
36	79	73.1	14	13.0	13	12.0	2	1.9	108
72	74	77.1	3	3.1	15	15.6	4	4.2	96
96	60	70.6	10	11.8	12	14.1	3	3.5	85
120	47	58.0	30	37.0	4	4.9	0	0.0	81

[a] Based on population-derived age-, sex-, and height-adjusted percentiles, in which normal was defined as <90th percentile for both systolic and diastolic blood pressure, prehypertension as ≥90th and <95th percentile for either systolic or diastolic blood pressure, hypertension stage 1 as ≥95th and <99th percentile for either systolic or diastolic blood pressure, and hypertension stage 2 as >99th percentile for either systolic or diastolic blood pressure. Six records listed normal systolic blood pressures but were missing diastolic blood pressure data; these records were set to missing for categorical blood pressure. One record listed an abnormal systolic blood pressure but was missing diastolic blood pressure data; this record was included as abnormal categorical blood pressure. In proportional odds models, with site and race (African American compared with non-African American) as covariates and current body mass index (BMI) and stimulant dosage as time-varying covariates, significant effects were observed for time ($p<0.0001$), site ($p<0.0001$), and BMI ($p<0.0001$), and none were observed for race, stimulant dosage, treatment group, or treatment group by time.

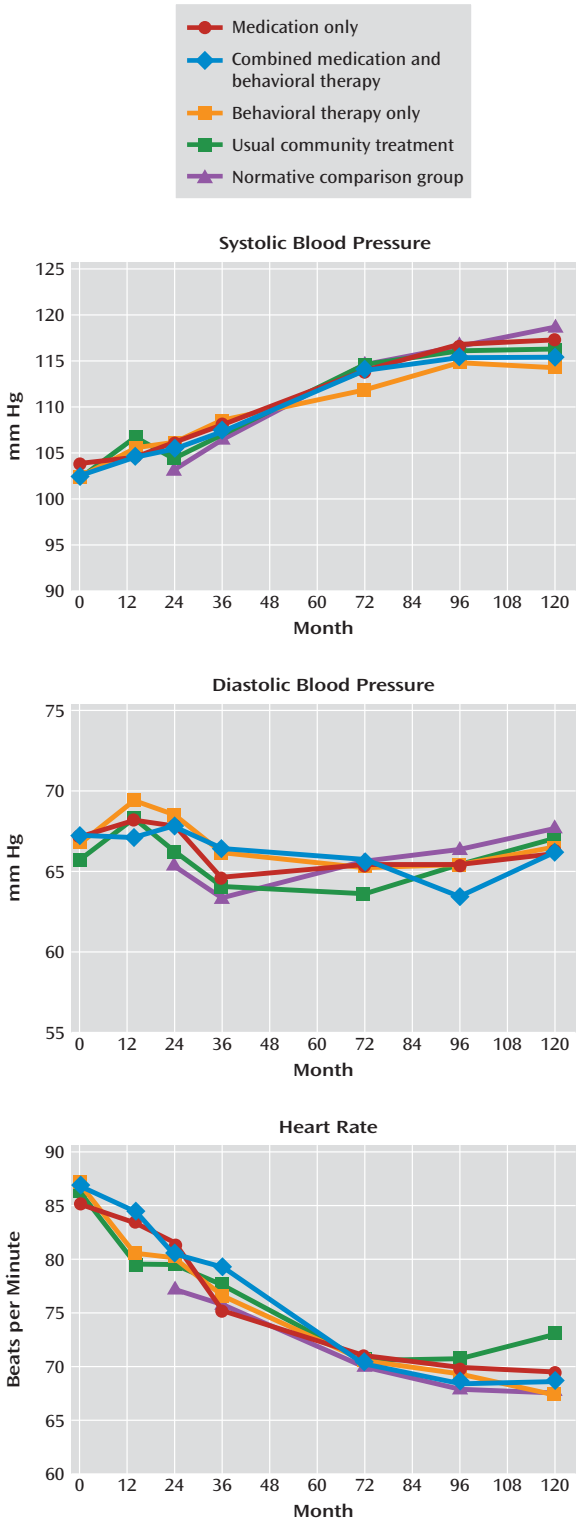
munity treatment group (mean=78.9 bpm [SD=12.0]). The incidence of tachycardia did not differ by treatment group: the rates were 0.8% (1/128) in the medication only group, 2.2% (3/135) in the combined treatment group, 0.8% (1/125) in the behavioral therapy only group, and 2.5% (3/119) in the usual community treatment group.

During the years beyond the initial 14-month period, no significant treatment effect on heart rate was observed with pairwise comparisons except a greater heart rate at year 3 in the combined treatment group as compared with the medication only group ($p=0.01$) and a greater heart rate at year 10 in the usual community treatment group than in the behavioral therapy alone group ($p<0.01$; p values were not corrected for multiple comparisons; a total of 29 pairwise comparisons were conducted).

Stimulant Exposure and Blood Pressure and Heart Rate Over 10 Years

No association was observed between current or previous stimulant use or cumulative methylphenidate-equivalent dose and risk for blood pressure levels in the prehypertensive or hypertensive range (Tables 3 and 4 and Figure 2). At year 10, the rates of abnormal blood pressure (defined as having blood pressure levels in the prehypertension or hypertension range at both years 8 and 10) were not statistically different between youths with the highest

FIGURE 1. Estimated Blood Pressure and Heart Rate Over 10 Years in Youths With ADHD Randomly Assigned to 14 Months of Medication, Behavioral Therapy, Combined Treatment, or Usual Community Treatment and in a Normative Comparison Group[a]



[a] No significant treatment-by-time effect was observed on systolic or diastolic blood pressure. A significant treatment-by-time effect was observed on heart rate (p=0.02), with significantly higher mean heart rates in the groups receiving medication at 14 months, but not afterward.

cumulative exposure and those with lower exposure or those in the normative comparison group (Table 5).

No significant treatment effects on hypertension categories emerged in any of the sensitivity analyses, including dichotomization of the cumulative stimulant dose into no medication or any medication; log transformation of the cumulative dose; combining of the blood pressure categories into three (normal, prehypertension, and hypertension) or two (normal and prehypertension/hypertension combined) categories; use of longitudinal generalized estimating equation models; use of average daily dose instead of cumulative dose; and control for being currently treated with a stimulant and having taken the medication the same day of the assessment.

No significant effect of stimulant exposure (defined as always, sometimes, or never, based on percentage of days in the past year at each assessment point) was observed for blood pressure or heart rate, using mixed effects with stimulant use as a time-varying covariate.

Significant effects of stimulant exposure on heart rate were detected at year 3 (p=0.019) and year 8 (p<0.001), but not at year 10 (Table 6). When controlling for current medication use, the effect remained significant at year 8, but not at year 3.

Discussion

These analyses, conducted with data from a 14-month controlled clinical trial that was followed by naturalistic treatment for a cumulative 10-year period of evaluation, extend findings from previous studies using much shorter periods of observation. Although this clinical trial was not specifically designed to evaluate cardiovascular function, it provides an opportunity to assess blood pressure and heart rate abnormalities as they are likely to emerge in clinical settings. Despite extensive analyses taking different approaches to the data, no evidence could be found that intensive, sustained, and continuous treatment with stimulant medication starting at ages 7–9 years increased the risk for prehypertension or hypertension over a period of 10 years of observation. This conclusion was supported by a comprehensive series of sensitivity analyses that were conducted to account for overall, recent, and current exposure.

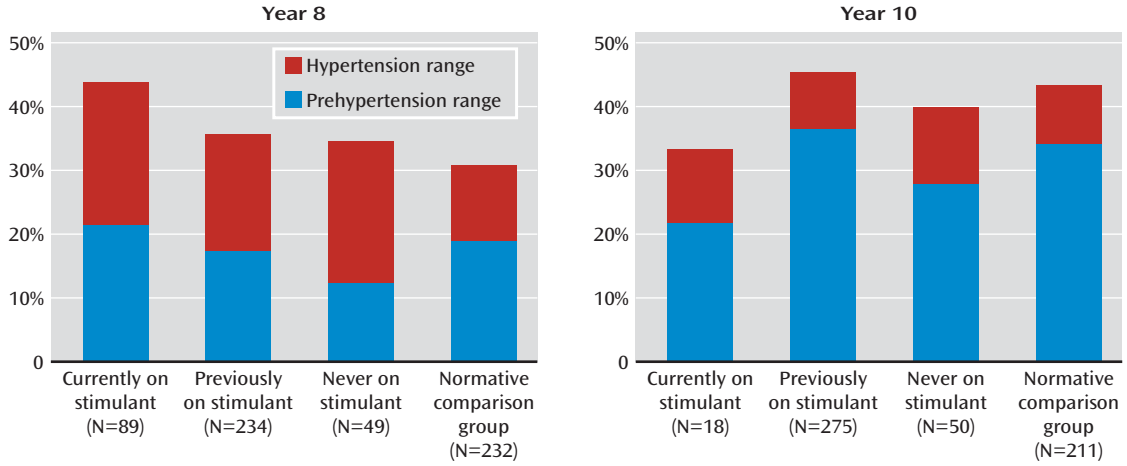
Stimulant treatment was, however, found to increase heart rate at several time points, as shown by intent-to-treat analyses at month 14 and significant associations with actual stimulant exposure at years 3 and 8. The effect on heart rate after 8 years of treatment indicates that complete tolerance to the adrenergic activity of stimulant medication does not develop. As shown in Table 6, the never medicated group had a consistently lower mean heart rate than the medicated groups, although the difference was no longer statistically significant at year 10, possibly because of the smaller number of patients still on medication at that time. The effect on heart rate was driven in large part by current use of medication, although

TABLE 3. Blood Pressure Categories, by Past and Current Stimulant Use, Over 10 years in Youths With ADHD and in a Normative Comparison Group[a]

Assessment Time and Stimulant Use Category[b]	Normal		Prehypertension		Hypertension Stage 1		Hypertension Stage 2		
	N	%	N	%	N	%	N	%	Total N
24 months									
Never	67	70.5	11	11.6	16	16.8	1	1.1	95
Currently	184	67.2	31	11.3	52	19.0	7	2.6	274
Previously	84	66.7	13	10.3	26	20.6	3	2.4	126
Local normative comparison group	197	69.4	42	14.8	43	15.1	2	0.7	284
36 months									
Never	45	63.4	10	14.1	13	18.3	3	4.2	71
Currently	184	73.3	25	10.0	39	15.5	3	1.2	251
Previously	82	66.7	14	11.4	21	17.1	6	4.9	123
Local normative comparison group	195	75.6	24	9.3	36	14.0	3	1.2	258
72 months									
Never	40	71.4	5	8.9	9	16.1	2	3.6	56
Currently	108	65.5	21	12.7	28	17.0	8	4.8	165
Previously	132	69.8	25	13.2	23	12.2	9	4.8	189
Local normative comparison group	171	72.2	28	11.8	30	12.7	8	3.4	237
96 months									
Never	32	65.3	6	12.2	8	16.3	3	6.1	49
Currently	50	56.2	19	21.3	16	18.0	4	4.5	89
Previously	150	64.1	41	17.5	33	14.1	10	4.3	234
Local normative comparison group	160	69.0	44	19.0	25	10.8	3	1.3	232
120 months									
Never	30	60.0	14	28.0	6	12.0	0	0.0	50
Currently	12	66.7	4	22.2	2	11.1	0	0.0	18
Previously	150	54.5	100	36.4	21	7.6	4	1.5	275
Local normative comparison group	119	56.4	72	34.1	19	9.0	1	0.5	211

[a] There were no significant differences in blood pressure categories between stimulant use groups.
[b] The stimulant use categories indicate whether the participant was never treated with stimulant medication, was currently taking stimulant medication (for the 30 days preceding the assessment), or was previously treated with stimulant medication but had no use for at least 30 days before the assessment. The local normative comparison group, which was added to the follow-up study after year 2, consisted of 289 children randomly selected from the same schools and grades and in the same sex proportion as the study participants; they met the same entry criteria except for ADHD diagnosis, although ADHD was not a reason for exclusion.

FIGURE 2. Prevalence of Blood Pressure Reading in the Prehypertension and Hypertension Ranges at Years 8 and 10, by Stimulant Use Category, in Youths With ADHD and in a Normative Comparison Group[a]



[a] Prehypertension is defined as a systolic or diastolic reading at or above the 90th percentile but below the 95th percentile for age, sex, and height. Hypertension is defined as a systolic or diastolic reading at or above the 95th percentile for age, sex, and height. These data are based on one reading only and hence are not necessarily evidence of hypertension. No statistically significant differences were observed between the groups.

TABLE 4. Blood Pressure Category, by Cumulative Stimulant Use Over Time, in Youths With ADHD and in a Normative Comparison Group[a]

Assessment Time and Cumulative Stimulant Dose Category	Normal		Prehypertension		Hypertension Stage 1		Hypertension Stage 2		
	N	%	N	%	N	%	N	%	Total N
24 months									
No medication	67	70.5	11	11.6	16	16.8	1	1.1	95
Cumulative dose ≤7,898 mg	74	68.5	8	7.4	24	22.2	2	1.9	108
Cumulative dose 7,899 mg to 43,460 mg	193	66.3	36	12.4	54	18.6	8	2.7	291
Cumulative dose >43,460 mg	1	100.0	0	0.0	0	0.0	0	0.0	1
Local normative comparison group	197	69.4	42	14.8	43	15.1	2	0.7	284
36 months									
No medication	45	63.4	10	14.1	13	18.3	3	4.2	71
Cumulative dose ≤7,898 mg	41	67.2	8	13.1	9	14.8	3	4.9	61
Cumulative dose 7,899 mg to 43,460 mg	191	73.2	26	10.0	39	14.9	5	1.9	261
Cumulative dose >43,460 mg	34	65.4	5	9.6	12	23.1	1	1.9	52
Local normative comparison group	195	75.6	24	9.3	36	14.0	3	1.2	258
72 months									
No medication	40	71.4	5	8.9	9	16.1	2	3.6	56
Cumulative dose ≤7,898 mg	28	75.7	3	8.1	5	13.5	1	2.7	37
Cumulative dose 7,899 mg to 43,460 mg	104	69.3	20	13.3	21	14.0	5	3.3	150
Cumulative dose >43,460 mg	108	64.7	23	13.8	25	15.0	11	6.6	167
Local normative comparison group	171	72.2	28	11.8	30	12.7	8	3.4	237
96 months									
No medication	32	65.3	6	12.2	8	16.3	3	6.1	49
Cumulative dose ≤7,898 mg	23	74.2	4	12.9	4	12.9	0	0.0	31
Cumulative dose 7,899 mg to 43,460 mg	73	64.0	20	17.5	15	13.2	6	5.3	114
Cumulative dose >43,460 mg	104	58.4	36	20.2	30	16.9	8	4.5	178
Local normative comparison group	160	69.0	44	19.0	25	10.8	3	1.3	232
120 months									
No medication	30	60.0	14	28.0	6	12.0	0	0.0	50
Cumulative dose ≤7,898 mg	16	61.5	6	23.1	3	11.5	1	3.8	26
Cumulative dose 7,899 mg to 43,460 mg	54	54.0	39	39.0	6	6.0	1	1.0	100
Cumulative dose >43,460 mg	92	55.1	59	35.3	14	8.4	2	1.2	167
Local normative comparison group	119	56.4	72	34.1	19	9.0	1	0.5	211

[a] The local normative comparison group, which was added to the follow-up study after year 2, consisted of 289 children randomly selected from the same schools and grades and in the same sex proportion as the study participants; they met the same entry criteria except for ADHD diagnosis, although ADHD was not a reason for exclusion. Proportional odds models with four (normal, prehypertension, hypertension stage 1, and hypertension stage 2), three (normal, prehypertension, and hypertension), or two (normal and prehypertension/ hypertension) blood pressure categories: no significant differences in any of these models.

TABLE 5. Rate of Sustained Increase in Blood Pressure, by Cumulative 10-Year Exposure to Stimulant Medication, in Youths With ADHD and in a Normative Comparison Group

Group and Cumulative 10-Year Stimulant Dose Category[b]	Blood Pressure ≥90th Percentile at Years 8 and 10[a]		
	N	%	95% CI
ADHD sample			
0 mg	50	18.0	6.2–29.8
1 mg to 7,898 mg	26	19.2	2.4–36.1
7,899 mg to 43,460 mg	100	23.0	13.6–32.4
>43,460 mg	169	21.3	14.3–28.3
Local normative comparison group			
0 mg	212	17.9	12.2–23.6

[a] Systolic or diastolic blood pressure ≥90th percentile for age, sex, and height. Based on one measurement each year.
[b] Cumulative stimulant medication exposure, in methylphendiate equivalents. Groups were defined based on cumulative exposure at year 10.

at one assessment point (8 years) there was a significant effect of cumulative exposure regardless of current use.

The clinical implications of persistent adrenergic stimulation, especially for individuals with underlying heart abnormalities, are unclear and cannot be elucidated from these data, but a graded relationship, independent of systolic blood pressure, between increasing resting heart rate and mortality is well documented epidemiologically in adults (26–29). Thus, the adrenergic effect of stimulants cannot be dismissed and should constitute reason for concern and further evaluation of the long-term safety of these medications. To that end, the recent launching of the publicly funded Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study in Europe seems especially timely.

No symptomatic cardiovascular events leading to medical attention were reported during the period of observation, and no stimulant treatment discontinuation conse-

TABLE 6. Heart Rate, by Cumulative Exposure to Stimulant Medication Over Time, in Youths With ADHD and in a Normative Comparison Group

Assessment Time and Cumulative Stimulant Dose Category[a]	Current Medication Use	N	Mean	SD
36 months[b]				
No medication	No	57	77.8	10.6
Cumulative dose ≤7,898 mg	No	39	77.6	13.8
	Yes	9	80.7	12.4
Cumulative dose 7,899 mg to 43,460 mg	No	75	77.1	11.7
	Yes	133	78.9	11.9
Cumulative dose >43,460 mg	No	7	78.7	12.1
	Yes	32	84.4	10.7
Local normative comparison group		199	76.1	11.8
96 months[c]				
No medication	No	50	66.4	8.7
Cumulative dose ≤7,898 mg	No	32	69.6	13.4
	Yes	1	74.0	
Cumulative dose 7,899 mg to 43,460 mg	No	106	69.3	12.5
	Yes	9	77.1	10.8
Cumulative dose >43,460 mg	No	128	70.4	11.7
	Yes	51	76.2	11.6
Local normative comparison group		233	67.9	10.4
120 months[d]				
No medication	No	50	68.9	11.0
Cumulative dose ≤7,898 mg	No	26	70.2	14.7
	Yes	0		
Cumulative dose 7,899 mg to 43,460 mg	No	98	68.1	11.3
	Yes	2	82.0	5.7
Cumulative dose >43,460 mg	No	145	70.7	12.7
	Yes	24	73.7	11.1
Local normative comparison group		212	67.7	10.4

[a] Cumulative stimulant doses are in methylphenidate equivalents. The local normative comparison group, which was added to the follow-up study at year 2, consisted of 289 children randomly selected from the same schools and grades and in the same sex proportion as the study participants; they met the same entry criteria except for ADHD diagnosis, although ADHD was not a reason for exclusion.
[b] At 36 months, the effect of stimulant exposure on heart rate was significant when not controlled for current stimulant use ($p=0.019$), but was not significant when controlled for current stimulant use ($p=0.084$).
[c] At 96 months, the effect of stimulant exposure on heart rate was significant ($p<0.001$) both when controlled for current use and when not controlled for current use.
[d] At 120 months, the effect of stimulant exposure on heart rate was not significant both when not controlled for current stimulant use ($p=0.122$) and when controlled for current stimulant use ($p=0.144$).

quent to cardiovascular adverse effects occurred during the 10-year period. This study sample may have been too small to detect the association between stimulant use and the elevated risk of emergency department visits for cardiac symptoms that has been reported in large epidemiological studies (30). Moreover, the study eligibility criteria excluded children with significant medical conditions. An issue of great concern has been a possible link between therapeutic use of stimulants and elevated risk for sudden cardiac death in youths (31, 32). While the rarity of this event prevents testing for causality through randomized prospective investigations, it is currently recommended that stimulants generally not be used in individuals with underlying cardiac abnormalities that may increase their vulnerability to the sympathomimetic effects of these medications (33). Whether or not stimulants can increase the risk for sudden death among children with no detectable structural heart abnormality is open to speculation. The MTA sample was selected for absence of history or physical signs of cardiovascular problems. Even though no cardiovascular adverse events were recorded during the 10-year period of observation, the sample size was too small to contribute information about an event for which the annual incidence is estimated to be between 0.6 and 6.2 per 100,000 young people (34). Our data do, however, indicate that therapeutic use of stimulants can be accompanied by detectable adrenergic stimulation even after years of ongoing treatment. Because a number of cardiac disorders, such as hypertrophic cardiomyopathy, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia, often entail adrenergic stimulation for arrhythmia induction, stimulant-induced sympathomimetic activity might have clinical implications for some individuals with underlying heart abnormalities (35, 36).

A number of limitations must be taken into account in considering these findings. The MTA was designed to evaluate treatment effects on behavioral outcomes and were not specifically focused on assessment of cardiovascular

parameters. The blood pressure and heart rate measurements were not conducted under double-blind conditions, and the measurement methods varied across the clinical sites, with most sites using a manual method while others used an automatic monitor. This variability does not vitiate the comparison of the randomized treatment groups, which were all measured the same way at a given site. Between-site differences were accounted for by including site as a covariate in the data analyses. It should be noted that at none of the six sites was there a treatment effect on blood pressure at the end of the 14-month controlled trial, which suggests that intersite variability in methods did not undermine the results. The time of the day when measurements were made was variable, according to when individual patients reported to the clinic for their visits. Moreover, the time since stimulant dosing on the day of the assessments could vary. This lack of standardization is likely to have introduced variability that contributed to experimental error, thus possibly obscuring effects that might have been detected with better standardization.

Another important limitation is that abnormal blood pressure values were not systematically confirmed over three separate assessments as required for a diagnosis of prehypertension or hypertension (21). In fact, blood pressure decreases with repeated measurements. In an epidemiological study of school-age children (37), abnormally elevated blood pressure was observed in 19.4% of the children after the first screening, but in 9.5% after the second and in only 4.5% after the third. Thus, the rates of elevated blood pressure that we report cannot be taken as evidence of clinically defined prehypertension or hypertension but only as an indication of increased risk for these clinical conditions. As a reference, the National Health and Nutrition Examination Survey estimated that an age-adjusted 28.7% of the U.S. adult population has hypertension (38), and there are indications that there is a historical trend for blood pressure to increase over the years (39).

With the stated limitations, these data obtained from a large sample over a period of 10 years suggest that intensive and chronic stimulant treatment does not increase the risk for developing blood pressure in the prehypertension or hypertension range. However, stimulant administration continues to have a detectable adrenergic effect even after years of treatment. This effect may have clinical implications, especially for individual patients with underlying heart abnormalities, and it deserves further investigation.

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