No Relation Between Therapeutic Response to Methylphenidate and its Cardiovascular Side Effects in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: The aim of this study was to examine the relation between therapeutic response to methylphenidate (MPH) and its associated short term cardiovascular side effects (Systolic Blood Pressure-SBP, Diastolic Blood Pressure-DBP and Heart Rate-HR changes) in children with ADHD, based on the hypothesis that these parameters share common underlying mechanisms.

Method: A double-blind placebo-controlled crossover clinical trial of children 6 to 12 years old diagnosed with ADHD was done. The children were given one week of 0.5 mg/kg MPH and one week of placebo (divided into two equal doses, given twice every day). On the morning of the third day of each week, Blood Pressure (BP) and HR were recorded immediately before (at time 0) and after (at time 10 and 45 minutes) administration of MPH. Children were grouped into 4 categories according to their therapeutic response (large, moderate, mild or no response) to MPH. A mixed model analysis of variance was performed to determine whether response groups were different with regard to cardiovascular side effects.

Results: All variables were comparable among the four groups 10 min after treatment with MPH and with placebo. Small but significant ($p < 0.001$) increases were seen in SBP (3.65 mm of Hg) and DBP (3.99 mm of Hg) 45 minutes after administration of MPH. A small but significant decrease in HR (3.3 beats per minute) was observed 45 min after administration of placebo. No significant differences in SBP, DBP and HR were found between response groups.

Conclusions: MPH causes a small but significant change in BP at 45 minutes after administration. No changes in HR were observed with MPH at 45 minutes. Responders to MPH treatment do not differ from non-responders in occurrence of BP and HR changes, at least within 45 minutes after administration and with the MPH dosage used in the study.

Keywords and Abbreviations: ADHD, attention deficit hyperactivity disorder; MPH, methylphenidate; BP, blood pressure; HR, heart rate

Introduction

ADHD affects 8%–12% of elementary school children, and is characterized by increased levels of hyperactivity, impulsivity and inattentiveness.[1] Methylphenidate (MPH) and other stimulants are the most widely used medications to treat ADHD. Most children treated with MPH show clinical improvement, especially when the administered doses are adequately titrated.[2] Although MPH is a well-tolerated medication, it has several side effects that need to be assessed and managed.[3,4] MPH is pharmacologically related to sympathomimetic amines, such as ephedrine, pseudoephedrine and phenylpropanolamine, which have potent cardiovascular effects. These pharmacological similarities have prompted the warnings by health authorities. Health Canada reported very rare but serious cardiovascular adverse events, including death, in some users of stimulant drugs and mandated cautionary warnings on nearly all ADHD medications in Canada.[5] Similarly, a black-box warning was issued by the FDA, describing the increased risk of cardiovascular adverse events associated with the use of stimulant drugs in the treatment of ADHD and developed patient medication guidelines.[6,7] It is cautioned that personal and/or family history of heart diseases should be weighed while prescribing psychostimulants and should prompt closer surveillance of their cardiovascular side effects.[8–10] In such situations the use of non-stimulant medications has also been suggested.[11]

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A detailed literature review of the cardiovascular side effects of MPH showed that BP and HR were among the consistently affected parameters.[12–24] Catecholamine neurotransmitters modulate a variety of central nervous system functions including memory, alertness, arousal and regulation of the autonomic nervous system.[25] The catecholamine hypothesis of ADHD suggests that this disorder is the result of deregulation of dopaminergic and noradrenergic drive in various brain circuits including the Prefrontal cortex,[26] although the exact mechanisms of this deregulation and whether there is a unifying model or multiple pathways to ADHD are still debated.[27] The therapeutic effects of MPH stem from increased dopaminergic and noradrenergic drive in the prefrontal cortex and basal ganglia.[28] The cardiovascular side effects of MPH stem from increased dopamine in the brain (hypothalamus and brain stem) and epinephrine in the plasma.[29,30] The primary purpose of this study is to investigate the relationship between therapeutic response and cardiovascular side effects induced by MPH as measured through a double blind placebo-controlled crossover trial with MPH. We hypothesized that given the commonalities in brain structures and pathways underlying behavioral and cardiovascular side effects, we will observe a correlation between these effects.

Methods

Subjects

259 boys and 58 girls aged between 6 to 12 years participated in the study. The children were recruited from the outpatient clinic and the Severe Disruptive Behavior Disorders program at the Douglas University Institute for Mental Health in Montreal. This study is part of a larger pharmacobehavioral genetics study. Children with pervasive developmental disorder, psychosis, history of Tourette's syndrome and an IQ score less than 70 on the WISC-III[31] were excluded from this study. Children taking any medication other than MPH were also excluded. Ninety-five percent of the patients who met the study criteria agreed to take part in the trial.

The diagnosis of ADHD was made by a child psychiatrist in accordance with the DSM-IV criteria.[32] This was further substantiated by a structured interview consisting of the Diagnostic Interview Schedule for Children Version 4 (DISC-IV-parent report),[33] information collected from different sources (school and parent reports). Following a 2-week washout period, baseline assessments comprising detailed behavioral and academic functioning evaluation were carried out. Ethical approval for the study was granted by the Research Ethics Board of Douglas Mental Health University Institute.

Study design

After obtaining informed consent from parents, all children agreed to participate in this 2-week, double-blind, placebo-controlled, crossover, randomized trial with MPH. Baseline assessments were done in the initial week, following which children randomly received either placebo or 0.5 mg/kg of MPH divided in 2 equal doses (morning and noon) daily over a 1-week period. The groups were then crossed over for the second week. A clinical pharmacist not associated with the study prepared MPH and placebo in colored gelatin capsules. The randomization of the medications was ensured by a research psychologist who had no contact with the patients.

In the morning of the third day of each week, the children came to the laboratory.

Three readings of blood pressure (SBP and DBP) and heart rate (HR) were obtained during the third day of the first week and then again on the third day of the second week. The first BP and HR measurements were obtained before administering the medication. The second and third recordings were obtained 10 and 45 minutes after administering the medication.

Assessment of therapeutic response to MPH was determined based on a series of ecological and laboratory measures performed during the MPH and placebo weeks.[34] The Restricted Academic Situation Scale (RASS) was administered to evaluate goal-oriented behaviour while the child is requested to solve math problems adjusted for their educational level. The Conners Continuous Performance Task is a vigilance task measuring inhibition and impulse control along with sustained attention.[35] The RASS and CPT were assessed before and 60 minutes after the administration of treatment. The effects of treatment on global behaviour in the laboratory were gauged by a research assistant (blinded) using the Clinical Global Impression Scales (severity and improvement scales).[36] The effects of treatment on

the child behavior in the school and home environments were assessed using Conners Global Index—Teacher's and—Parent's Versions (CGI-T and CGI-P).[37]

The research team (2 child psychiatrists, a psychologist, child care workers and research assistants) met at the end of the trial to assign a consensus clinical response (CCR) score. After the CCR is blindly determined, the blind was lifted. The CCR score was based on overall degree of improvement during the active week compared with the placebo week of the trial on the following 4-point Likert scale: large response = 3, moderate response = 2, mild response = 1 and no response = 0. Multiple factors ranging from objective and acute measures such as RASS to personal impressions of clinicians, researchers and parents were taken into consideration when giving the CCR score. Overall, the CCR is in line with the results of quantitative measures of behavioral changes under MPH (Table 1).

Statistical Analysis

Quantitative variables were expressed as means ± standard deviation (SD). Categorical variables were expressed as proportions (%). Chi Square analysis was used to compare proportions between groups. ANOVA was used to compare quantitative variables. Mixed model analysis of variance was used to analyze the cardiovascular data. The analysis was done in two stages. In the first stage, the independent factors were medication (2 levels for placebo and MPH) and time (2 levels for time 10 and 45). The dependent variables (SBP, DBP and HR) were analyzed separately. This stage was aimed at determining the effect of treatment and time on the outcome variables.

In the second stage, the independent variable factors were time (2 levels for time 10 and 45) and group improvement (4 levels for none, mild, moderate, large improvement) and the outcome variables were SBP, DBP, HR. In the event of an interaction, the full model was split to evaluate the individual effects of the independent variables on the dependent variable. In both stages, the crossover effect was included in the analysis as an independent factor and the baseline values (before administration of treatment) were included as covariates. All analyses were performed using SPSS 15.0 for Windows; $p < 0.05$ for full models, and $p < 0.017$ (corrected Bonferroni alpha values) for splitted analyses were considered to indicate statistical significance.

Results

Demographics and baseline clinical characteristics of the children with ADHD are presented in Table 2. Patients in different therapeutic response groups did not differ with respect to gender distribution, age, family income levels or Child Behavior Checklist scores(CBCL).

No crossover effects were seen between the active and placebo weeks in all analyses. The effect of time on SBP, DBP and HR when on placebo was different from its effect when on MPH ($P \leq 0.006$), therefore we conducted split analyses. In the first step, the medication was fixed and in the second step, time was fixed. This was done separately for each independent variable SBP, DBP and HR. SBP was not significantly different at time 10 between placebo and MPH ($P = 0.272$), showed no change with time for placebo ($P = 0.832$), but significantly increased by an estimated 3.647 mm of Hg at time 45 for MPH ($P < 0.001$). DBP was not significantly different at time 10 between placebo and active medication ($P = 0.127$), showed no change with time for placebo ($P = 0.576$), but significantly increased by an estimated 3.99 mm Hg at time 45 for MPH ($P < 0.001$). HR was not significantly different at time 10 between placebo and MPH ($P = 0.191$), showed no change with time for MPH

Table 1. Mean (±SD) improvement on three main clinical evaluations for each of the four consensus clinical response (CCR) categories.

	No	Mild	Moderate	Large	p-value
Δ Conners' Parents	5.2(0.9)	–4.0(1.1)	–3.0(0.2)	–11.0(1.9)	0.000
Δ Conners' Teachers	–0.7(0.1)	–2.6(0.2)	–10.1(1.1)	–17.2(0.8)	0.000
Δ RASS	–9.0(1.4)	0.8(6.6)	–16.7(1.3)	–25.7(4.5)	0.009

RASS, restricted academic situation scale; Δ, difference in total score before and after MPH administration; Negative Δ indicate improvement.

($p = 0.778$), but was significantly decreased by an estimated 3.3 beats per minute at time 45 under placebo ($p < 0.001$).

In the second full model no interaction effects were noted between time and group improvement ($p > 0.12$). No significant effect of group improvement was noted on SBP, DBP and HR (all p-values ≥ 0.18). The results are summarized in Table 3.

Discussion

To our knowledge, this is the first study looking at the relationships between therapeutic response to MPH and the short-term cardiovascular side effect profile. Our results showed that MPH caused a small and statistically significant ($p < 0.001$) increase in SBP and DBP 45 min after administration of MPH. Significant increases in plasma catecholamines and accompanying HR and BP changes have been demonstrated following an intravenous infusion of MPH (0.3 mg/kg).[38] At therapeutic doses of MPH, there is increased sympathetic drive due to increased dopamine in the brain and epinephrine in the plasma.[39]

Contrary to expectations, we found that HR showed a significant fall in the placebo group at 45 minutes but no change was seen in the MPH group. However, this result might be due to anxiety and timing of HR measurement.[40] The child has anticipatory anxiety while beginning new experimental procedures. As the study progresses, the child adjusts to the experimental set up and there is a natural fall in HR. This explanation is compatible with the observed results as the fall in HR is nullified under MPH administration.

There were no crossover effects, in that the BP and HR changes induced by MPH returned to baseline values and did not persist into the placebo week. MPH has a short half-life and its absorption is not hindered by the presence of food within the gut.[41] Peak pharmacokinetic levels in serum and in the brain are achieved within 1 hour, which mirrors the timing of its pharmacodynamic (behavioural) effects.[42] Thus, cardiovascular side effects and therapeutic response are manifest within the time period of our study.

Responders and non-responders to treatment with MPH are no different in terms of the BP and HR side effects they experience. Indeed, while the therapeutic effects of MPH could be mainly attributed to its influence on cortical activity and basal ganglia, its effects on cardiovascular parameters may be predominantly dependent on subcortical influences (hypothalamus and brain stem).[29,43] Prefrontal cortex performance is optimized with moderate stimulation of postsynaptic dopaminergic and noradrenergic receptors, and is reduced by either higher or lower levels of receptor stimulation.[44] Thus, MPH has to be administered within the therapeutic range in order to best alleviate the abnormal behaviour.

The hypothalamus and brainstem modified by higher cortical inputs are responsible for central regulation of the sympathetic nervous system. Complex dopaminergic and noradrenergic system interactions, as well as interaction with other systems such as the serotonergic system, are accountable for the regulation of sympathetic nervous system. At the fixed dose administered in this trial, the absence of relation between therapeutic response and cardiovascular side effects suggests that cardiovascular and therapeutic effects may be due to predominantly non-overlapping or weakly coupled pathways in the brain.

Table 2. Mean (±SD) of clinical and demographic characteristics for each of the four consensus clinical response (CCR) categories.

	No (47)	Mild (51)	Moderate (123)	Large (N = 96)	p-value
Sex: (Male/Female)	36/11	42/9	95/28	86/10	0.15
Age	9.2(1.9)	9.3(1.8)	8.8(1.8)	8.9(1.7)	0.42
Income Level Category	4.7(1.5)	4.5(1.5)	4.2(1.7)	3.8(1.6)	0.05
CBCL Total at baseline evaluation	66.2(9.3)	68.5(10.4)	70.1(7.4)	70.9(8.8)	0.27
CBCL Internalization	61.7(10.9)	62.6(11.4)	65.1(9.9)	64.8(10.5)	0.37
CBCL Externalization	65.4(10.0)	69.4(10.9)	69.2(8.9)	71.8(9.7)	0.11

Table 3. Mean (±SD) on each of the four consensus clinical response (CCR) categories for Blood Pressure and Heart Rate Changes in children with ADHD.

	Blood pressure								Heart rate			
	Placebo week				MPH week				Placebo week		MPH week	
	10 min		45 min		10 min		45 min		10 min	45 min	10 min	45 min
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP				
None	103.9 (12.8)	61.6 (6.6)	102.5 (11.5)	59.8 (7.3)	102.4 (11.7)	61.7 (9.4)	104.3 (11.0)	64.2 (20.3)	83.5 (12.6)	80.0 (12.1)	83.0 (12.5)	79.3 (10.8)
Mild	99.5 (9.7)	58.5 (6.7)	103.9 (12.2)	61.2 (14.9)	80.3 (10.5)	57.6 (8.2)	102.3 (13.1)	60.4 (6.4)	82.1 (10.4)	79.0 (12.0)	81.9 (11.5)	81.0 (11.4)
Moderate	102.2 (13.3)	60.0 (10.6)	102.1 (11.2)	60.2 (9.1)	101.8 (13.3)	58.3 (7.4)	103.9 (12.4)	62.1 (10.8)	78.6 (12.3)	76.5 (13.1)	79.0 (11.3)	78.1 (12.2)
Large	102.5 (12.1)	60.8 (7.8)	103.6 (14.1)	61.9 (11.5)	101.3 (10.7)	59.2 (7.6)	107.9 (12.5)	64.0 (9.5)	83.7 (12.2)	80.1 (12.3)	79.2 (10.0)	82.8 (14.5)
All groups	103.0 (0.9)	60.3 (0.7)	103.2 (0.9)	60.8 (0.7)	102.1 (0.1)	59.3 (0.1)	105.7* (0.9)	63.2* (0.7)	81.7 (0.9)	78.4* (0.9)	80.5 (0.9)	80.9 (0.9)

*P-Value < 0.001 (Parameters at 10 and 45 minutes after treatment as compared to before treatment), SBP, systolic blood pressure; DBP, diastolic blood pressure.

Limitations

Our study comprised a smaller cohort of girls as compared to boys, making data analysis by gender impossible. We did not have a sizeable cohort of various racial groups in order to allow for data analysis by race. Our study was conducted based on the immediate (45 minutes) and short term (third day of each week) side effects of low-dose (0.5 mg/kg divided into two equal doses) MPH. Children with poor response to MPH would be more likely to become long-term high-dose poly-pharmacy recipients. It would be interesting to perform further studies looking at the side effect profiles of higher doses of MPH in longer terms and poly-pharmacy situations.

Conclusions

This study shows that MPH has a clinically modest, but statistically significant effect of increasing the BP within 45 minutes of its oral administration and is in line with previous similar studies. This acute increase becomes important in the context of cardiovascular disease, risk factors for cardiovascular disease and use of other drugs having cardiovascular side effects. There appears to be no relation between the therapeutic response to MPH and its effects on BP and HR, at least, within 45 minutes after its oral administration. Thus, responders to MPH treatment do not differ from non-responders in occurrence of short-term side effects (BP and HR), and there is no need for differential surveillance of cardiovascular side effects among patients with different therapeutic responses to MPH.

Conflict of Interest

This work was supported by grants from FRSQ and CIHR to RJ and NG. RJ receives consultancy honorarium from Janssen Ortho and Pfizer Canada. All other authors deny any conflict of interest with respect to this study.

References

[1] Biederman, J. and Faraone, S.V. 2005. Attention-deficit hyperactivity disorder. *The Lancet*, 366:237–48.

[2] Elia, J., Borcherding, B.G., Rapoport, J.L. and Keysor, C.S. 1991. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry research*, 36:141–55.

[3] Barkley, R.A., McMurray, M.B., Edelbrock, C.S. and Robbins, K. 1990. Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. *Pediatrics*, 86:184–92.

[4] Vetter, V.L., Elia, J., Erickson, C. et al. 2008. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder: A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation*, 117:2407–23.

[5] Wooltorton, E. 2006. Medications for attention deficit hyperactivity disorder: cardiovascular concerns. *Canadian Medical Association Journal*, 175:29.

[6] Food, U.S. and Administration, D. FDA Patient Safety News: Show# 63, May 2007. *Cardiovascular and psychiatric risks with ADHD drugs*.

[7] Rosack, J. 2007. FDA Orders New Guides for ADHD Prescriptions. *Psychiatric News*, 42:1.

[8] Kociancic, T., Reed, M.D. and Findling, R.L. 2004. Evaluation of risks associated with short-and long-term psychostimulant therapy for treatment of ADHD in children. *Eds.*, 3:93–100.

[9] Wilens, T.E., Prince, J.B., Spencer, T.J. and Biederman, J. 2006. Stimulants and Sudden Death: What Is a Physician to Do? *Pediatrics*, 118:1215.

[10] Shader, R.I. and Oesterheld, J.R. 2006. Facts and Public Policy: Should I Keep My Child on ADHD Drugs? *Journal of Clinical Psychopharmacology*, 26:223.

[11] Wood, J.G., Crager, J.L., Delap, C.M. and Heiskell, K.D. 2007. Literature Review: Beyond Methylphenidate: Nonstimulant Medications for Youth With ADHD. *Journal of Attention Disorders*, 11:341.

[12] Samuels, J.A., Franco, K., Wan, F. and Sorof, J.M. 2006. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatric Nephrology*, 21:92–5.

[13] Stein, M.A. et al. 2003. A Dose-Response Study of OROS Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*, 112:1101–6.

[14] Martin, W.R., Sloan, J.W., Sapira, J.D. and Jasinski, D.R. 1971. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin. Pharmacol. Ther.*, 12:245–58.

[15] Werry, J.S. and Aman, M.G. 1975. Methylphenidate and haloperidol in children. Effects on attention, memory, and activity. *Archives of General Psychiatry*, 32:790–5.

[16] Ballard, J.E., Boileau, R.A., Sleator, E.K., Massey, B.H. and Sprague, R.L. 1976. Cardiovascular responses of hyperactive children to methylphenidate. *JAMA*, 236:2870–4.

[17] Volkow, N.D. et al. 1996. Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects. *Psychopharmacology*, 123:26–33.

[18] Joyce, P.R., Donald, R.A., Nicholls, M.G., Livesey, J.H. and Abbott, R.M. 1986. Endocrine and behavioral responses to methylphenidate in normal subjects. *Biological psychiatry*, 21:1015–23.

[19] Wilens, T.E., Biederman, J. and Lerner, M. 2004. Effects of once-daily osmotic release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. *J. Clin. Psychopharmacol.*, 24:36–41.

[20] Findling, R.L. 2001. Short-term cardiovascular effects of methylphenidate and Adderall. *J. Am. Acad. Child Adolesc Psychiatry*, 40:525–9.

[21] Donner, R., Michaels, M.A. and Ambrosini, P.J. 2007. Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in the Treatment of School-Aged Children with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, 61:706–12.

[22] Findling, R.L. et al. 2005. Short-and Long-Term Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in Children. *The Journal of Pediatrics*, 147:348–54.

[23] Brown, R.T., Wynne, M.E. and Slimmer, L.W. 1984. Attention deficit disorder and the effect of methylphenidate on attention, behavioral, and cardiovascular functioning. *J. Clin. Psychiatry*, 45:473–6.

[24] Greenberg, L.M. and Yellin, A.M. 1975. Blood pressure and pulse changes in hyperactive children treated with imipramine and methylphenidate. *Am. J. Psychiatry*, 132:1325–6.

[25] Kobayashi, K. 2001. Role of Catecholamine Signaling in Brain and Nervous System Functions: New Insights from Mouse Molecular Genetic Study. *Journal of Investigative Dermatology Symposium Proceedings*, 6:115–21.

[26] Levy, F. 2008. Pharmacological and therapeutic directions in ADHD: Specificity in the PFC. *Behavioral and Brain Functions*, 4:12.

[27] Williams, J. 2008. Working toward a neurobiological account of ADHD: Commentary on Gail Tripp and Jeff Wickens, Dopamine transfer deficit. *Journal of Child Psychology and Psychiatry*, 49:705–11.

[28] Pliszka, S.R. 2005. The Neuropsychopharmacology of Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, 57:1385–90.

[29] Jansen, A.S.P., Nguyen, X.V., Karpitskiy, V., Mettenleiter, T.C. and Loewy, A.D. 1995. Central Command Neurons of the Sympathetic Nervous System: Basis of the Fight-or-Flight Response. *Science*, 270:644.

[30] Franz, D.N., Madsen, P.W., Peterson, R.G. and Sangdee, C. 1982. Functional roles of monoaminergic pathways to sympathetic preganglionic neurons. *Clin. Exp. Hypertens. A.*, 4:543–62.

[31] Wechsler, D. 1991. Wechsler Intelligence Scale for Children-third edition: Manual. *The psychological corporation, San Antonio, TX*.

[32] American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

[33] Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K. and Schwab-Stone, M.E. 2000. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39:28–38.

[34] Milich, R., Loney, J. and Landau, S. 1982. Independent dimensions of hyperactivity and aggression: a validation with playroom observation data. *J. Abnorm. Psychol.*, 91:183–98.

[35] Conners, C.K. 1995. Conners'Continuous Performance Test computer program 3.0: User's manual. *Toronto, Ontario, Canada: Multi-Health Systems Inc*.

[36] Barkley, R.A. 1990a. Tests and observational measures. In: Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment, Barkley RA, ed. New York: Guilford Press, 327–53.

[37] Conners, C.K., Sitarenios, G., Parker, J.D. and Epstein, J.N. 1998. The revised ADHD sleep monitoring on methylphenidate. *J. Abnorm. Psychol.*, 91:183–98.

[38] Joyce, P.R., Nicholls, M.G. and Donald, R.A. 1984. Methylphenidate increases heart rate, blood pressure and plasma epinephrine in normal subjects. *Life Sc.*, 34:1707–11.

[39] Volkow, N.D. et al. 2003. Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. *Psychopharmacology*, 166:264–70.

[40] Friedman, B.H. 2007. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. *Biol. Psychol.*, 74:185–99.

[41] Modi, N.B., Wang, B., Hu, W.T. and Gupta, S.K. 2000. Effect of food on the pharmacokinetics of osmotic controlled-release methylphenidate HCl in healthy subjects. *Biopharmaceutics and Drug Disposition*, 21:23–31.

[42] Wigal, S. et al. 2004. A Double-Blind, Placebo-Controlled Trial of Dexmethylphenidate Hydrochloride and d, l-threo-Methylphenidate Hydrochloride in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43:1406–14.

[43] Pliszka, S.R., McCracken, J.T. and Maas, J.W. 1996. Catecholamines in attention-deficit hyperactivity disorder: current perspectives. *J. Am. Acad. Child Adolesc. Psychiatry*, 35:264–72.

[44] Russell, V.A. 2002. Hypodopaminergic and hypernoradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorderùthe spontaneously hypertensive rat. *Behavioural Brain Research*, 130:191–6.