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REVIEW ARTICLE

Cardiovascular Effects of Methylphenidate, Amphetamines and Atomoxetine in the Treatment of Attention-Deficit Hyperactivity Disorder: An Update

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Abstract Several million children and a growing number of adults are currently being treated for attention-deficit hyperactivity disorder (ADHD) worldwide. Concerns have been expressed about possible cardiac effects of the common treatments, namely methylphenidate, amphetamines and atomoxetine. Small increases in mean heart rate (HR) and mean blood pressure (BP) have been reported for all three drugs, but most of the studies have not yielded statistically significant results. These studies also have limitations, particularly regarding the lack of accepted and standardised measurement methods. Several large studies of the very rare phenomenon of sudden death in children have failed to show any convincing association with ADHD treatment. Whether minor increases in HR and BP have a cumulative effect over many years and have a long-term adverse effect on cardiovascular health remains undetermined.

Key Points

There are generally consistent reports of small clinically insignificant increases in mean heart rate and blood pressure with methylphenidate, amphetamines and atomoxetine

None of the studies on sudden death in children has shown a convincing association with attention-deficit hyperactivity disorder treatment

There is a lack of research on the very long-term outcome of any small changes in heart rate and blood pressure that might occur as a result of taking stimulant medication or atomoxetine

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1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is very common. Visser et al. [1] reported that over 3 million children in the USA alone are receiving treatment for this condition. ADHD is also increasingly being recognised and treated in adults. Against this background, it is very important for clinicians, patients and families to be aware of any clinically significant adverse effects of treatment. Because the common treatments, namely methylphenidate, dexamfetamine and atomoxetine, are all sympathomimetic, there has been understandable concern about possible adverse cardiovascular effects. A number of papers and reviews have been published on this subject. For example, in a systematic review, Westover and Halm [2] asked the question: "Do prescription stimulants increase the risk of adverse cardiovascular events?" Ten population-based observational studies were evaluated. Six of the seven studies in children and adolescents did not show an association between stimulant use and adverse cardiovascular events. Two of three studies in adults found an association. Bushe and Savill [3] carried out a systematic review of atomoxetine data from 2009 to 2012 and concluded that, from epidemiological databases, cardiovascular events were similar to those associated with methylphenidate. Winterstein et al. [4] examined claims data from 1,219,847 children and young people in the USA from 1999 to 2006; they concluded that stimulant medication was not significantly associated with an increase in the short-term risk of

severe cardiac events. As well as drawing the same general conclusions as other reviews with regard to the cardiovascular effects of ADHD treatment, Elia and Vetter [5] discussed how these findings should influence prescribing practice. They pointed out that any negative cardiovascular effects need to be weighed against the "potentially catastrophic events" that could result from withholding treatment for ADHD. While there are many studies examining the short-term effects of ADHD medication, there is a paucity of long-term studies.

The purpose of this review is to provide an update on the evidence available for any effects of methylphenidate, dexamfetamine and atomoxetine on heart rate (HR), blood pressure (BP) or sudden cardiac death.

2 Methods

Because one of the authors of this paper is co-author on a previous review on the effects of methylphenidate, dexamfetamine and atomoxetine on HR and BP, covering published literature from 1952 to February 2009 [6], the current review has focused on publications since that period. Similarly, one of the authors has also previously published a commentary on the issue of sudden death in children treated for ADHD in 2009 [7] and, for this reason, the current review has focused on publications that have appeared since that paper.

PubMed/MEDLINE, Embase, PsycINFO, the Wolters Kluwer OVID database and the SAGE Journal database were searched over the period from March 2009 to January 2014 using the search terms 'ADHD' or 'attention deficit hyperactivity disorder' and 'cardiovascular' or 'cardiac' or 'heart rate' or 'HR' or 'blood pressure' or 'BP' or 'QTc'. This search returned 278 abstracts covering the relevant time period. A separate search was also conducted using the following drug names: 'methylphenidate', 'atomoxetine', 'dexamfetamine', 'mixed amphetamine salts', 'lisdexamfetamine', 'Concerta', 'Ritalin', 'Medikinet', 'Strattera' and 'Adderall', combined with each of the following words and abbreviations: 'adverse', 'side-effect', 'blood pressure' or 'BP', 'heart rate' or 'HR', 'QT' or 'QTc' and 'sudden death'. This provided 572 results, although several papers appeared in both searches. The searches were limited to papers published in English. All the results were screened. This resulted in 75 papers of possible relevance. On further scrutiny, 20 of these 75 papers were identified as being of likely relevance on the basis of their containing data or providing commentary on the cardiovascular effects of ADHD medication. The reference lists of these papers were also searched for any relevant articles. Unless otherwise specified, the results presented refer only to publications since February 2009.

Statistical advice was sought on the possibility of carrying out meta-analyses of the results in the various studies. However, in addition to the difficulty of obtaining the necessary basic information, the interpretation would have been complicated by the non-standardised way in which the measurements were made and the differing follow-up times. Instead, graphical and tabular summaries of the data have been prepared where appropriate. These provide an overview of the results, while making no assumptions with regard to standardisation of measurement, follow-up times or the other clinical variables discussed above.

3 Methylphenidate Heart Rate (HR) and Blood Pressure (BP): Clinical Data

Nine studies contained data on the effects of methylphenidate treatment on BP and HR in children or adolescents with ADHD (Table 1). Of the nine studies, eight contained statistical analysis of data on BP and eight contained statistical analysis of data on HR. Of the nine studies, only three focused on the cardiovascular effects of methylphenidate as a primary outcome: Hammerness et al. [10], Vitiello et al. [16] and Arcieri et al. [15]. The majority of the studies included measures of BP and HR as secondary outcomes.

Of the eight studies with statistical analysis of HR data, five showed a statistically significant change in HR in children and adolescents treated with methylphenidate compared with baseline. Green et al. [8] reported that, 90 min after the administration of a single methylphenidate dose to children with velocardiofacial syndrome (VCFS), a statistically significant increase in HR of +5.5 bpm (82.4 ± 13.5 bpm at baseline vs. 87.9 ± 17.8 bpm after 90 min) was recorded ($p < 0.05$). They commented that these results were consistent with those in children who did not have VCFS. Hammerness et al. [10] reported statistically significant increases in HR at 6 weeks (+4.3 bpm; $p < 0.05$) and 3 months (+3.8 bpm; $p < 0.05$); Arcieri et al. [15] reported a statistically significant increase in mean pulse rate at 6 months (+2.1 ± 15.04 bpm; $p = 0.01$); Cho et al. [13] reported a statistically significant increase in HR at 12 weeks (+3.83 bpm; $p = 0.001$). Vitiello et al. [16] also reported a statistically significant increase in HR of +0.8 bpm ($p = 0.02$) after 14 months; however, they reported statistically significant decreases in HR at year 3 (−6.8 bpm; $p = 0.019$) and year 8 (−12.4 bpm; $p < 0.001$). By year 10, the decrease was −13.5 bpm, but this decrease was not statistically significant ($p > 0.05$). The authors concluded that methylphenidate had a 'persistent adrenergic effect' on HR.

Table 1 Summary of publications of effects of methylphenidate on systolic blood pressure, diastolic blood pressure and heart rate in children and adolescents with attention-deficit hyperactivity disorder; data are listed in order of the duration of the period over which data were collected

Endpoint	Change in mean from baseline to endpoint			MPH type; dose	Age range and no. of subjects	Design	References
	SBP (mmHg)	DBP (mmHg)	HR (bpm)				
90 min	+0.6	**+4.0**	**+5.5**	Single MPH dose; +15.7 ± 5.6 mg (mean)	5–20; 22[a]	ran, pc, wo	[8]
5 w	**+2.0 ± 9.5**	**+3.0 ± 7.8**	No data	MPH transdermal system; 10–30 mg MTS	6–12; 140	ol, phase IV, multisite, dose op, wo	[9]
6 w	+2.1	**+2.9**	**+4.3**	OROS MPH; clinically adjusted; 63.1 ± 25.0 (mean dose at 6 w)	12–18; 114	ol, pro	[10]
7 w	+0.3 ± 11.1	+1.7 ± 9.9	+5.0 ± 12.8	OROS MPH; 18, 36, 54 mg	6–17; 111	wo, ran, pc, db	[11]
12 w	−4.3	−1.0	+3.7[b]	OROS MPH; 18–54 mg/day	8–14; 11	ol, rand, pro, h2h	[12]
12 w	No data	No data	**+3.83 ± 10.5**	OROS MPH; final mean dosage 0.98 (±0.52) mg/kg/day	6–12; 101	Multisite (6), pro, ol	[13]
3 mo	+2.6	+0.8	**+3.8**	OROS MPH; no data	12–18; 75	ol, pro	[10]
6 mo	**+4.5**	+1.3	+4.4	OROS MPH; clinically adjusted; 67.2 ± 24.3 (mean dose at 6 mo)	12–18; 57	ol, pro	[10]
6 mo	+4.2 ± 10.59	+1.7 ± 8.59	+5.9 ± 13.40	MPH transdermal system; 10–30 mg/9 h patches	13–17; 63	Multisite (30), ol, dose op	[14]
6 mo	+0.26 ± 13.18	+0.82 ± 10.99	**+2.1 ± 15.04**[b]	MPH; 0.4 ± 0.2 mg/kg/dose/day	6–18; 315	ol, pro, multimodal, h2h	[15]
12 mo	−0.49 ± 14.83	+1.35 ± 12.40	+1.25 ± 12.69[b]	MPH; 0.4 ± 0.2 mg/kg/dose/day	6–18; 194	ol, pro, multimodal, h2h	[15]
14 mo	+1.4	+1.6	**+0.8**	IR MPH; mean daily dose of 38.1 mg (medication-only group)	7–9; 125	ran, multisite (8)	[16]
24 mo	−1.0 ± 16.10	**−3.90 ± 11.23**	**−3.80 ± 12.82**[b]	MPH; 0.4 ± 0.2 mg/kg/dose/day	6–18; 61	ol, pro, multimodal, h2h	[15]
2 y	+3.4	+1.6	−1.8	IR MPH; mean daily dose of 22.6 mg	7–9; 115	ran, multisite (8)	[16]
3 y	+6.8	−1.0	**−6.8**	IR MPH; mean daily dose of 22.6 mg	7–9; 106	ran, multisite (8)	[16]
6 y	+15.4	+0.9	−11.2	IR MPH; mean daily dose of 22.6 mg	7–9; 96	ran, multisite (8)	[16]
8 y	+18.8	+0.8	**−12.4**	IR MPH; mean daily dose of 22.6 mg	7–9; 89	ran, multisite (8)	[16]
10 y	+21.2	+1.6	−13.5	IR MPH; mean daily dose of 22.6 mg	7–9; 77	rand, multisite (8)	[16]

Bold indicates a statistically significant result

ADHD attention-deficit hyperactivity disorder, *db* double blind, *DBP* diastolic blood pressure, *dose op* dose optimised, *HR* heart rate, *h2h* head to head, *IR* immediate release, *mo* month, *MPH* methylphenidate, *MTS* methylphenidate transdermal system, *ol* open label, *OROS* osmotic release oral system, *pc* placebo-controlled, *pro* prospective study, *ran* randomised, *SBP* systolic blood pressure, *VCFS* velocardiofacial syndrome, *w* week, *wo* washout period, *y* year

[a] Children with VCFS; ADHD defined by ADHD module of the K-SADS-Present (a subset of DSM-IV-TR). *p* Values that were quoted as <0.05 are marked as statistically significant although no specific comment on significance was made by the authors

[b] Pulse rate

No other data reporting statistically significant differences in HR from baseline were found. None of the data were described as being clinically significant.

Figure 1 shows that the change in HR over different endpoints up to 6 months with methylphenidate administration across the studies in Table 1 is consistently positive and between +2 and +6 bpm. None of the results have been described as clinically significant.

Eight studies reported results of the effects of methylphenidate on BP in children with ADHD. Of these, four reported a statistically significant change in BP. In our previous review, we reported that there were few studies on the immediate effect of methylphenidate on HR and BP. This is still the case. The only paper containing data for the immediate effects of methylphenidate was Green et al. [8]. In a small ($n = 34$) study of children with ADHD and VCFS, they recorded the systolic BP (SBP), diastolic BP (DBP), HR and corrected QT interval (QTc) 90 min after a single dose of methylphenidate. The authors stated that there was a 'minimal', statistically significant increase in DBP (60.6 ± 8.4 at baseline vs. 64.6 ± 6.9 mmHg after 90 min; $p < 0.05$). They found a clinically significant increase in SBP in two of the children and concluded that a 'comprehensive cardiological evaluation' should be performed before and after the initiation of stimulant medication. They recommended measuring HR and BP before and after initiation of stimulant medication, and further testing, such as 24-h ambulatory BP monitoring, should there be a clinically significant change in cardiovascular parameters.

Mick et al. [9] performed a genome-wide association study (GWAS) of BP response to methylphenidate treatment of 140 children with ADHD, none of whom met the clinical criteria for paediatric hypertension. The study reported a statistically significant change in mean SBP of 2.0 ± 9.5 mmHg (from 102.5 ± 9.0 to 104.5 ± 8.4; $p = 0.01$) and in mean DBP of 3.0 ± 7.8 mmHg (from 61.6 ± 7.7 to 64.6 ± 7.5; $p < 0.0001$) from the baseline to the endpoint 5 weeks later. It is important to note that BP response to methylphenidate varied with differences in genetic background; this may have implications for future prescription of the medication.

Hammerness et al. [10] examined the effect of high doses of osmotic release oral system (OROS) methylphenidate and reported a +2.9 mmHg ($p < 0.05$) increase in mean DBP after 6 weeks and a +4.5 mmHg ($p < 0.05$) increase in mean SBP after 6 months. They also reported a statistically significant decrease in mean DBP between 6 weeks and 3 months. The mean DBP with methylphenidate went from 65.4 ± 9.2 after 6 weeks to 63.3 ± 8.3 after 3 months. The calculation at 3 months was above the baseline calculation (62.5 ± 9.0), but the difference was not statistically significant.

Arcieri et al. [15] assessed the cardiovascular effects of methylphenidate and atomoxetine used to treat 1,758 drug-naïve children and adolescents (6–18 years old) with ADHD enrolled in the Italian ADHD national registry. BP and HR were evaluated at 6, 12 and 24 months. A small, statistically significant decrease in DBP (−3.90 ± 11.23; $p = 0.009$) was observed after 24 months. No other BP changes were statistically significant.

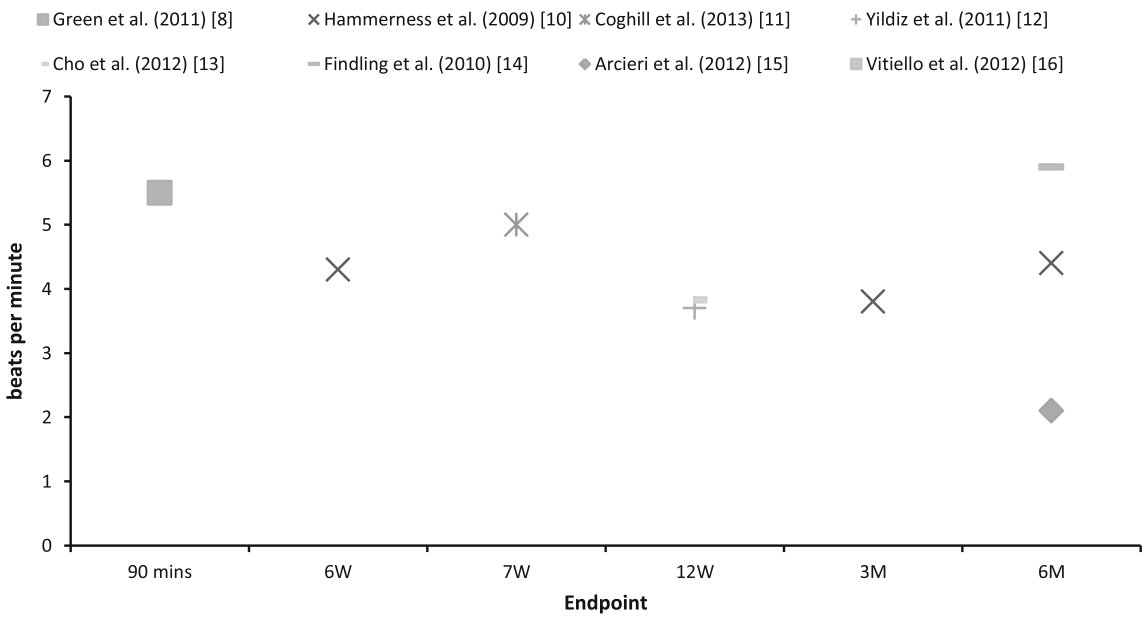

Fig. 1 Graphical representation of mean HR changes attributed to methylphenidate administration in Table 1 indication remarkably little variation between published results

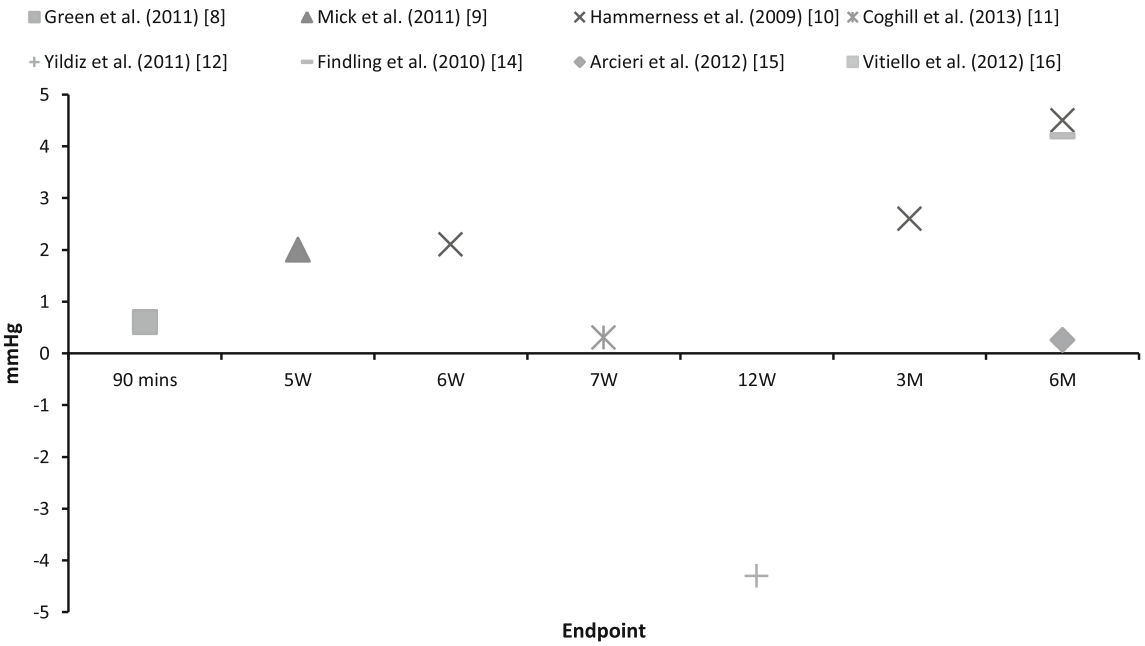

Fig. 2 Changes in systolic blood pressure with methylphenidate administration across the studies in Table 1 indicate clinically insignificant results

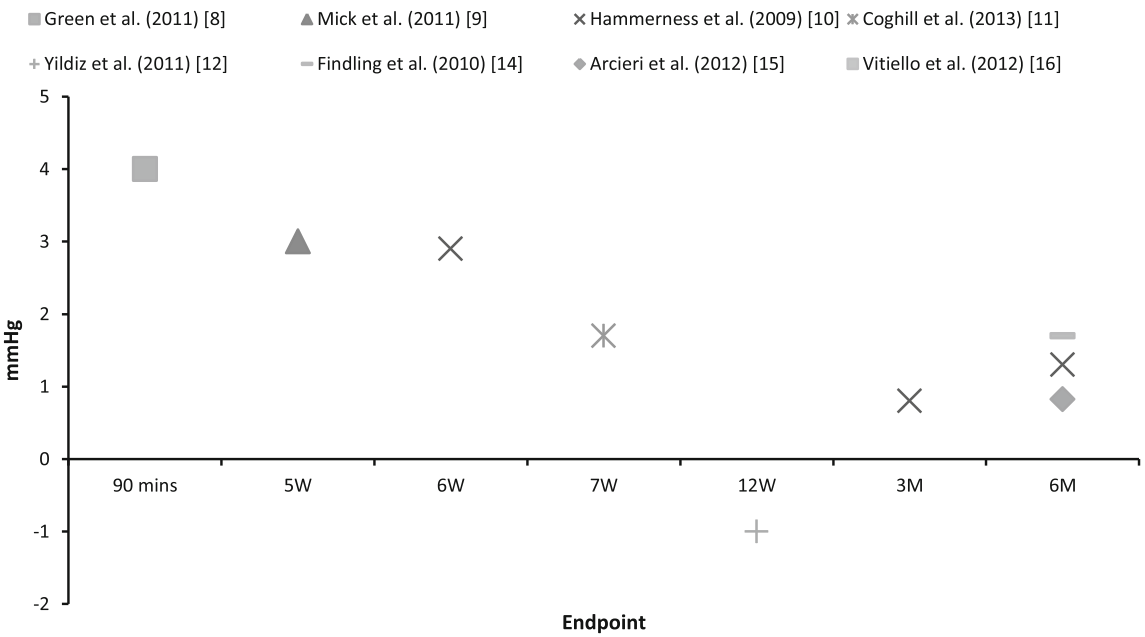

Fig. 3 Changes in diastolic blood pressure with methylphenidate administration across the studies in Table 1 indicate clinically insignificant results

Coghill et al. [11], Yildiz et al. [12] and Findling et al. [14], in 7-week, 12-week and 6-month studies, respectively, and Vitiello et al. [16], in a study with various long-term endpoints, found no statistically significant changes in BP (see Table 1).

Figures 2 and 3 show the changes in SBP and DBP, respectively, up to 6-month endpoints across the papers highlighted in Table 1. For both SBP and DBP, the changes are relatively small and not clinically significant.

Methylphenidate HR and BP: Discussion

The reported changes in BP across all these studies ranged from +21.2 to −4.3 mmHg for mean SBP, and +4.0 to −4.7 mmHg for mean DBP; the reported changes in HR ranged from +5.9 to −12.9 bpm (Table 1). It appears that, in the short term (≤6 months), methylphenidate is associated with small increases in BP that are not statistically

significant and small increases in HR that are statistically significant. The data show a more mixed picture when the endpoint is 6 months or longer, with some decreases in SBP and DBP and several decreases in HR reported. However, it should be noted that these longer-term results have not been corrected for age. The results need to be adjusted for the increase in BP and decrease in HR that occurs naturally with age.

No other data examining the immediate effects of methylphenidate were found. This implies that there are insufficient additional data to confirm the conclusion in the previous review [6] that relatively small but statistically significant increases in HR and BP are associated with short-term administration of methylphenidate.

There are still very few published studies that have examined the cardiovascular effects of methylphenidate over several years. In a long-term study, Vitiello et al. [16] measured BP and HR over 10 years in children with ADHD treated with stimulant medication. After a 14-month initial controlled trial ($n = 506$), all patients were assessed 2 ($n = 505$), 3 ($n = 455$), 6 ($n = 419$), 8 ($n = 376$) and 10 years ($n = 346$) later. During the first 14 months, most (85 %) of the children were treated with immediate-release methylphenidate but patients who did not respond were given dexamfetamine in the first instance and then treated with other agents. The authors stated that they found "no association between current or previous stimulant use or cumulative methylphenidate equivalent dose and risk for BP levels in the prehypertensive or hypertensive range." After 10 years, they also found no statistically significant difference in the BP between subjects with the highest cumulative exposure and those with lower or no exposure. Statistically significant effects of stimulant exposure on HR were found at year 3 ($p = 0.019$) and year 8 ($p < 0.001$) but not at year 10. The authors concluded that, despite extensive sensitivity analysis, there was no evidence that sustained use of stimulant medication increased BP. However, stimulant treatment was found to increase HR at several time points. They commented that stimulant administration continues to have a detectable adrenergic effect even after years of treatment, adding that this effect may have clinical implications, especially for individual patients with underlying heart abnormalities.

It appears that methylphenidate treatment results in some increases in BP and HR, at least in the short term. However, when the endpoints are 3 years or more after the commencement of treatment, the increases have not been judged to be clinically or statistically significant. The recent long-term studies, over years rather than months, notably those by Vitiello et al. [16] and Arcieri et al. [15], reported no statistically significant changes in SBP or DBP; Vitiello et al. [16] did report a minor statistically significant increase in HR after 14 months and statistically significant decreases after 3 and 8 years (uncorrected for age—see earlier comment).

The results discussed above appear to support the conclusion drawn in our previous paper that, in the short-term, methylphenidate does not appear to have a clinically significant effect on BP and HR.

4 Atomoxetine HR and BP: Clinical Data

We could find no study that examined the immediate cardiovascular effects of atomoxetine in children within hours of administration. A few studies examined the effect of atomoxetine on cardiovascular measures in children with ADHD over several weeks up to 24 months (Table 2).

Sert et al. [17] recorded mean SBP, DBP, HR, QTc interval, QT dispersion, and ventricular systolic functions at baseline and after 5 weeks of treatment with atomoxetine in 40 children and adolescents with ADHD. Patients who had seizures, bipolar disorder, psychotic illness, mental retardation, or pervasive developmental disorder and those who were taking psychotropic medications were excluded. The study was also confined to children who had no history of structural cardiac disease. None of the patients was taking drugs known to affect heart rhythm. The study found that SBP, DBP and HR were lower after 5 weeks of treatment compared with the baseline values. However, these lower values were not statistically significant. The study cites Donnelly et al. [20] who pointed out that a decrease in HR may be consistent with decreases in healthy individuals, i.e. HR in children decreases with age. The study concluded that short-term atomoxetine treatment did not cause statistically significant changes in SBP, DBP or HR in children with ADHD.

Kratochvil et al. [18] evaluated atomoxetine for the treatment of ADHD in children aged 5–6 years in a double-blind, placebo-controlled study. At the 8-week endpoint, the authors found no clinically or statistically significant change in mean SBP, DBP or HR compared with placebo.

Dittmann et al. [19] reported the change in SBP, DBP and HR (pulse rate) as part of a study comparing the effects of lisdexamfetamine dimesylate (LDX) and atomoxetine in children and adolescents (aged 6–17 years) with ADHD and a prior inadequate response to methylphenidate. The study required that patients discontinued any psychoactive medications for a 7-day washout period before their baseline assessment. The authors found that, from baseline to 9 weeks, atomoxetine was associated with mean increases in SBP and DBP ($+0.6 \pm 7.96$ and $+1.3 \pm 8.24$, respectively) as well as pulse rate ($+3.7 \pm 10.75$). The authors did not state whether these results were statistically or clinically significant; it should be noted that changes in

Table 2 Summary of publications of effects of atomoxetine on systolic blood pressure, diastolic blood pressure and heart rate in children and adolescents with attention-deficit hyperactivity disorder; data listed in order of endpoint

Endpoint	Change in mean from baseline to endpoint			ATX dose	Age range and no. of subjects	Design	References
	SBP (mmHg)	DBP (mmHg)	HR (bpm)				
5 w	−1.3	−0.5	−2.9	0.8–1.2 mg/kg/day	8–14; 40	ol, single centre	[17]
8 w	+3.9 ± 0.8 vs. PL	No clinically or statistically significant changes	No clinically or statistically significant changes	Max. dose 1.8 mg/kg	5–6 (at time of consent); 44	Multisite (3), db, pc, random, pro	[18]
9 w	+0.6 ± 7.96	+1.3 ± 8.24	+6.4 ± 10.08[a]	<70 kg body weight: 0.5–1.2 mg/kg ≥70 kg body weight: 40, 80, 100 mg	6–17; 134	rand, db, wo	[19]
12 w	+3.5	**+4.6**	+1.9[b]	18–60 mg/day	8–14; 14	ol, ran, pro	[12]
6 mo	+0.01 ± 12.68	**+1.61 ± 11.25**	**+2.94 ± 13.11**[b]	0.5–1.2 mg/day	6–18; 316	ol, pro, multimodal, Italian, multisite (87)	[15]
12 mo	+0.36 ± 13.52	+0.13 ± 10.83	**+3.26 ± 14.32**	0.5–1.2 mg/day	6–18; 166	ol, pro, multimodal, Italian, multisite (87)	[15]
24 mo	+2.13 ± 9.51	+1.11 ± 10.76	+0.21 ± 13.33	0.5–1.2 mg/day	6–18; 38	ol, pro, multimodal, Italian, multisite (87)	[15]

Bold indicates a statistically significant result

ATX atomoxetine, *db* double blind, *DPB* diastolic blood pressure, *dose op* dose optimised, *HR* heart rate, *h2h* head to head, *mo* month, *ol* open label, *pc* placebo controlled, *PL* placebo, *pro* prospective study, *ran* randomised, *SBP* systolic blood pressure, *w* week, *wo* washout period

[a] Visit 4; week 4

[b] Pulse rate

Table 3 Summary of publications of effects of lisdexamfetamine dimesylate on systolic blood pressure, diastolic blood pressure and heart rate in children and adolescents with attention-deficit hyperactivity disorder; data ranked chronologically by endpoint

Endpoint	SBP (mmHg)	DBP (mmHg)	HR (bpm)	LDX dose	Age range and no. of subjects	Design	References
4 w	−0.8 ± 1.22	−0.5 ± 1.05	+5 ± 1.18[a]	30 mg	13–17; 78	ran, db, multisite (45), pc	[23]
4 w	+0.3 ± 1.01	+0.4 ± 0.84	+3.8 ± 1.37[a]	50 mg	13–17; 77	ran, db, multisite (45), pc	[23]
4 w	+1.7 ± 1.21	+3.4 ± 0.80	+5.4 ± 1.27[a]	70 mg	13–17; 78	ran, db, multisite (45), pc	[23]
4–5 w	+5.38	+1.00	+1.62	12 of 13 on 30 mg; 1 of 13 on 50 mg	6–12; 13	sb, ol, wo	[24]
7 w	+1.0 ± 9.8	+0.2 ± 9.6	+5.7 ± 15.3	30, 50, 70 mg	6–17; 111	wo, ran, pc, db	[11]
9 w	+0.7 ± 9.08	+0.1 ± 8.33	+3.5 ± 12.73	30, 50, 70 mg	6–17; 128	ran, db, wo	[19]

db double blind, *DBP* diastolic blood pressure, *dose op* dose optimised, *HR* heart rate, *h2h* head to head, *LDX* lisdexamfetamine dimesylate, *ol* open label, *pc* placebo controlled, *pro* prospective study, *ran* randomised, *sb* single blind, *SBP* systolic blood pressure, *w* week, *wo* washout period

[a] Pulse rate

cardiovascular function were not the primary outcome of the study. However, they referred to the increases as 'modest' and stated that no patients withdrew from the study as a result of a clinically significant change in BP or pulse.

Yildiz at al. [12] studied the effects of methylphenidate and atomoxetine on executive functions in children with ADHD from baseline to 12 weeks. BP and HR were reported as part of this study but were not primary outcomes. A statistically significant increase in DBP of +4.6 mmHg ($p = 0.039$) was recorded in the group treated with atomoxetine.

Arcieri et al. [15] studied the cardiovascular effects of atomoxetine in children and adolescents with ADHD. At 6 months they reported a small increase in SBP (+0.01 ± 12.68), which was not statistically significant, and small, statistically significant increases in DBP (+1.61 ± 11.25; $p = 0.01$) and pulse rate (+2.94 ± 13.11; $p = 0.001$). At 12 months, small increases in SBP (+0.36 ± 13.52) and DBP (+0.13 ± 10.83) were confirmed, although these were not statistically significant. A statistically significant increase of HR (+3.26 ± 14.32; $p = 0.004$) was also recorded after 12 months. At 24 months, increases were found in SBP (+2.13 ± 9.51), DBP (+1.11 ± 10.76) and HR (+0.21 ± 13.33), which were not statistically significant.

Atomoxetine HR and BP: Discussion

The interpretation of the Yildiz et al. [12] results was limited by a number of factors: only 14 patients were included in the group treated with atomoxetine, there was no placebo group and there was no discussion of the techniques for measuring the BP and HR data. With such a small number of subjects, any variability in measuring techniques could be a confounding factor that could have affected HR and BP at baseline or at 12 weeks.

The small increases in BP and HR reported by Arcieri et al. [15] are consistent with those found by Wilens et al. [21] and Donnelly et al. [20], which were reported in our previous review. As already stated, BP and HR need to be adjusted for the natural changes that occur in children with age. No adjustment was made in this study. The authors stated that no serious clinical implications related to BP and HR were observed. However, they do recommend an evaluation of individual cardiovascular risk prior to treatment in each patient. It should also be noted that large differences in serum atomoxetine levels would be expected between extensive metabolisers and poor metabolisers of this drug [22]. No studies on BP or HR appear to have investigated any effect of serum atomoxetine level.

From the studies reviewed, it would appear that atomoxetine is associated with small clinically insignificant changes in BP (<5 mmHg) and HR (<6 bpm) over the short term, up to 6 months.

5 Amphetamines HR and BP: Clinical Data

A small number of studies were found on the effects of LDX on HR and BP. They are summarized in Table 3. All were short term.

In a 4-week study across 45 US sites, Findling et al. [23] studied the effect of LDX on adolescents aged 13–17 years with ADHD. They found that LDX was associated with small increases in mean HR, SBP and DBP. They also looked at outliers in the SBP and DBP results. They defined outliers for SBP in terms of a hierarchy: first, those participants having any SBP value ≥120 mmHg at any post-baseline week; then adding to that having two consecutive readings of ≥130 mmHg; and then adding to those two criteria a reading ≥10 mmHg from baseline to endpoint. For DBP, they defined outliers as participants having a

DBP value ≥80 mmHg; then added the criteria of those having DBP values ≥90 mmHg over two consecutive weeks; and finally added the criteria of those participants with a change in DBP ≥10 mmHg. They found few participants met the SBP and DBP outlier criteria. Of the participants on 30 mg/day of LDX, only two were found to have had two consecutive weeks with SBP ≥130 mmHg, compared with two on placebo. When the criteria of an SBP post-baseline reading ≥10 mmHg from baseline was added, the number in the placebo group fell to zero, while those taking 30 mg/day of LDX remained at two. The figures were similar for those participants taking 50 and 70 mg/day. The number of DBP readings ≥80 mmHg and increases ≥10 mmHg from baseline to endpoint for participants taking 30, 50, 70 mg/day and placebo were 0, 3, 4 and 2, respectively. The authors stated that "Comparisons between dose groups … were not part of the a priori analyses and were not conducted." However, the authors concluded that LDX demonstrated a safety profile consistent with previous studies in children.

Wigal et al. [24] examined the effect of LDX on 28 children aged 6–12 years with ADHD over 4–5 weeks. They concluded that changes in cardiovascular parameters during the study were "of minimal clinical concern" in children pre-screened as being healthy, with no pre-existing cardiac history. However, they did note two cases of cardiac abnormality: one of tachycardia and one of BP ≥95th percentile. They commented that these were isolated incidents with single-visit readings and, although the BP reading was ≥95th percentile, it was not at a "dangerous level." They commented that this stimulant-naïve child had a positive family history of hypertension and early myocardial infarction, which may have indicated an increased risk of developing hypertension.

In a study examining the effects of LDX on 336 European children and adolescents with ADHD across 48 treatment centres in ten European countries over 7 weeks, Coghill et al. [11] found that this drug was associated with a 'modest' increase in HR, SBP and DBP. The study did not state whether the results were statistically or clinically significant. Cardiovascular parameters were not the primary outcome of the research.

Dittman et al. [19] studied the effect of LDX in children and adolescents aged 6–17 years with ADHD over 9 weeks. They found that LDX was associated with mean (standard deviation) increases in SBP of +0.7 mmHg (9.08), DBP of +0.1 mmHg (8.33) and pulse rate of +3.6 bpm (10.49). They described the increases in SBP, DBP and pulse rate as "modest" and concluded that LDX displayed a safety profile consistent with findings from previous clinical trials. Dittman et al. [19] also looked at outliers. Of the patients receiving LDX, they found 4/127 (3.1 %) were classified as having a low pulse rate (defined as ≤50 bpm) whereas 19/127 (15 %) met the outlier criteria for high pulse rate (defined as ≥100 bpm). They also reported that 12/94 (12.8 %) children aged 6–12 years had high SBP (defined as >120 mmHg) and 11/94 (11.7 %) had high DBP (defined as >80 mmHg). No adolescents (aged 13–17 years) met the outlier criteria for high SBP (>140 mmHg) or high DBP (>90 mmHg), but 2/33 (6.1 %) had an SBP >130 mmHg at some point during the study and 7/33 (21.2 %) had a DBP >80 mmHg at some point during the study. The authors stated that no patients withdrew from the study as a result of a clinically significant increase in BP or HR reading, but they recognised that some patients receiving ADHD medications may have BP and HR values above the 95th percentile.

Amphetamines HR and BP: Discussion

It is difficult to draw specific conclusions about the effects of amphetamines on BP and HR from the small number of studies found since February 2009. None of the studies examined BP and/or HR as primary outcomes. There is still no convincing evidence of a short-term effect on BP, and the effect on HR appears to be inconclusive, although a small (<6 bpm) increase has been reported in all the studies found. No dose-dependent relationship has been reported in any of the studies. Although all four studies used three different doses of LDX, none was designed to evaluate a dose-dependent relationship.

Dittman et al. [19] highlighted the point that clinical guidelines recommend an assessment for heart disease or signs of significant cardiovascular disease prior to commencing treatment and recommended that once treatment has begun BP and HR be monitored at least every 6 months. If either BP or HR is above the 95th percentile, the authors recommended a dose reduction, a drug holiday or referral to a cardiologist. However, with the very limited information available, although the first two of these recommendations might be considered as being wise clinical management, they cannot be viewed as being evidence based.

Children often take amphetamines for long periods; the four studies in Table 3 are all short term, allowing no conclusions to be drawn about long-term effects. Further studies are required to assess any long-term consequences of the small increases in HR and BP found in the shorter-duration studies.

None of the studies that provided data for this review evaluated BP or HR as a primary outcome. Authors did not discuss whether any of the changes were of clinical or statistical significance.

6 Electrocardiogram (ECG) Changes with Attention-Deficit Hyperactivity Disorder (ADHD) Medication

Because, as already stated, methylphenidate, dexamfetamine and atomoxetine are all sympathomimetic, there has been concern that these drugs might result in ECG changes or arrhythmias, particularly in subjects who have pre-existing ECG or structural cardiac abnormalities. Evaluation of ECGs may provide some indication of the risk of adverse cardiac events. Prolongation of the QTc interval is used as a surrogate marker for the risk of adverse cardiac events, particularly sudden death. The QTc data are summarised in Tables 4, 5 and 6.

Green et al. [8] examined the effect of a single dose of methylphenidate on 34 children and adolescents with ADHD and VCFS. All the subjects were examined by a paediatric cardiologist; ECGs were conducted just before prescribing methylphenidate and 90 min after taking methylphenidate. The authors reported no changes in mean QTc from baseline to 90 min after methylphenidate administration (0.40 ± 0.015 vs. 0.40 ± 0.019, respectively) or pulse rate interval (0.13 ± 0.017 vs. 0.13 ± 0.017, respectively).

Hammerness et al. [10] monitored ECG indices (mean pulse rate, QRS, QT and QTc) in a study examining the longer-term cardiovascular effects of high-dose OROS methylphenidate in 114 adolescents aged 12–18 years. Subjects were treated with OROS methylphenidate in daily doses of up to 1.5 mg/kg. They found no statistically significant or clinically significant changes in mean pulse rate, QRS or QTc interval at the study endpoint of 6 months. The QTc interval did not exceed 460 ms in any subject. Four subjects reported subjective cardiovascular complaints at more than one visit but they all had a lifetime history of comorbid anxiety disorder(s). One of the four subjects discontinued treatment because of recurrent palpitations. The authors noted that this subject had heightened anxiety, a lifetime history of comorbid generalised anxiety disorder, and an 8 pound weight loss, concurrent with palpitations, during dose titration. They also noted that the complaints of all four subjects were "mild, brief" events not associated with significant ECG abnormalities.

Findling et al. [14] reported abnormal ECG parameters and commented on whether they were "potentially clinically important" in their 6-month, open-label extension study of the tolerability and effectiveness of a

Table 4 Summary of publications of effects of methylphenidate on corrected QT interval in children and adolescents with attention-deficit hyperactivity disorder; data ranked chronologically by endpoint

Endpoint	Change in QTc interval (ms)	Medication	Age range and no. of subjects	Design	References
90 min	0.0	Single MPH dose; $+15.7 \pm 5.6$ mg	5–20; 22[a]	ran, pc	[8]
6 w	+1.6	OROS MPH; clinically adjusted; 63.1 ± 25.0 (mean dose at 6 w)	12–18; 114	ol, pro	[10]
7 w	$+0.2 \pm 15.9$	OROS MPH; 18, 36, 54 mg	6–17; 111	wo, ran, pc, db	[11]
3 mo	+3.3	OROS MPH; clinically adjusted; 67.2 ± 24.3 (mean dose at 6 mo)	12–18; 75	ol, pro	[10]
6 mo	+2.8	OROS MPH; clinically adjusted; 67.2 ± 24.3 (mean dose at 6 mo)	12–18; 57	ol, pro	[10]
6 mo	$+2.0 \pm 16.59$	MPH transdermal system; 10–30 mg/9 h patches	13–17; 63	Multisite (30), ol	[14]

ADHD attention-deficit hyperactivity disorder, *db* double-blind, *dose op* dose optimised, *h2h* head to head, *MPH* methylphenidate, *ol* open label, *OROS* osmotic release oral system, *pc* placebo controlled, *pro* prospective study, *QTc* corrected QT interval, *ran* randomised, *sb* single blind, *VCFS* velocardiofacial syndrome, *w* week, *wo* washout period

[a] Children with VCFS; ADHD defined by ADHD module of the K-SADS-Present (Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present; a subset of the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision*)

Table 5 Summary of publications of effects of atomoxetine on corrected QT interval in children and adolescents with attention-deficit hyperactivity disorder; data ranked chronologically by endpoint

Endpoint	Change in QTc interval (ms)	Atomoxetine dose	Age range and no. of subjects	Design	References
4 w	$+1.9 \pm 13.41$	<70 kg: 0.5–1.2 mg/kg ≥70 kg: 40, 80, 100 mg	6–17; 134	ran, db, wo	[19]
5 w	+5.0	0.8–1.2 mg/kg/day	8–14; 40	ol, single centre	[17]

db double-blind, *ol* open label, *QTc* corrected QT interval, *ran* randomised, *w* weeks, *wo* washout period

Table 6 Summary of publications of effects of lisdexamfetamine dimesylate on corrected QT interval in children and adolescents with attention-deficit hyperactivity disorder; data ranked chronologically by endpoint

Endpoint	Change in QTc interval (ms)	LDX dose	Age range and no. of subjects	Design	References
4 w	−0.3 ± 14.74	30, 50, 70 mg	6–17; 76	ran, db, wo	[19]
4–5 w	+5.15	12 of 13 on 30 mg; 1 of 13 on 50 mg	6–12; 13	sb, ol, wo	[24]
7 w	+0.3 ± 15.6	30, 50, 70 mg	6–17; 111	wo, ran, pc, db	[11]

db double blind, *LDX* lisdexamfetamine dimesylate, *ol* open label, *pc* placebo controlled, *QTc* corrected QT interval, *ran* randomised, *sb* single blind, *w* weeks, *wo* washout period

methylphenidate transdermal system in subjects aged 13–17 years with ADHD. They found that 30 of 162 subjects (18.5 %) had "potentially clinically important abnormal ECG parameters", but none of these was considered clinically significant by investigators. No subjects had changes in QT interval that were considered to be clinically important. At endpoint, the mean (standard deviation) increase in QTcF (QT interval corrected using Fridericia's formula) from baseline was 2.0 (16.59) ms with a final value of 394.7 (19.78; range 342–455) ms. Two subjects had QTcF intervals ≥450 ms, which were considered to be potentially clinically significant, but neither subject had to discontinue treatment as a result.

In a 5-week study into the effects of atomoxetine on mean SBP, DBP, QTc interval and QT dispersion, Sert et al. [17] reported that atomoxetine did not cause clinically significant changes in QT dispersion, QTc interval or left ventricular systolic functions during short-term treatment. However, they did find a statistically significant increase in maximum QT interval of 7 ms ($p = 0.046$) after 5 weeks compared with baseline. Minimum QT interval, QTc and QT dispersion also increased compared with baseline but the changes were not statistically significant ($p = 0.227$, 0.245 and 0.432, respectively).

Dittman et al. [19] recorded HR, PR interval and QT interval corrected using the Fridericia formula (QTcF) in 267 children and adolescents aged 6–17 years treated for ADHD with LDX and atomoxetine in a 9-week clinical trial. Two of 83 subjects (2.4 %) treated with LDX and one of 90 subjects (1.1 %) treated with atomoxetine had an increase in QTcF of ≥30 ms. However, no patients had a QTcF reading of ≥450 ms and there were no withdrawals from the study as a result of a potentially clinically significant ECG change.

Wigal et al. [24] investigated whether prior exposure to stimulants impacts BP, pulse and ECG measures in children with ADHD treated with LDX. In this small study of 28 subjects with an endpoint of 4–5 weeks, one stimulant-naïve subject had a prolonged QTc in response to LDX (461 ms). It was a single-visit reading; on further review, this 8-year-old child was found to have a positive family history of hypertension and early myocardial infarction, both in a paternal grandparent. The LDX was discontinued briefly and he was evaluated by a paediatric cardiologist. The QTc returned to normal and remained normal after LDX treatment was resumed. The authors concluded that no clinically meaningful trends were observed in ECG parameters.

The studies that follow provided commentary on the ECG results but not the numbers. They are not included in Tables 4, 5 and 6.

Yildiz et al. [12], in a 12-week study of 30 Turkish children treated with atomoxetine ($n = 14$) and OROS methylphenidate ($n = 11$), found no statistically or clinically significant changes in QTc intervals with either drug.

Cho et al. [13] investigated the possible association between norepinephrine genes and cardiovascular side effects in 101 Korean children diagnosed with ADHD treated with OROS methylphenidate over 12 weeks. ECG monitoring revealed no changes in QT or QRS interval after 12 weeks of treatment compared with baseline.

Stein et al. [25] compared the dose effects and comparative effectiveness of extended-release dexmethylphenidate and mixed amphetamine salts. Of the 56 patients who passed the screening process, six did not complete the study due to an adverse event. There was one serious adverse event; a child receiving 20 mg of extended-release dexmethylphenidate was hospitalised for observation after an abnormal ECG following a possible seizure. The ECG normalised and the child continued stimulant medication outside the study. Otherwise, the authors reported no clinically significant changes in ECG from baseline to the 8-week endpoint.

Kratochvil et al. [18] reported no clinically significant changes in laboratory tests or ECGs over an 8-week, double-blind, placebo-controlled randomised clinical trial of 101 children aged 5–6 years, although the ECG results were not the primary outcome of the study.

ECG Changes in ADHD Medication: Discussion

The available data do not appear to indicate any concerns arising from possible ECG changes and methylphenidate,

amphetamines or atomoxetine. However, as has been stated for other parameters, evaluation of the ECG has not been the primary outcome of those studies and the numbers have generally been small.

7 Sudden Death and ADHD Medication

Since our last commentary in 2009, the debate regarding the association between children and adolescents receiving ADHD stimulant treatment and sudden death has continued. In 2009, the study funded by the US FDA and National Institute of Mental Health (NIMH) was published in the *American Journal of Psychiatry*; it concluded there may be an association between the use of stimulant medications for ADHD and sudden death in otherwise healthy children [26]. Taking into account limitations of the study, the FDA concluded that these data could not be taken as evidence affecting judgements regarding the overall risk and benefit profile of ADHD medication and advised parents not to use it as a basis to discontinue stimulant medication. In November 2011, in a further safety announcement, the FDA updated their information and reported that a large study by Cooper et al. [27] in children and young adults treated with medication for ADHD had not shown an association between certain ADHD medications, namely amphetamines, methylphenidate, atomoxetine and pemoline (which is no longer marketed) and adverse cardiac events, including sudden death. The rate of sudden death in current users of ADHD medication was not statistically significantly different from that of non-users (hazard ratio 0.88; 95 % confidence interval [CI] 0.23–3.35). This cohort study examined 1,200,438 children and young adults between 2 and 24 years of age; there were 2,579,104 person-years of follow-up, including 373,667 person-years relating to those who were currently taking ADHD medication. Only seven serious cardiovascular events (three of sudden death) were found in those who were current users. The study reported no evidence of increased risk of serious cardiovascular effects among the cohort taking ADHD medication, although a 'small to modest' increase in risk could not be ruled out because a small number of serious cardiovascular events did occur. The magnitude of any potential increase in risk would be very small in absolute terms, as the rate of overall serious cardiovascular events in the cohort was low (3.1 events per 100,000 patient-years). However, it should be noted that subjects with serious illnesses, including severe underlying cardiac disease, were excluded from the cohort. It is possible that these individuals are the ones who are most at risk of sudden death from stimulant medication. The implications are that the results might accurately describe the risk of sudden death in healthy children but might underestimate the risk in the total population of children with ADHD treated with stimulant medication. The FDA continues to advise patients and caregivers to see a healthcare professional if the patient develops chest pain, shortness of breath or fainting while taking ADHD medication.

Schelleman et al. [28] compared the rate of severe cardiovascular events and death in 241,417 children (aged 3–17 years) treated with ADHD medications with that of children who were not taking such medication. The study found no statistically significant difference in the incidence of validated sudden death or ventricular arrhythmia between users of ADHD medications and non-users (hazard ratio 1.60; 95 % CI 0.19–13.60). This large cohort study found a very low incidence of validated sudden death or ventricular arrhythmia but the power of the results was affected by a low retrieval rate of medical records. In addition, the records might not have included all the possible confounding factors that the authors would have preferred to have evaluated. Furthermore, because of the small number of serious cardiovascular events, the authors were unable to adjust simultaneously for multiple potentially confounding factors.

Olfson et al. [29] used insurance claims data to study the association between stimulant use and the risk of cardiovascular events in young people (aged 6–21 years) with ADHD. They observed only one severe cardiovascular event, corresponding to an incidence of approximately 0.3 per 100,000 years of follow-up. No significant associations were found between stimulant use and severe cardiovascular events, although the authors argue that stimulants may contribute in a small way to the risk of palpitations or other minor symptoms.

Winterstein [30] reviewed five controlled population-based studies that all utilised administrative claims insurance data to compare the risk of stimulant use. Stimulants showed an association with some of the milder cardiac events such as tachycardia but no association with the more serious events such as sudden death, stroke or myocardial infarction. Sudden death, stroke and myocardial infarction are extremely rare in healthy children treated with ADHD stimulant medication over the short term, with a reported incidence rate of approximately three per 100,000 patient-years of stimulant use. However, none of the studies reviewed utilized sufficiently long follow-up or sufficient sample size to examine the effects in long-term users of stimulant medication; consequently, the results cannot be generalised to children treated with stimulants over the long term, i.e. >2 years.

Winterstein et al. [4] found no support for concerns that amphetamines may have a larger propensity to cause serious cardiac events than methylphenidate. They found a slightly increased risk when both drugs are used concurrently and also cautioned that the use of claims data, being prone to misclassification, may underestimate the rate of adverse effects.

In a retrospective, population-based cohort study using healthcare records from four US healthcare providers, Habel et al. [31] examined whether current use of ADHD medication was associated with an increased risk of sudden death, stoke or myocardial infarction in young adults (aged 24–44 years) and middle-aged adults (aged 45–64 years). They found no evidence of an increased risk of serious cardiac events associated with current use compared with non-use or prior use of ADHD medication, although the authors could not rule out a slightly elevated risk given the limited power of the study and a lack of data on some important risk factors. The results were similar across age groups and did not appear to be influenced by prior cardiovascular disease.

As reported in the previous commentary, McCarthy et al. [32] found a higher incidence of suicide among patients treated with ADHD medication. This was a secondary outcome of their study into the association between sudden death and stimulants or atomoxetine. For children with ADHD ≤14 years, the authors found a 162-fold higher rate of suicide than for the general population at the 1 % two-sided significance level. In a prospective outcome study, Barbaresi et al. [33] studied the long-term outcomes of 5,718 adults with childhood ADHD and non-ADHD controls from the same birth cohort. They found that the cause-specific mortality for suicide only was statistically significantly higher among patients with childhood ADHD versus controls (standardized mortality rate 4.83; 95 % CI 1.14–20.46; $p = 0.032$).

Discussion of Sudden Death

The studies by McCarthy et al. [32] and Barbaresi et al. [33] indicated there is an increase in suicide risk in children with ADHD who were treated with medication but this does not necessarily imply that the medication was the cause of the increase in suicide. ADHD itself may be a predisposing factor, especially since one of the core features of ADHD is impulsivity. Other features of ADHD could also be associated with low mood and increased risk of suicide. For example, poor concentration resulting in academic underperformance could result in low mood. Further evaluation of the finding of increased suicide risk is required to determine whether it is the ADHD itself, treatment of the ADHD or some other factors such as comorbidity that is the cause of this association.

With regard to sudden cardiac death, this is a very rare phenomenon in childhood. Several reviews and studies, including those that have covered large populations, have concluded that there is no association with ADHD treatment in the short term [4, 7, 34]. Many children are prescribed ADHD medication into their adulthood. More research is required to assess the long-term impact of stimulant and atomoxetine use.

8 Analysis of Research Design

Of nine studies containing data on the effect of treatment with methylphenidate on children and adolescents with ADHD, three focused on cardiac effects. Even in these three studies, the method for obtaining the measurements was not optimal or standardised. Hammerness et al. [10] collected BP and HR data as a single, first reading, "typically 7–10 h after morning administration." BP and HR were measured in the sitting position, but there is no mention of a rest period before measurement as stated in the recommendations discussed later. Vitiello et al. [16] recommended a 5-min rest period before taking the measurements but drew attention to the fact that there was variability in the BP and HR examination procedures across the eight sites used in their study. This variation included the equipment that was used across the sites as well as the time of day the measurements were taken. Arcieri et al. [15] did not discuss in detail how the BP and HR measurements were performed. The implication here is that the results of these papers must be interpreted with caution.

Several national and international bodies, such as the US Department of Health and Human Services, the American Heart Association, European Society of Hypertension, the UK National Institute for Health and Care Excellence (NICE) and the Canadian Cardiovascular Society, have made recommendations with regard to best practice for measuring BP. Most of the studies have not followed standard recommendations for BP measurement in children, such as taking three measurements with a 5-min rest period before the first measurement, which should be discarded, after which the mean of the second and third measurements should be used. A rest period before the measurements are made is recommended by NICE [35], the European Society of Hypertension [36], Hypertension Canada [37], the US Department of Health and Human Services [38] and the American Heart Association [39]. The NICE Hypertension Quick Reference Guide [35] suggests measuring BP at home or in clinic where a standardised environment should be created, providing a relaxed setting, with the person either supine or seated and at rest for at least 1 min. The BP monitoring device should be regularly calibrated and maintained; an appropriate cuff size should be used. The US Department of Health and Human Services recommends a rest period of at least 5 min and does not recommend a supine position for the patient. Frese et al. [40] list many factors that can lead to error in BP

measuring technique: cuff size, inflation/deflation method, arm position, rest period, concentration of the measurer, lack of repeated measures, time between repeated measures, lack of calibration/maintenance of measurement devices, body position, muscle tension, and the level of training of the measurer. Furthermore, medications, anxiety (e.g. 'white coat hypertension'), time of day, background noise, food, exercise, posture (e.g. not having crossed legs), talking and doing mental tasks can all affect BP readings.

Equipment and technique are important if accurate and reliable results are to be obtained. For example, Kay [41] spent 9 days rechecking as many of the staff BP readings as possible using an experienced and recently retrained nurse in three family practice centres. The average absolute differences between control and study nurse SBP and DBP readings were 6.2 and 4.7 mmHg, respectively.

Some of the studies reviewed here failed to make use of a washout period, or to control for other stimulants consumed by children, such as caffeinated soft drinks.

A further issue that is of major clinical importance, as discussed in our previous review, is the limitation that group mean data can mask clinically significant changes in individual patients. Some authors appropriately draw attention to 'outliers' in the dataset.

Of the longer-term studies reviewed, the methodology often did not appear to control for factors that could affect BP and HR. In particular, as already noted, BP tends to increase and HR tends to decrease with age in childhood.

Very few of the reported studies were double blind and/or placebo controlled. Some of the reports were on quite small numbers [8, 12], implying that there was no justification for concluding that the results could be generalised. In a number of reports, the authors did not state whether the results they obtained were statistically or clinically significant.

In the majority of papers examined, the study of cardiovascular safety was not the primary aim of the paper, and investigators failed to control for factors that could influence BP and HR.

There is still a need for more research focused on the cardiovascular safety of methylphenidate that takes into account the study design factors described above. Future studies could be improved by adhering to the following:

(a) Measure BP and HR at set times after the administration of methylphenidate.
(b) Use standardised best practice in the taking of the measurements.
(c) Adjust the BP and HR measurements for the natural changes with age.
(d) Conduct studies over long time periods.

9 Conclusions

There are generally consistent reports of small increases in mean HR and BP with methylphenidate, amphetamines and atomoxetine for treatment periods of less than 2 years. Although the changes are small and have been described as being clinically insignificant, with increasing numbers of children with ADHD continuing treatment into adulthood, it should be noted that the long-term effects of these small increases remain undetermined. Most of the studies have presented mean data, although some have also examined 'outliers' to allow for the fact that individuals may have larger, clinically significant increases, that are not reflected by the mean values. Because of many confounding factors, reliance should not be placed on individual readings of HR or BP. It is recommended that standard measurement guidelines be followed. It is also recommended that individuals who might be at higher risk because of a personal or family history of relevant cardiovascular conditions be assessed carefully before treatment, with referral to a cardiologist if any safety doubts remain. The benefits of treating ADHD with medication continue to outweigh any potential cardiovascular risks in most cases.

Over the short term, none of the studies on sudden death in children and adolescents has shown a convincing association with ADHD treatment; it should be noted that sudden death in childhood is a very rare event. In contrast to the situation in childhood, sudden cardiac death in the general population of adults is relatively common. It remains to be determined whether ADHD treatment increases the risk of sudden cardiac death in adults. Long-term prospective studies should help to resolve some of the unanswered questions with regard to the cardiac risk of ADHD treatment in adults.

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