REVIEW ARTICLE

Drug Saf 2010; 33 (10): 821-842
0114-5916/10/0010-0821/$49.95/0

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

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Contents

Abstract

Attention-deficit hyperactivity disorder (ADHD) is a very common condition in children and often extends into the adult years. Drugs such as methylphenidate, amphetamines and atomoxetine are frequently prescribed as part of management. The use of these drugs has been increasing and significant clinical benefit is achieved but safety has been questioned. In this review, the cardiovascular safety of these drugs is examined with regard to effects on blood pressure (BP), heart rate (HR), ECG parameters and the risk of sudden death. Methylphenidate appears to cause minor increases in BP and HR. There are no strong data to suggest that methylphenidate increases

the corrected QT interval (QTc). Amphetamines appear to cause minor increases in HR and BP over the long term. There is growing evidence to suggest that amphetamines do not cause statistically or clinically significant increases in QTc. Sudden death remains an extremely rare event and there is no clear evidence to attribute this to methylphenidate. Some data even suggest that the risk of sudden death in treated children may be less common than in the background population. Limited data suggest that atomoxetine may increase BP and HR in the short term; in the long term it appears to increase BP. The effects of atomoxetine on QTc remain uncertain. Use of this drug does not appear to be associated with sudden death. Because the current evidence is based on research that has not been specifically designed to investigate the cardiovascular effects of these drugs it is difficult to draw firm conclusions, and further work is required specifically to address these questions.

Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioural condition in school-aged children. Estimates of prevalence depend on the diagnostic criteria. In the UK, a survey of 10 438 children between the ages of 5 and 15 years reported ADHD (as defined in the *Diagnostic and Statistical Manual of Mental Disorders [4th Edition, Text Revision]*; DSM-IV-TR)[1] as occurring in 3.62% of boys and 0.85% of girls.[2] The more restricted diagnosis of hyperkinetic disorder in the *International Classification of Diseases (10th Edition)*,[3] representing a severe subgroup of DSM-IV-TR combined type ADHD, is estimated as occurring in 1.5% of boys in the primary school years.[4] Very large numbers of children with ADHD around the world are treated with medication, including methylphenidate, amphetamines and atomoxetine. In the US, 2.5 million children take stimulants for ADHD.[5] There is good evidence that these medications, combined with behavioural management, have a beneficial effect.[4] However, in view of the large numbers of people taking them, it is important to identify the prevalence of any serious adverse effects.

There have been several safety assessments of ADHD medications in recent years, some of which have resulted in withdrawals and warnings. In February 2005, Health Canada suspended the sale of Adderall XR® (an extended-release formulation of mixed amphetamine salts), based on reports of sudden deaths in children, but this drug was reinstated in August 2005.[6] The US FDA Drug Safety and Risk Management Advisory Committee recommended a 'black box' warning about possible cardiovascular risks associated with stimulant medication in February 2006.[6] However, the FDA Pediatric Advisory Committee did not support this view. In the end, a 'black box' warning was not implemented. In addition, there have also been differing professional opinions regarding recommendations for cardiovascular investigations prior to the treatment of ADHD. For example, recommendations about stimulants from the American Heart Association (AHA)[7] have differed slightly from those of the American Academy of Pediatrics (AAP).[8]

Issues that need to be examined include whether there are any clinically important effects of ADHD medications on heart rate (HR), blood pressure (BP), ECG parameters, specifically QT interval, and the risk of sudden death. It is also important to determine whether any changes in HR or BP have short- or long-term implications. The aims of this review are to examine the available evidence on the cardiovascular effects of methylphenidate, amphetamines and atomoxetine, to assess the safety implications, particularly with regard to whether current concerns about these drugs are justified, and to indicate where further research is required.

1. Literature Search Methodology

The published evidence on the cardiovascular effects of methylphenidate, amphetamines and atomoxetine was identified using the following

search strategy. MEDLINE (1950–February 2009) and PubMed (1966–February 2009) searches were used. Each of the following drug names: 'methylphenidate', 'Equasym', 'Concerta', 'Ritalin', 'Medikinet', 'atomoxetine', 'Strattera', 'dexamphetamine', 'dexamfetamine', 'Dexedrine', 'mixed amphetamine salts', 'Adderall' and 'lisdexamfetamine' were combined with ['ADHD' or 'attention deficit hyperactivity disorder'] and ['cardiovascular side effects' or 'cardiac side effect' or 'cardiovascular adverse effects'] or ['adverse effects' and 'side effects']. Each of the drugs were then combined with each of the following words: 'heart rate', 'blood pressure', 'electrocardiogram changes', 'ECG changes', 'QT', 'arrhythmias', 'sudden death', 'cardiac death' or 'death'. This resulted in 2243 abstracts being reviewed, although several were replicated. Of these, 106 papers were screened and 48 articles were identified. In addition, relevant articles found in references of those identified by the searches were examined. Individual drug companies were also contacted for further information. The Medicines and Healthcare Products Regulatory Agency (MHRA) was contacted in order to provide further information from Download Drug Analysis Prints (DAPs), which list reports of possible drug adverse reactions from healthcare professionals and patients.

For each of these medications, the published evidence has been summarized in terms of HR and BP, ECG changes, and sudden (cardiac) death. Comment sections that follow these discussions represent the current authors' assessments. To conserve space, many of the details of trials appear only in the tables.

2. Methylphenidate

2.1 Heart Rate and Blood Pressure

Several studies have examined the efficacy, safety and adverse effects of methylphenidate. These studies have often included measures of HR and BP (table I) as secondary outcomes but most have not been specifically designed to examine these parameters.

In 2002, Rapport and Moffitt[25] examined 14 studies that evaluated the effects of methylphenidate on HR and BP. Of these, seven studies showed there was a statistically significant increase in HR in children treated with methylphenidate compared with placebo. The increases were reported as ranging from 3 to 10 beats per minute (bpm). Ten studies examined the effects of methylphenidate on BP in children. Of these, five showed a statistically significant increase in systolic BP (SBP) when methylphenidate was compared with placebo or with baseline measurements, and six studies reported a statistically significant increase in diastolic BP (DBP). The reported increases in the studies ranged from 3.3 to 8 mmHg for SBP and from 1.5 to 14 mmHg for DBP. The authors concluded that in some children methylphenidate treatment increased both HR and BP, but they did not specifically discuss the short- and long-term data.

There are very few studies on the immediate effect of methylphenidate on HR and BP. Kelly et al.[9] specifically examined the effects of methylphenidate in children with attention-deficit disorder/hyperactivity (a diagnosis made according to *DSM [3rd Edition]*[26] criteria). Care was taken to try to avoid other factors that might have influenced HR. The HR was statistically significantly higher for methylphenidate doses of 15 and 20 mg at 120 and 180 minutes after ingestion compared with the placebo group. However, when the predose HR was compared with the postdose HR, there were no statistically significant time effects except in the placebo and 5 mg groups, in which HR was significantly decreased at 180 minutes. The study went on to suggest that, from a clinical perspective, simply measuring the child's HR pre- and postdose might not detect statistically significant increases in HR. This is because with placebo a characteristic drop in HR from baseline to up to 3 hours was apparent, whereas at higher doses of methylphenidate there is not a fall in HR but an increase, which may not appear to be significantly different from baseline. Therefore, the authors stated that caution should be exercised when interpreting the results of other studies, as they do not take into account variables such as a characteristic drop in HR with time, as demonstrated in this study.

Martin et al.[10] assessed the immediate effects of methylphenidate, although measuring

Table I. Summary of publications of effects of methylphenidate (MPH) on heart rate (HR) and blood pressure (BP) in patients with attention-deficit hyperactivity disorder (ADHD)

Study	Design	MPH type and dose	No. and ages of subjects	Results
Immediate (effects of drug within hours of administration)				
Kelly et al.[9]	db, co study to four doses of MPH and PL; HR measured at 0, 120 and 180 min	MPH 0, 5, 10, 15, 20 mg/day	47 children (6–12 y)	MPH 15 and 20 mg/day vs PL showed significantly greater HR at 120 and 180 min ($p < 0.01$)
Martin et al.[10]	r, db; HR and BP measured up to 3 h postdose in laboratory setting	MPH 0 and 0.25 mg/kg/day	24 children (11–15 y)	Statistically significant increases in HR, SBP and DBP ($p < 0.05$)
Silva et al.[11]	5-way, 6 wk, r, sb, pc, co study in laboratory classroom. Measurements including HR and BP performed over 12 h	PL, ER-MPH 20 and 40 mg/day, OROS-MPH 18 and 36 mg/day	53 children (6–12 y)	'Minor rise' in HR, SBP and DBP in all five groups, including PL
Findling et al.[12]	pc study; children given either MPH or Adderall® (mixed amphetamine salts). Each dose given for a week, with HR and BP measured on day 7	PL, MPH 5, 10 and 15 mg/day	137 children (4–17 y); 82 received MPH	Grouped data of MPH and Adderall® showed statistically significant dosage effects on HR and DBP. Judged not clinically significant
Short-term (effects of drug within 12 wk of administration)				
Kratochvil et al.[13]	10 wk, ol trial; children randomly assigned to ATX or MPH	MPH 5 mg (up to tid, maximum total daily dose 60 mg)	228 children (boys 7–15 y, girls 7–9 y); 44 children received MPH	Statistically significant increases in mean HR (5.65 bpm [$p = 0.009$]), SBP (3.35 mmHg [$p = 0.026$]), DBP (2.95 mmHg [$p = 0.04$])
Wilens et al.[14]	Multisite controlled study with up to a 4-wk ol titration phase and then a 2-wk db phase of PL or individualized OROS-MPH dose	OROS-MPH 0, 18, 36, 54 and 72 mg/day	220 adolescents (13–18 y)	'No clinically important effects' on HR or BP
McGough et al.[15]	8 wk, ol extension of the study by Wilens et al.[14]	OROS-MPH 18, 36, 54 and 72 mg/day	171 adolescents (13–18 y)	Mean change from baseline in SBP approached statistical significance ($p = 0.06$). No significant changes in HR or DBP
Greenhill et al.[16]	3 wk, db, pc study of MR-MPH looking at efficacy, safety and tolerability	MR-MPH 20–60 mg/day	321 children and adolescents (6–16 y)	No significant difference in mean SBP, DBP or HR
Wolraich et al.[17]	4 wk, r, db, pc trial to determine safety and efficacy of OROS-MPH. Randomized to PL, IR-MPH and OROS-MPH	OROS-MPH 18, 36 and 54 mg/day; MPH 5, 10 and 15 mg tid	282 children (6–12 y)	'No clinically significant changes' in vital signs (HR and BP) between the three groups
Findling et al.[18]	4 wk, db, pc trial in youths with bipolar disorder and co-morbid ADHD to determine efficacy of MPH; co-design; children received PL and three doses of MPH for a week	MPH 5, 10 and 15 mg bid	20 children and adolescents (5–17 y)	No clinically or statistically significant changes in mean SBP ($p = 0.15$), mean DBP ($p = 0.78$) or mean HR ($p = 0.95$)
Findling et al.[19]	3 wk, r, db, mc, 3-arm, pg study to compare efficacy and safety of MR-MPH and IR-MPH	MR-MPH 20, 40 and 60 mg/day and IR-MPH 10, 20 and 30 mg bid	346 children (6–12 y)	'No clinically important' trends of untoward effects on vital signs
Gau et al.[20]	4 wk, r, ol, active-controlled trial of OROS-MPH and IR-MPH to determine efficacy and safety of OROS-MPH	IR-MPH 10–40 mg/day, OROS-MPH 18 and 36 mg/day	64 children and adolescents (6–15 y)	No statistically significant difference in vital signs on day 28 (SBP, $p = 0.212$; DBP, $p = 0.244$; HR, $p = 0.968$). No significant difference in changes from baseline to day 28 in vital signs

Continued next page

Table I. Contd

Study	Design	MPH type and dose	No. and ages of subjects	Results
Stein et al.[21]	pc, co study with three doses of MPH given for 1 wk each to examine the dosage effects on ADHD and adverse effects	Total daily amount OROS-MPH 18, 36 or 54 mg/day	47 children and adolescents (5–16 y)	No significant changes in HR, SBP or DBP
Long-term (effects of drug after 12 wk of administration)				
Gadow et al.[22]	2 y, prospective, nb, follow-up study of children with ADHD and chronic multiple tic disorder to determine changes in behaviour and tics	MPH 5–90 mg/day	34 children (6–12 y)	Statistically (but not clinically) significant increase in HR (approximately 10 bpm; no p-value). No significant changes in SBP or DBP
Wilens et al.[23]	1 y, open-extension trial to evaluate the effects of OROS-MPH on vital signs	OROS-MPH 18, 36 and 54 mg/day	432 children (6–13 y)	Statistically significant increases in mean SBP and HR at 3, 6, 9 and 12 mo compared with baseline ($p < 0.001$) or in mean DBP at 3, 6 and 12 mo compared with baseline ($p < 0.001$). At 12 mo, mean increases for HR, SBP and DBP were 3.9 bpm, 3.3 mmHg and 1.5 mmHg, respectively
Wilens et al.[24]	ol, multisite study of OROS-MPH to determine effectiveness and tolerability for up to 24 mo	OROS-MPH 18, 36 and 54 mg/day	407 children (6–13 y)	Significant changes in SBP (from 104.7 ± 81 mmHg at baseline to 108.1 ± 8.7 mmHg at study end; $p < 0001$). No significant effects on HR or DBP

ATX = atomoxetine; **bid** = twice daily; **bpm** = beats per minute; **co** = crossover; **db** = double-blind; **DBP** = diastolic blood pressure; **ER** = extended release; **IR** = immediate release; **mc** = multicentre; **MR** = modified release; **nb** = non-blind; **ol** = open-label; **OROS** = osmotic-release oral system; **pc** = placebo-controlled; **pg** = parallel-group; **PL** = placebo; **r** = randomized; **sb** = single-blind; **SBP** = systolic blood pressure; **tid** = three times daily.

cardiovascular parameters was not a primary aim of the study. Statistically significant increases in HR, SBP and DBP were seen with methylphenidate compared with placebo. The mean maximum increase in HR (9 bpm) occurred 2 hours postdose. Another study was performed for 12 consecutive hours each week for 6 weeks in children taking methylphenidate.[11] Data on HR and BP showed there was 'a minor rise' in HR, SBP and DBP in all groups, including placebo. This was illustrated in a table. The tables in the study indicated that there appeared to be differences at some timepoints between placebo and some of the methylphenidate doses but there were no documented statistical analyses.

The immediate cardiovascular effects of methylphenidate and Adderall® (mixed amphetamine salts) were studied.[12] Unfortunately, the statistical analysis was performed on the grouped data of methylphenidate and Adderall®, not on data for the individual drugs. There were statistically significant dosage effects on HR and DBP in children. The authors concluded that both drugs had clinically insignificant effects on BP and HR but it is difficult to assess whether this conclusion was justified because the authors did not present separate data for the two drugs.

It appears from these publications that there is some evidence for relatively small but statistically significant increases in HR and BP with short-term administration of methylphenidate.

Several longer term studies have examined the effects of methylphenidate. Again, there are very few in which the cardiovascular responses to methylphenidate were assessed as a primary outcome; the measurements were part of an overall assessment of the safety of methylphenidate. As a result, the methodology does not appear to eliminate or control for factors that could affect BP and HR.

Kratochvil et al.[13] studied children assigned to either atomoxetine or methylphenidate. There were statistically significant increases in mean HR, SBP and DBP of 5.65 bpm, 3.35 mmHg and 2.95 mmHg, respectively. Wilens et al.[14] performed a study to evaluate osmotic-release oral system (OROS) methylphenidate. A 1-week washout period was followed by a dose titration phase (up to 4 weeks), a 2-week double-blind phase and finally

an 8-week individualized OROS methylphenidate dose phase. In the double-blind phase, there were no clinically important effects on HR and BP in any of the subjects. No other information was offered in the paper. The same group reported on the 8-week part of the trial.[15] There was no statistically significant difference in mean changes in DBP and HR in the adolescents at 4 and 8 weeks compared with baseline. The mean change from baseline in SBP over the same period approached statistical significance. These findings were supported by a study of modified-release (MR) methylphenidate.[16] This trial revealed that there were no significant differences between treatment groups in mean and median SBP, DBP or HR. The authors did not state whether they were referring to statistical or clinical significance. Similarly, children randomized to placebo, immediate-release (IR) methylphenidate or OROS methylphenidate in a 28-day trial showed no clinically significant changes in BP and HR.[17] A placebo-controlled, crossover study also revealed no statistically significant changes in HR, SBP and DBP.[21]

There are further studies in children over 3- to 4-week periods that appear to support the finding that methylphenidate does not have a clinically significant effect on HR and BP.[18,19] Finally, Gau et al.[20] compared the effects of OROS methylphenidate and IR methylphenidate and found no statistically significant difference in baseline HR, SBP or DBP values compared with values at 28 days in either group. However, this study was not specifically designed to detect cardiovascular effects. In addition, the half-lives of the methylphenidate medications differ; consequently, a 'one-off' reading might not be sufficient to identify differences.

So far, data have been reviewed on the short-term effects (up to 12 weeks) of methylphenidate on vital signs. Many children with ADHD require treatment for several years and it is therefore important to know whether methylphenidate has longer lasting effects. Gadow et al.[22] evaluated this but not as a primary aim. After 2 years, these authors noted that there were 'small changes' in BP compared with placebo; however, there was a statistically significant increase in mean HR of approximately 10 bpm. These changes were not considered to be clinically significant. No other specific data were provided.

A further long-term study in children taking OROS methylphenidate was conducted for up to 24 months.[24] Twelve months into this study, Wilens et al.[23] reported on the effects of treatment on BP and HR. Compared with baseline, statistically significant increases in HR, SBP and DBP were associated with methylphenidate treatment at 3, 6, 9 and 12 months. At 12 months these effects (values expressed as mean changes) were +3.9 bpm, +3.3 mmHg and +1.5 mmHg, respectively. No data were available for the other months and no dose-dependent relationship was detected. After 24 months, the authors stated that there were slight changes in HR and DBP during the study, although no figures were provided.[24] However, there was a statistically significant increase in SBP (from mean ± SD 104.7 ± 8.1 mmHg at baseline to 108.1 ± 8.7 mmHg at the end of the study). Interestingly, methylphenidate was stopped in one child because of elevated BP on two readings. This consisted of an SBP >130 mmHg, which was greater than the 95th percentile for that child's age group. The child's BP normalized after the medication was discontinued. No other child had clinically significant changes in vital signs.

The studies discussed so far excluded children and adolescents with cardiac abnormalities and hypertension. There are very limited data on the effects of methylphenidate in this group of children. Gothelf et al.[27] carried out a small trial in 12 children and adolescents with velocardiofacial syndrome and ADHD. The cardiovascular data revealed that none of the patients had hypertension, tachycardia or a change in ECG recordings after 4 weeks. The authors concluded that larger studies were required but that the treatment appeared to be safe and effective.

2.1.1 Comment

The overwhelming majority of the studies were not specifically designed to investigate the effects of methylphenidate on HR and BP. Because of this, adequate account has not been taken of factors that may influence HR and BP, and strategies to standardize these measurements have not been used. Factors to consider include measurement

of the BP after an allotted time of rest and at given timepoints after the methylphenidate dose. Because these factors have not been taken into account, the measured changes cannot be considered as being reliable. In addition, at the start of these studies, many children had been taking other medication for ADHD and, although there was generally a washout period, there is a possibility that the previous medication may have affected the results, implying that a true baseline may not have been obtained. Both BP and HR are constantly changing and single measurements, as taken in several of the studies, may not have been representative. Furthermore, different preparations of methylphenidate with differing half-lives cannot be accurately compared and such data should not be grouped together. As a result of these limitations, many of the available data have to be interpreted with caution. In addition, grouped data may indicate small, clinically insignificant rises in HR and/or BP but such data do not exclude the possibility of clinically significant increases in individuals within the group. However, with one possible exception, there was no indication that such increases did actually occur in these studies.

Despite these reservations, there appears to be some evidence to suggest that methylphenidate may have an effect on BP and HR within hours of administration. However, the studies are on small numbers of subjects. The studies examining the effects of methylphenidate treatment over a few weeks were not designed to investigate these effects and do not have the methodological rigour required to assess them. However, the majority reported that methylphenidate did not result in a statistically significant increase in HR and BP or that the effects were not thought to be clinically significant. Finally, the long-term studies over several months again suggested that methylphenidate might increase HR and BP. As already stated, measuring BP and HR at one point in time does not provide an adequate assessment of the effect of methylphenidate. Measuring these variables at set times after administration of methylphenidate and using more stringent methodological strategies would be required. For example, 24-hour monitoring at specified timepoints would increase reliability. It remains to be seen whether there are any long-term implications on cardiovascular morbidity and mortality of the relatively small mean increases in HR or BP that have been reported. No study so far has investigated this. Such studies would need to run for several years to provide valid results and there would be other important factors to take into consideration. For example, HR decreases and BP increases with age. Any assessments would need to take these changes into account. Age-related centile charts for HR and BP are available; the best approach might be to examine consistent deviation from centiles. Finally, there are very limited data in children with cardiac abnormalities, and this is an area that also warrants further research.

2.2 ECG Changes

There are limited data on the ECG effects of methylphenidate. Ventricular arrhythmias and suppression of cardiac function have been reported with methylphenidate abuse.[7] In addition, although methylphenidate is taken orally for ADHD, there is a report of an arrhythmia following intravenous methylphenidate administration.[28] MHRA data include conduction and rhythm disorders that were thought to be a result of methylphenidate.[29] These reports, which include patients of all ages, are suspected reactions, without confirmation that methylphenidate is the cause.

Safer[30] reviewed the cardiovascular safety of psychostimulants in ADHD. Four studies evaluated ECG data read by cardiologists. No cardiac irregularities were noted except for an increased HR in one study. However, the ECG data were limited. McGough et al.[15] conducted an 8-week study of methylphenidate. At the end of the trial there were abnormal ECGs in 19 of 156 (12%) children. Seven of these children had abnormal ECGs prior to starting the study; the other 12 children had normal initial ECGs. However, the abnormalities were not considered to be clinically significant by the cardiologists. There is no further information available about the abnormalities. Interestingly, 11 ECGs were initially abnormal but normal at the end of the study.

Although there are many important parameters measured by ECGs, the QT interval has particular significance. A prolonged QT interval may

be associated with fatal cardiac arrhythmia and has therefore become a surrogate marker for a potential increased risk of sudden cardiac death.[31] In children, the QT interval needs to be corrected (QTc) to compensate for the HR. Various methods are used to do this, typically the Bazett's (QTc-B) or Fridericia's (QTc-F) formulae.

Kratochvil et al.[13] assessed changes in QTc as part of their 10-week study and found no statistically or clinically significant changes. Ilgenli et al.[32] investigated the effects of methylphenidate on QT interval dispersion in 25 children. Two hours after methylphenidate administration, there was a reduction in QT dispersion. No other studies specifically assessing QT interval were found.

2.2.1 Comment

There is little evidence available on ECG changes with methylphenidate. No evidence supports that methylphenidate increases the QTc interval. Methylphenidate may cause other ECG changes but these appear to be very rare. It is important to note that the current National Institute for Health and Clinical Excellence (NICE)[4] and AAP[8] guidelines state that children commencing methylphenidate do not routinely require an ECG. Again, data are lacking in this area and further research is required, although methylphenidate appears to be safe in this regard. However, a standardized procedure for performing and collecting ECG data needs to be established. In addition, specific ECG abnormalities that are considered to be drug induced need to be identified and studied. Furthermore, many so-called abnormal ECGs in the above studies may simply be a reflection of normal changes within the population. Normal limit data, such as those provided in the study by Rijnbeek et al.[33] and in the ADHD population by Prasad et al.,[31] may need to be used in future investigations to make results comparable. With such limited evidence, it is not possible to make recommendations for children with cardiac abnormalities.

2.3 Sudden Death

Sudden death is a very rare event and the risk of occurrence in children and adolescents in the general population is between 0.6 and 6 in 100 000 per year.[6] Data from the US, using FDA estimates, suggest that the risk of sudden death in children aged <18 years is 1.3–8.5 per 100 000 patient-years, while that associated with methylphenidate, amphetamine products and atomoxetine is 0.2–0.5 per 100 000 patient-years.[34] The risk of sudden cardiac death in patients taking methylphenidate for ADHD in the US has been estimated to be 0.22 deaths per 1 million prescriptions.[35] The FDA Adverse Event Reporting System (AERS), which is a voluntary healthcare provider reporting system, revealed seven cases of children aged 1–18 years taking methylphenidate who met the WHO criteria for sudden death.[5] The AERS has been criticized because it has been suggested that only 1–10% of serious adverse effects are actually reported.[5] In the UK, the MHRA has a similar system in the form of DAPs, which reflects public and healthcare worker reporting of possible or suspected adverse effects. The DAP for methylphenidate dates from 1964 and includes data on all age groups.[29] There have been 12 fatalities in total. One death was placed in each of the categories of sudden death, death, accidental death, cardiac arrest, cardiomegaly, brain oedema, neonatal respiratory distress syndrome, cerebral haemorrhage and fibrosarcoma.[29] In addition, three deaths were under the category of completed suicide. It must be stressed that these figures reflect the reporting but do not establish any causal agent. Although it is difficult to compare these figures directly, sudden death remains a very rare event. In addition, it is difficult to attribute these deaths to methylphenidate because there are often confounding factors. Continued monitoring of these rare events is required, with full investigation of each case.

In 2009, Gould et al.[36] reported on a study to determine whether there was a significant association between the use of stimulants and the rare event of sudden unexplained death in children and adolescents. This was a matched case-control study focusing on sudden deaths (not only in those taking ADHD medication) and matching this group to children who died as passengers in motor vehicle accidents. In 1.8% of the sudden unexplained deaths

it was determined that the children were taking stimulants, specifically methylphenidate; the use of stimulants was found in only 0.4% of the motor vehicle accident group. There was a significant association between stimulants and sudden unexplained death (odds ratio 7.4; 95% CI 1.4, 74.9). The authors concluded that this study provides support for an association between stimulants and sudden unexplained death in children and adolescents. It is important to note that both the authors and the FDA recognized several limitations of the study.[37] The FDA has not altered its advice; however, it has stated that it is "continuing its review of the strengths and limitations of this and other epidemiological studies that evaluate the risks of stimulant medications used to treat ADHD in children."[37] In the UK, McCarthy et al.[38] attempted to identify sudden unexplained deaths in children and young adults with ADHD using the General Practice Research Database. They confirmed that these events are very rare. A comment on this study and on the issue of sudden death in children treated for ADHD has recently been published in this journal.[39] It is evident that further research is still required to determine the safety of stimulant medications.

3. Amphetamines

In the UK market, the only licensed amphetamine in use is dexamfetamine (dextroamphetamine). There are several amphetamine products in the US market. The amphetamines used in each study are specified in the following review.

3.1 Heart Rate and Blood Pressure

The effects of amphetamines on HR and BP are summarized in table II. Samuels et al.[40] examined the immediate effects of stimulant medications on 24-hour ambulatory blood pressure monitoring (ABPM). Only five patients were taking either amphetamine or dexamfetamine. In the waking hours, an approximate mean 3–4 mmHg rise in both SBP and DBP and a mean 6 bpm increase in HR were observed. There were statistically significant higher total DBP, awake DBP, total HR and rate pressure product (a marker of myocardial oxygen demand) values in the treatment group compared with placebo. Although increases of this magnitude have not been considered to be of clinical significance, the authors in this study suggested that the cardiovascular profile of children treated with stimulants was worsened and that further studies were required. The study involved very small numbers and a satisfactory subgroup analysis of various stimulant treatments could not be performed.

As described in section 2.1, Findling et al.[12] found that the short-term cardiovascular effects of amphetamines are modest. There were statistically significant dosage effects for DBP and HR in the group sample of children treated with Adderall® or methylphenidate. Spencer et al.[48] examined Adderall XR® in children with ADHD. There were no clinically significant changes in BP and HR, although there was a statistically significant rise in HR (table II). Biederman et al.[42] also assessed Adderall XR® in a 4-week trial. These investigators stated that there were no significant changes in vital signs but did not indicate whether they were referring to statistically or clinically significant changes.

In a further study, Findling et al.[43] assessed the short-term cardiovascular effects of Adderall XR®. Measurements were taken at least 3 minutes after being seated and the same arm, cuff and study personnel were used. These investigators found that short-term treatment with Adderall XR® had no statistically significant effect on SBP, DBP or HR, but the timing of the measurements relative to medication was not standardized. Wilens et al.[44] performed a similar study. At the end of the short-term part of the study there were no statistically or clinically significant differences in BP between the groups at various doses. However, seven patients had a ≥20 mmHg increase in SBP (placebo, n = 1; Adderall XR®, n = 6) and 41 children had a ≥10 mmHg increase in DBP (placebo, n = 12; Adderall XR®, n = 29). There were statistically significant increases in mean HR of 5.0 and 8.5 bpm with Adderall XR® 20 and 50 mg/day, respectively. Similar findings were reported by Biederman et al.[45] in their assessment of the prodrug stimulant lisdexamfetamine. There were no significant mean changes in SBP

Table II. Summary of publications of effects of amphetamines on heart rate (HR) and blood pressure (BP) in patients with attention-deficit hyperactivity disorder (ADHD)

Study	Design	Amphetamine type and dose	No. and ages of subjects	Results
Immediate (effects of drug within hours of administration)				
Samuels et al.[40]	r, db, co trial, effects on BP: 24-hourly ambulatory BP over 8 days[a]	Adderall® (mixed amphetamine salts), Adderall XR® and dexamfetamine (no doses stated)	11 children (5–15 y), 5 received amphetamines	Statistically significant higher total DBP, wake DBP and total HR ($p < 0.05$) compared with PL. Changes not clinically significant. Included patients taking MPH
Findling et al.[12]	pc study, MPH or Adderall®, each dose was given for 1 wk, HR and BP measured on day 7	PL, Adderall® 5, 10 and 15 mg/day	137 children (4–17 y), 55 received amphetamines	Grouped data of MPH and Adderall® showed statistically significant dosage effects on BP and DBP. Changes not clinically significant
Short-term (effects of drug within 12 wk of administration)				
Spencer et al.[41]	4 wk, r, db, pc, pg study assessing safety and efficacy of Adderall XR®	PL, Adderall XR® 10, 20, 30 and 40 mg/day	287 adolescents (13–17 y)	HR statistically significantly increased from baseline relative to PL in Adderall XR® 20 mg group after 4 wk (mean 4.9 bpm; $p = 0.023$). Change not clinically significant
Biederman et al.[42]	4 wk, mc, r, db, pc, pg study to assess safety and efficacy of Adderall XR®	PL, Adderall XR® 10, 20 and 30 mg/day	649 children (6–12 y)	No significant changes in vital signs
Findling et al.[43]	4 wk, r, db, pc, forced-dose titration study to assess cardiovascular effects of Adderall XR®	PL, Adderall XR® 10, 20 and 30 mg/day	580 children (6–12 y)	No significant effects
Wilens et al.[44]	4 wk, r, db, pc, pg, forced dose-escalation study with Adderall XR® assessing cardiovascular safety	PL, Adderall XR® 10–60 mg/day	327 adolescents (13–17 y)	Statistically significant increase in mean HR in 20 and 50 mg Adderall XR® groups compared with PL (mean 5.0 vs 0.5 bpm; $p = 0.022$ and mean 8.5 vs −4.5 bpm; $p = 0.004$). No statistically significant differences in SBP or DBP
Biederman et al.[45]	mc, r, db, pg, forced-dose study assessing efficacy and tolerability of LDX over approximately 6 wk	PL, LDX 30, 50 and 70 mg/day	290 children (6–12 y)	Significant increase in HR in LDX groups relative to PL group. No p-values stated. No significant difference in SBP or DBP
Long-term (effects of drug after 12 wk)				
Donner et al.[46]	Prospective, ol, noncomparative, community-based study assessing cardiovascular effects of Adderall XR® for up to 17 wk	Adderall XR® 10–40 mg/day	2968 children (6–12 y), 441 children completed the extension phase	Statistically significant increase in mean HR, SBP and DBP at end of study compared with baseline (1.5 bpm; $p < 0.05$, <1 mmHg; $p < 0.05$)

Continued next page

Table II. Contd

Study	Design	Amphetamine type and dose	No. and ages of subjects	Results
Wilens et al.[44]/ Spencer et al.[41]	6 mo, ol extension study with flexible Adderall XR® dosing	Adderall XR® 10–60 mg/day	138 adolescents (13–17 y)	Statistically significant increase in mean sitting SBP from baseline (mo 3–6; $p < 0.05$). At 6 mo the mean increase was 1.7 mmHg ($p = 0.025$). Statistically significant but clinically non-significant increase in HR from baseline to endpoint observed (mean 4.4 bpm; $p = 0.0001$)
Findling et al.[47]	11 mo, mc, ol study to determine long-term effectiveness and safety of LDX	LDX 30, 50 and 70 mg/day	272 children (6–12 y)	Mean (±SD) changes from baseline to endpoint were 1.4 ± 13.7 bpm for HR, 0.7 ± 10 mmHg for SBP and 0.6 ± 8.3 mmHg for DBP. Judged not clinically significant
Findling et al.[43]	2 y, ol extension study in subjects previously enrolled in one of two db, pc Adderall XR® studies	Adderall XR® 10, 20 and 30 mg/day	568 children (6–12 y)	Statistically significant increases ($p < 0.05$) in mean SBP (mo 8, 11–14 and 16–24), mean DBP (mo 1–2, 6–14 and 17–24) and mean HR (mo 1–24) compared with baseline. Judged not clinically significant

a Children already on a long-term stable dose of stimulant (amphetamine, dexamfetamine or MPH).

bpm = beats per minute; **co** = crossover; **db** = double-blind; **DBP** = diastolic blood pressure; **LDX** = lisdexamfetamine; **mc** = multicentre; **MPH** = methylphenidate; **ol** = open-label; **pc** = placebo-controlled; **pg** = parallel-group; **PL** = placebo; **r** = randomized; **SBP** = systolic blood pressure; **XR** = extended release.

and DBP; however, there were significant increases in HR in the treatment groups relative to the placebo group. The maximum placebo-adjusted mean HR was approximately 4–5 bpm in the lisdexamfetamine 70 mg/day group. The authors did not state whether they were referring to clinically or statistically significant differences.

The cardiovascular safety of Adderall XR® was assessed in a longer trial.[46] In this trial, BP and HR measurements were taken after the patients had been sitting at rest for 5 minutes. The mean increase in both SBP and DBP from baseline to final visit was <1 mmHg and the mean increase in HR was 1.5 bpm. All these increases were found to be statistically significant but were not considered to be clinically significant. In addition, approximately 2.5% of subjects had two consecutive SBP or DBP values >95th percentile for age, sex and height, and in 3.6% of the subjects, HR increased by ≥25 to ≥110 bpm. In a further study, statistically significant mean increases in SBP (1.7 mmHg; $p = 0.025$) and HR (4.4 bpm; $p = 0.0001$) were seen 6 months after starting Adderall XR®.[41] These were deemed not to be clinically significant.

Findling et al.[43] carried out a 2-year study of Adderall XR®. After 2 years, the mean increases in SBP (3.5 mmHg), DBP (2.6 mmHg) and HR (3.4 bpm) were statistically significant but not clinically significant. The mean increases were observed in several months over the 2-year period; however, no dose-response relationship was found. As previously stated by Kratochvil et al.,[49] these increases in BP may be due to those that would be expected in children aging by 2 years. Findling et al.[47] also performed a long-term trial of lisdexamfetamine in which small changes in vital signs were observed. These were not deemed to be clinically significant; however, at endpoint, 7% of children who had an SBP <120 mmHg at baseline had an SBP ≥120 mmHg, and 4.8% had a DBP change from <80 mmHg to ≥80 mmHg.

3.1.1 Comment

It is difficult to draw specific conclusions about the effects of amphetamines on HR and BP from studies in which the stimulant drugs were grouped together. There is no convincing evidence of a short-term effect on BP but there may

be an effect on HR. There might be clinically significant effects in some individuals. If a dose-dependent relationship had been found, the evidence for an effect of amphetamines on HR would have been stronger.

As previously noted, because children often take such medication for long periods, these studies are of considerable importance from a clinical perspective. Long-term studies have tended to show minor changes in HR and BP that were considered to be not clinically significant. However, Samuels et al.[40] have suggested that these changes may have long-term cardiovascular effects. It is difficult to know whether the reported long-term effects on BP simply reflect the natural increase that occurs with age. Although difficult to perform, perhaps even longer duration studies are required to assess any long-term consequences of these minor increases in HR and BP. 24-hour ABPM may provide stronger data that will help to decide whether the reported increases in HR and BP are reliable.

3.2 ECG Changes

Spencer et al.[48] performed an ECG at the beginning and end of their study of Adderall XR®. No data are available but the authors stated that the overall changes were not clinically significant. In the study by Biederman et al.[45] (see section 3.1) lisdexamfetamine was not associated with any significant changes in mean ECG parameters, including QTc. The authors did not specifically state whether they were referring to statistical or clinical significance. However, Donner et al.[46] concluded that there were statistically significant changes in mean ECG parameters (HR and PR, QRS, QT and QTc intervals) with Adderall XR®, although these were not clinically significant and remained within age-specific normal ranges. In five children there were end-of-study increases in QTc-F equal to 60 msec. The change in mean QT interval was not clinically significant and only 1 child of 2968 had a change in QT interval of >25%. These investigators also noted small dose-dependent increases in HR and PR interval between screening and endpoint. In addition, 63 children (2.1%) had a total of 72 ECG abnormalities that were present at the end-of-study visit but not at baseline. The most common abnormalities were ectopic atrial rhythm, left anterior hemi-block and complete or incomplete right-bundle-branch block. In two cases, the abnormalities resulted in discontinuation of study medication. Thirty-two of the changes were considered clinically significant and reported as adverse effects, and 19 were considered as being possibly treatment related.

In the short-term part of the study of Adderall XR® by Wilens et al.,[44] there were no clinically or statistically significant changes in mean ECG parameters, including PR, QRS and QTc intervals, in any of the treatment groups. In the extension phase of the trial there was a statistically but not clinically significant decrease in the QTc-B when the results at 6 months were compared with baseline. The QTc decreased by a mean ± SD 4.6 ± 19.9 msec. There were no statistically significant changes in PR or QRS intervals. Finally, there were 34 ECG abnormalities at baseline and 24 at the end of the study but none of these was considered to be clinically significant.

Findling et al.[43] found no statistically significant differences between mean ECG interval measurements in the Adderall XR® groups compared with placebo. The group mean QTc-B was not statistically significantly different from baseline after 12, 18 and 24 months of Adderall XR® treatment. The most common ECG abnormalities included 25 sinus arrhythmias, five ST-T wave abnormalities and four poor anterior R-wave progressions. These were considered to be not clinically significant. In a 1-year open-label trial of lisdexamfetamine the mean ± SD changes from baseline to endpoint were 1.4 ± 15.5 msec for QTc-F and 4.2 ± 19.3 msec for QTc-B.[47] These changes, along with other ECG parameter measurements, were not considered to be clinically significant.

3.2.1 Comment

Amphetamines do appear to have an effect on ECG parameters but the effects do not seem to be of any clinical significance. With reference to QTc interval, there is a growing evidence base to suggest that amphetamines do not cause a statistically

or clinically significant increase in QTc interval. Although there are reports of a few children with an increased QTc interval, these changes did not appear to be of clinical significance. Many other ECG changes have been reported but, again, these have not been considered to be clinically significant. Amphetamine drugs have been grouped together in this discussion and it is difficult to draw specific conclusions about individual drugs.

3.3 Sudden Death

In the US, data collected from 1999 to 2003 revealed 17 reports of sudden death in patients taking amphetamines.[6] Twelve reports involved children and in 8 of 12 autopsies there was a structural cardiac defect. The authors also stated that autopsy evidence of cardiac defects requires special procedures that are not always performed and, consequently, the validity of a 'negative' autopsy depends on the quality of the procedure. Over the last 5 years, the risk of sudden cardiac death in patients taking amphetamines for ADHD has been estimated to be 0.56 deaths per 1 million prescriptions.[35] Six deaths have been reported to the MHRA in all patient age groups taking dexamfetamines; two of these deaths were described as sudden death.[50] As noted in section 2.3, this does not necessarily imply that dexamfetamine is the causal agent but rather indicates that a healthcare worker or member of the public suspected this to be an effect of the drug.

These limited data suggest that sudden death is a very rare event in patients taking amphetamines and the risk appears to be lower than in the background population; however, this result must be interpreted with caution because of the underreporting of potential serious adverse effects of drugs. Continued monitoring and encouragement of health workers to report adverse effects is of major importance. In relation to the use of stimulant drugs, Knight[35] has stated "It would seem the risk of sudden cardiac death is very low and the benefits of therapy, after an appropriate, thoughtful evaluation, outweigh the risks in otherwise healthy patients." (See section 2.3 on methylphenidate and sudden death for further discussion of this issue.)

4. Atomoxetine

4.1 Heart Rate and Blood Pressure

There are a few studies that specifically aimed at assessing the effects of atomoxetine on both HR and BP (table III). No study has examined the immediate cardiovascular effects of atomoxetine in children within hours of administration. However, Kelly et al.[51] conducted a study in healthy men and found a statistically significant increase in HR and BP. The mean maximum HR changes were 19 bpm for atomoxetine compared with 15 bpm for placebo, while the mean increases in SBP and DBP were 10 mmHg and 5 mmHg, respectively, compared with placebo. However, adult data cannot be extrapolated to children.

Stojanovski et al.[52] have commented on HR and BP effects in children exposed to atomoxetine reported to a poison centre. Twenty-one of the 64 cases had reported adverse drug reactions. Of these, nine patients had BP recordings. The authors identified four cases with elevated BP and/or HR. One 6-year-old child had a BP of 144/81 mmHg and a HR of 132 bpm. No further results of recordings were provided. A 16-year-old boy had initial readings of 139/96 mmHg and 116 bpm; within 4 hours these values were 126/72 mmHg and 82 bpm. An 11-year-old girl had a BP of 98/70 mmHg and a HR of 100 bpm. Finally, an 11-year-old male had an initial BP of 160/120 mmHg and a HR of 78 bpm. Within an hour, these values were 92/48 mmHg and 62 bpm. The authors stated that in three of the four cases, the BP and HR normalized within hours and the fourth child had normal readings the following day. It is difficult to draw any conclusions from these limited data. As indicated earlier, there could have been confounding factors such as the children being in a stressful environment, which could affect HR and BP. In addition, the dose of atomoxetine was greater than the recommended daily dose of 1.2 mg/kg in these four children.

The effects of treating children with atomoxetine over longer periods have been studied. A case series report on three adolescent boys diagnosed with ADHD and other co-morbidities who were treated with atomoxetine showed unacceptable

Table III. Summary of publications of effects of atomoxetine (ATX) on heart rate (HR) and blood pressure (BP)

Study	Design	ATX type and dose	No. and ages of subjects	Results
Immediate (effects of drug within hours of administration)				
Kelly et al.[51]	r, db, pc, 3-period co study to assess haemodynamic effects of ATX and MPH	ATX 120 mg/day	12 adults (22–27 y)	Statistically significant increase in HR with ATX compared with PL at 1, 1.5, 2.5, 3, 3.5, 4 and 5 h post-ingestion ($p < 0.05$). Statistically significant increase in BP from 1–8 h post-ingestion in ATX vs PL ($p < 0.05$)
Stojanovski et al.[52]	Evaluation of ATX adverse drug reactions in relation to dose in a poison centre over a 1 y period	ATX 10–300 mg/day	64 children and adolescents (≤18 y)	Four cases with elevated BP and/or HR (SBP and DBP ranged from 139–160/81–120 mmHg and HR ranged from 100–132 bpm)
Short-term (effects of drug within 12 wk of administration)				
Spencer et al.[53]	11 wk, ol, dose-ranging study of ATX treatment in children to assess tolerability and effectiveness	ATX 10–90 mg/day	30 children (7–14 y)	Statistically significant increases in mean seated DBP (59 mmHg at baseline vs 70 mmHg at endpoint; $p < 0.001$) and mean HR (88 bpm at baseline vs 97 bpm at endpoint; $p < 0.01$)
Wernicke et al.[54] (included data from Spencer et al.[55] and Michelson et al.[56])	Short-term cardiovascular safety in children, adolescents and adults was assessed in five r, db trials (up to 10 wk) with ATX and PL (long-term effects shown below)	ATX 0.5–2 mg/kg/day	550 children and adolescents	Statistically significant mean increase in HR from baseline to endpoint (ATX vs PL, 7.8 vs 1.5 bpm; $p < 0.001$). Statistically significant increases in mean DBP at endpoint compared with baseline (ATX vs PL, +2.1 vs −0.5 mmHg; $p = 0.002$)
Spencer et al.[55]	Two identical 12 wk, stratified, r, db, pc trials in children to determine the effectiveness of ATX	Maximum ATX dose 2 mg/kg/day or 90 mg/day; maximum MPH dose 1.5 mg/kg/day or 60 mg/day	291 children (7–13 y)	Statistically significant changes from baseline to endpoint in DBP and HR in ATX groups compared with PL ($p < 0.05$). Mean changes in DBP and HR were 2 mmHg and 9.2 bpm
Michelson et al.[56]	8 wk, pc, dose-response study assessing effectiveness of ATX at varying doses compared with PL	ATX 0.5, 1.2 and 1.8 mg/kg/day	297 children and adolescents (8–18 y)	Statistically significant increases in mean DBP at ATX 1.2 and 1.8 mg/kg/day compared with PL (2.8 and 1.7 vs −1.4 mmHg; $p < 0.05$). Increases in mean HR at ATX 0.5, 1.2 and 1.8 mg/kg/day compared with PL (5.8, 6.3 and 8.3 vs 1.6 bpm; $p < 0.05$)

Continued next page

Table III. Contd

Study	Design	ATX type and dose	No. and ages of subjects	Results
Michelson et al.[57]	Pooled data from four db, pc studies to assess the efficacy of ATX and pooled data from 14 studies to assess the safety and tolerability of ATX in children with polymorphisms of the cytochrome P450 2D6 enzyme	Unclear (84% had an ATX dose >1.2 mg/kg/day)	Safety and tolerability data in 3254 children and adolescents (6–18 y)	For poor metabolizers, the mean changes in HR and DBP were statistically significantly higher at endpoint compared with baseline than for the extensive metabolizer group (9.7 vs 5.8 bpm; $p < 0.001$ and 4.2 vs 2.6 mmHg; $p = 0.014$) No significant difference in SBP
Long-term (effects of drug after 12 wk)				
Wernicke et al.[54]	Long-term cardiovascular safety in children, adolescents and adults was assessed from ol extension or blinded continuation (at least 1 y) following short-term treatment with ATX	ATX 0.5–2 mg/kg/day	169 children and adolescents	After initial increase, HR, SBP and DBP stabilized during the titration phase. Mean increases in BP were small and judged not clinically significant
Allen et al.[58]	db, pc study for up to 18 wk to test hypothesis that ATX does not worsen tics in patients with ADHD and tic disorder	ATX 0.5–1.5 mg/kg/day	166 children and adolescents (7–17 y)	Statistically significant mean ± SD increase in HR in ATX group compared with PL (8.3 ± 12.0 vs −1.2 ± 12.7 bpm; $p < 0.001$). Significantly larger numbers of children with increases in HR ≥25 bpm to ≥110 bpm in ATX group vs PL (10/75 vs 2/70; $p = 0.032$)
Donnelly et al.[59]	Pooled data from 13 db, pc trials and 3 ol extension studies to determine the long-term safety of treatment with ATX for ≥3 and ≥4 y	ATX 0.5–1.8 mg/kg/day	1553 children and adolescents enrolled (6–17 y), 714 completed ≥3 y and 508 ≥4 y	Significant decrease in mean HR from baseline for those treated for ≥3 and ≥4 y (−2.0 and −2.7 bpm; $p < 0.001$) Significant increase in mean DBP (2.9 and 3.4 mmHg; $p < 0.001$) and SBP (8.0 and 8.8 mmHg; $p < 0.001$) at ≥3 and ≥4 y compared with baseline. Values not corrected for age increase
Kratochvil et al.[49]	13-study (7 db, pc, 6 ol) meta-analysis to determine the effectiveness and tolerability of ATX treatment in children with ADHD over a 2-y period	Maximum dose ranged from 1.5–2.0 mg/kg/day	272 children (6 and 7 y), 97 completed 2 y ATX treatment	Statistically significant increases in HR (mean change 7.2 bpm; 95% CI 5.5, 8.8; $p < 0.001$), DBP (mean change 3.4 mmHg; 95% CI 2.3, 4.6; $p < 0.001$) and SBP (mean change 3.7 mmHg, 95% CI 2.4, 4.9; $p < 0.001$)
Wilens et al.[60]	Data from 13 studies (6 db, 7 ol) to determine the efficacy and safety of ATX in adolescents treated for ADHD for up to 2 y	Target dose of ATX 1.2 mg/kg/day (maximum dose 1.8 mg/kg/day)	601 adolescents (12–18 y), 217 completed 2 y ATX treatment	Significant increases in HR (mean change 5 bpm; 95% CI 4.0, 6.0; $p < 0.001$), DBP (mean change 3.1 mmHg; 95% CI 2.3, 3.9; $p < 0.001$) and SBP (mean change 4.4 mmHg; 95% CI 3.4, 5.3; $p < 0.001$). Increases were judged not clinically significant

ADHD = attention-deficit hyperactivity disorder; **bpm** = beats per minute; **co** = crossover; **db** = double-blind; **DBP** = diastolic blood pressure; **MPH** = methylphenidate; **ol** = open-label; **pc** = placebo-controlled; **PL** = placebo; **r** = randomized; **SBP** = systolic blood pressure.

rises in BP, which resolved with a reduction in the dose of atomoxetine.[61] In the first patient, the atomoxetine dose was increased from 60 to 80 mg/day. The maximal BP measurement was 140/86 mmHg. Atomoxetine was decreased to 40 mg/day and controlled-release methylphenidate 18 mg/day was started. The patient had subsequent BP readings of 100/78 and 100/70 mmHg. No timeframe was given by the authors for the reduction in BP in the above patient and the subsequent two patients discussed below. In the second patient, the dose was increased to 80 mg/day and the BP rose to 142/90 mmHg. The BP readings reduced to 112/60 and 122/70 mmHg when the dose of atomoxetine was lowered to 60 mg/day and Adderall XR® 15 mg was added. The third patient had BP readings of 150/80 and 140/90 mmHg, which decreased to 122/74 mmHg once the atomoxetine dose was altered from 80 mg once daily to 40 mg twice daily. These patients were taking other medications and had co-morbidities, which may have been confounding factors in addition to the issues already discussed.

Spencer et al.[53] conducted a small study in which there was a statistically significantly increased mean seated DBP at the endpoint (59 vs 70 mmHg; $p < 0.001$). In addition, the mean HR increased significantly from 88 bpm at baseline to 97 bpm at endpoint ($p < 0.01$). There was no statistically significant change in mean SBP.

Wernicke et al.[54] assessed the short-term cardiovascular effects of atomoxetine in three studies of up to 10 weeks' duration.[54-56] As part of the studies, vital signs were measured. Two measurements of sitting HR and BP were taken at least 3 minutes apart and the mean value was used. However, no further information was given on how the measurements of vital signs were standardized. There was a statistically significantly increased HR in children receiving atomoxetine compared with placebo. The mean HR increased by 5–9 bpm ($p < 0.001$). There was also a statistically significant increase in the proportion of children with an increase in HR by ≥25 bpm to a value ≥110 bpm (3.6% vs 0.5% with placebo). In two of the studies there was a drug discontinuation phase; 1 week after atomoxetine discontinuation, the mean HR decreased by 3.8 bpm.[54,55]

Following this short-term trial, children continued the medication for up to 1 year.[54] This demonstrated that a HR increase occurred during the titration period and then stabilized. When BP was examined, there was a statistically significant increase in mean DBP (2.1 mmHg) with atomoxetine. There was no statistically significant difference between the groups with respect to SBP. Over a 12-month period, once there had been an initial small rise in BP, this tended to stabilize.

In a more recent study by Allen et al.,[58] children treated with atomoxetine for 18 weeks had an increase in HR compared with the placebo group (mean ± SD +8.3 ± 12.0 vs −1.2 ± 12.7 bpm). Kratochvil et al.[49] carried out a meta-analysis of 13 studies conducted over a 2-year period. Data on the cardiovascular parameters showed there were statistically significant increases in HR, DBP and SBP. However, the authors noted that these BP increases were consistent with expected age-associated increases in BP that naturally occur from 7 to 9 years of age.[62] The increases in HR cannot be explained in this way because HR usually falls with age in childhood.

Wilens et al.[60] also assessed the long-term safety of atomoxetine. There were significant increases in HR, DBP and SBP when all 601 adolescents were analysed. Only 217 patients completed 2 years of treatment and there was no specific analysis of this subgroup. However, the authors stated that the increases in DBP and SBP over 2 years were consistent with expected age-associated increases between 13 and 15 years of age.

Donnelly et al.[59] examined atomoxetine after at least 3 years of treatment. This involved pooled data from two long-term, open-label extension trials. In the group that discontinued, six patients stopped because of cardiovascular adverse effects (heart murmur, prolonged QT interval, tachycardia, hypertension, increased HR and Wolff-Parkinson-White syndrome). There was a statistically significant decrease in HR from baseline to endpoint in patients treated for ≥3 years and ≥4 years. Mean DBP and SBP increased significantly (table III) but the authors described these effects of atomoxetine as not being clinically significant. They pointed out that a decrease

in HR is consistent with decreases in normal healthy children and that a mean increase in BP of 8.4/3.2 mmHg is consistent with increases observed in the general population from 10 to 15 years of age.

A further factor that needs to be considered when discussing atomoxetine is the metabolism of the drug. Atomoxetine is metabolized through the cytochrome P450 (CYP) 2D6 enzyme pathway and there are polymorphisms in this enzymatic pathway in the population. Different children may metabolize atomoxetine at different rates and this might influence its safety and, in particular, its effects on the cardiovascular system. Michelson et al.[57] examined the effects of CYP2D6 in children treated with atomoxetine. Analysis of vital signs demonstrated a greater increase in HR and DBP in poor metabolizers of atomoxetine compared with extensive metabolizers.

Finally, there is evidence from a small adult study that patients with central autonomic failure can have a rise in mean ± SD seated and standing BP 1 hour after administration of atomoxetine of 54 ± 26 mmHg ($p = 0.004$) and 45 ± 23 mmHg ($p = 0.016$), respectively.[63] This effect was not noted in adults with peripheral autonomic failure.

4.1.1 Comment

In children, atomoxetine may have an immediate effect, increasing HR and BP within hours of administration. In the short term (up to 18 weeks), there is slightly more convincing evidence to suggest that atomoxetine can increase BP and HR; however, the studies do not have the rigorous methodology that is necessary to exclude confounding factors, as indicated in the discussion of methylphenidate (see section 2.1.1). On the basis of the evidence that is available, the increases in BP and HR appear to be mild and atomoxetine has been described as causing 'benign cardiovascular effects'.[53] This might well be the case in the short term but often these drugs are continued for prolonged periods. While long-term data are available, the relevant studies have generally not been designed to measure the effects of atomoxetine on HR and BP. There appears to be a small, significant increase in BP. The effect on HR is less clear, with conflicting data. As previously noted, increases in BP over the long term may simply be a result of the natural increase in BP with age. Whether these apparent small effects will have long-term consequences on cardiovascular morbidity and mortality remains to be seen. The stated view is often that they are likely to be 'clinically insignificant' but the evidence to support such statements is lacking. Further specifically designed studies would be required to investigate this. In addition, there is very limited knowledge of the effect of atomoxetine on children with congenital cardiac abnormalities, hypertension or other forms of cardiovascular disorders, as many studies excluded these patients. Further research is required to elicit this information.

4.2 ECG Changes

There has been spontaneous reporting of QT interval prolongation with atomoxetine to the MHRA. Indeed, during the period 26 November 2002 to 26 November 2004 there were 27 cases of reported QT/QTc interval prolongation in patients taking atomoxetine.[64] The number of children involved is not clear from the data. The assessor's comments suggest that atomoxetine may be associated with QTc prolongation in overdose. In two cases, in which atomoxetine was used at the therapeutic dose, no alternative cause could be found. In addition, there are at least seven cases, despite concomitant medication, in which the role of atomoxetine could not be excluded. Furthermore, in 18 of the cases in which atomoxetine was discontinued, the prolongation of QTc resolved in 15 patients after drug discontinuation, and in the remaining three cases no follow-up information is available.

In addition, there is a reported case of prolonged QTc interval in a 15-year-old boy who took an overdose of atomoxetine.[65] The patient had a history of major depression and ADHD, and was taking various medications, including atomoxetine, alprazolam, risperidone and bupropion. He ingested a dose of atomoxetine 22 mg/kg and this resulted in seizures as well as a QTc interval of 607 msec at 3 hours after ingestion; the abnormality subsequently resolved.

There has also been a case report in the literature of an 11-year-old boy treated with atomoxetine who demonstrated unusual repolarization changes following the T waves, in association with palpitations.[66] These changes and symptoms resolved with drug discontinuation. The authors concluded that further research is needed to study the long-term effects of atomoxetine on the cardiovascular system.

Data from Spencer et al.[53] revealed no evidence of atomoxetine affecting QTc, PR and QRS intervals, mean conduction or repolarization. Furthermore, Kratochvil et al.[49] found no statistically or clinically significant changes in QTc interval with the use of atomoxetine. However, Allen et al.[58] reported a decrease in QTc interval in the atomoxetine-treated group. Evidence for the lack of an effect of atomoxetine on increasing the QTc interval is supported by Wernicke et al.,[54] who found no evidence of a prolonged QT interval with up to 1 year of treatment. Further support can be found in the study by Kratochvil et al.,[49] who reported that atomoxetine caused no statistically or clinically significant changes in QTc interval over a 2-year period. However, in this study, treatment with atomoxetine in children was associated with a statistically significant reduction in PR interval (mean change −4.3 msec; 95% CI −5.8, −2.8; $p < 0.001$).

Finally, data from Donnelly et al.[59] on patients treated with atomoxetine for ≥3 years and those treated for ≥4 years revealed no statistically significant changes in QTc-F from baseline. Although no patient had a QTc interval >500 msec, 1.4% (10/711) with ≥3 years' exposure and 1.2% (6/507) with ≥4 years' exposure had prolonged QTc-F intervals (≥450 msec in men and ≥470 msec in women). The corresponding values using Bazett's formula were 16.1% (113/700) and 17.1% (85/497) with ≥3 and ≥4 years' exposure, respectively. An increase of ≥30 msec in QTc interval was noted in 15.5% (110/711) and an increase of ≥60 msec in QTc interval was noted in 0.7% (5/711) of patients treated for ≥3 years. Using Bazett's formula, a ≥30 msec increase in QTc interval was noted in 30.7% (218/711) and a ≥60 msec in QTc interval was noted in 2.5% (18/711) of patients treated for ≥3 years. Similar results were found in the ≥4-year treatment group. The authors concluded there were no clinically significant effects of atomoxetine on ECG parameters.

4.2.1 Comment

Much of the data presented suggests atomoxetine does not prolong the QTc interval when used at the correct doses; however, recent long-term data have indicated that, although there was no overall significant change in QTc interval, there were several patients with an increased QTc interval at the end of the study. This has been described as clinically insignificant. It appears that a few patients treated with atomoxetine have a QTc interval ≥450 msec; however, no specific baseline data are available, and the findings might not be related to atomoxetine. Normal baseline ECG data in children and adolescents with ADHD has been collected by Prasad et al.[31] If the results for atomoxetine are taken at face value and compared with the results of Prasad et al.,[31] there is a suggestion that a greater proportion of children treated with atomoxetine in the study by Donnelly et al.[59] have a raised QTc interval.

Overall, it is still not clear whether atomoxetine increases the QTc interval, as there are conflicting data. Furthermore, if there were an increase in QTc interval, would this have clinically significant long-term effects in patients? This question remains unanswered.

Other ECG changes have been noted, such as unusual repolarization changes and a shortened PR interval, which may be due to atomoxetine. Further research is required to determine the extent of ECG changes with atomoxetine and their clinical significance.

The current advice given by the MHRA is for caution when prescribing atomoxetine in the presence of a history of QT interval prolongation or co-prescription with other drugs that are known to have the same effect.[67] The NICE guidelines do not recommend performing an ECG before administering atomoxetine unless there is a clinical indication to do so.[4]

4.3 Sudden Death

There are no published data in the literature with respect to atomoxetine causing sudden death;

however, during the period 26 November 2002 to 30 September 2005, there were 11 case reports of cardiac disorders resulting in death in patients taking atomoxetine.[64] Five of the cases were adolescents or children. In two of the cases involving children, there were no obvious confounding factors; however, it is difficult to determine whether atomoxetine had any role in these deaths.[64] There are no sudden cardiac deaths related to atomoxetine in data available from the DAPs.[68]

On the basis of the available data, it is not possible to attribute sudden cardiac death to use of atomoxetine; however, it is important to continue monitoring patients taking atomoxetine and to ensure accurate reporting of potential adverse effects. Even if further information were to indicate that atomoxetine can be associated with sudden cardiac death, this would appear to be an extremely rare occurrence. (See section 2.3 on methylphenidate and sudden death for further discussion of this issue.)

5. Conclusions

There are still gaps in our knowledge of the cardiovascular effects of methylphenidate, amphetamines and atomoxetine. In particular, it is not known whether use of these drugs over the long term has associated cardiovascular morbidity, although the fact that methylphenidate and amphetamines have been used for decades without such adverse effects becoming evident might be considered as somewhat reassuring. Many of the data have been collected in studies that have not been specifically designed to evaluate cardiovascular effects and have recruited children with no known cardiovascular morbidity. The available evidence suggests that the cardiovascular effects of these drugs are generally not clinically significant and do not pose a risk to patients but some doubt remains about a few individual patients who, in various studies, have been withdrawn from the medication because of apparent elevated BP and/or HR.

The value of these drugs in the management of ADHD and the large number of children taking them imply that safety issues are of great importance. The NICE guidelines in the UK reflect the opinion that these drugs are a valuable treatment but that there is a need for monitoring for possible cardiovascular adverse effects.[4] The recommendation includes monitoring HR and BP, and recording the values on a centile chart before and after each dose change, and after every 3 months. Routine ECGs are not recommended. The AHA and AAP both recommend taking a history and conducting an examination focused on cardiovascular disease.[8,69] Both individual and family cardiovascular histories should be obtained. The AHA states that it is reasonable to consider obtaining an ECG as part of an evaluation but that this is not mandatory; the AAP does not recommend the routine use of ECGs before initiating stimulant therapy for ADHD. The AHA has stated "Some of these medications can increase or decrease heart rate and blood pressure. While these side effects are not usually considered dangerous, they should be monitored in children with heart conditions as the physician feels necessary."[69] This is in keeping with the view stated in many papers, suggesting that changes in BP and HR are clinically insignificant.

The variations in the statements made by professional bodies with respect to cardiovascular monitoring reflect the gaps in the literature. Further targeted specific cardiovascular research on ADHD medications is required to give more definitive data on the cardiovascular effects of these drugs. Studies need to be designed specifically to assess the cardiovascular safety of ADHD medications. A standardized method for collecting data on BP, HR and ECGs is required to ensure studies are comparable. Furthermore, there needs to be a consensus on parameters that are considered to be clinically significant, and perhaps assessing the drugs on a dose/kg basis. This research should minimize or avoid confounding factors, for example by taking account of, or excluding, concomitant medication, including herbal preparations. The conditions under which BP and HR are measured should be standardized, as indicated earlier. There is also a need for research in populations of children with cardiovascular morbidity. Continued monitoring and vigilance with regard to any suspected adverse effects, including cardiovascular effects, together

with reporting of such occurrences to the relevant agencies, may enable more definitive information about the cardiovascular effects of methylphenidate, amphetamines and atomoxetine to be provided in the future.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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