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Cardiovascular Effects of Atomoxetine in Children, Adolescents, and Adults

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Abstract

Background: Atomoxetine is a highly specific presynaptic inhibitor of the noradrenaline (norepinephrine) transporter that was recently approved in the US for the treatment of patients with attention-deficit/hyperactivity disorder (ADHD). Adverse effects on the cardiovascular system, including abnormalities in heart rate, blood pressure, or cardiac rhythm have been associated with several noradrenergic medications.

Objective: To further elucidate the magnitude and impact of blood pressure and pulse elevations in patients taking atomoxetine.

Study Design: Short-term cardiovascular safety in children, adolescents, and adults with ADHD was assessed in five randomised, double-blind trials (duration up to 10 weeks) with atomoxetine (n = 612) or placebo (n = 474). Long-term cardiovascular safety in children and adolescents (n = 169) was assessed in patients who entered an open-label extension or a blinded continuation following short-term treatment.

Methods: Adverse events, blood pressure, sitting pulse, and electrocardiograms (ECGs) were collected throughout the trials. QT intervals were corrected for heart rate by a data-specific correction factor (QTcD; derived from baseline ECGs) as well as standard methods.

Results: Atomoxetine treatment was associated with small but statistically significant increases in mean systolic blood pressure in adults and diastolic blood pressure in children and adolescents. Mean pulse rate increased for all atomoxetine treatment groups. The increases in blood pressure and pulse tended to occur early in therapy, stabilised, and returned toward baseline upon drug discontinuation. There was no significant difference between atomoxetine and placebo treatment groups in change in QTcD interval for all study populations. Palpitations in the adult patient population were the only significant cardiovascular adverse event ($p = 0.037$) occurring more frequently in the atomoxetine treatment group (3.7%) than in the placebo group (0.8%). Discontinuations due to cardiovascular-related events were very uncommon in the adult group, and did not occur in the child/adolescent group.

Conclusion: While atomoxetine has noradrenergic activity, increases in pulse and blood pressure were small and of little, if any, clinical significance. Atomoxetine was not associated with QT interval prolongation. Cardiovascular effects of atomoxetine were minimal, and atomoxetine was well tolerated in short- and long-term studies.

Atomoxetine is a nonstimulant, highly specific, presynaptic inhibitor of the noradrenaline (norepinephrine) transporter recently approved in the US for the treatment of attention-deficit/hyperactivity disorder (ADHD) in paediatric, adolescent, and adult patients. It is currently under review in other countries. The effectiveness of atomoxetine given either once or twice daily in the treatment of ADHD in children, adolescents, and adults has been demonstrated in eight double-blind, placebo-controlled studies.[1-5] In each of these studies, atomoxetine was clinically and statistically superior to placebo in reducing symptoms of ADHD. Atomoxetine has very little affinity for other neurotransmitter receptor or transporter sites. Atomoxetine appears to increase noradrenaline concentrations in the CNS, which may account for improvement in ADHD symptoms.[6]

Apparently because of its noradrenergic effect, atomoxetine has been associated with cases of increased blood pressure and heart rate, usually without clinical consequences.[7] Cardiovascular safety is a significant therapeutic issue in drug product selection. Medications such as dextroamphetamine, ephedrine, venlafaxine, and systemic decongestants that possess noradrenergic qualities have been associated with elevated blood pressure and/or heart rate.[8-12] These vital sign changes may aggravate underlying cardiovascular disease in some patients and have the potential for increased risk of cardiovascular morbidity and/or mortality. For patients with heart rate and blood pressure within the normal range, these effects are often slight and of little clinical significance in the short term, but long-term effects are less understood.

To further elucidate the magnitude and impact of blood pressure and pulse elevations in patients taking atomoxetine, we undertook a pooled analysis of the cardiovascular data from five clinical trials[1,3,5] in children, adolescents, and adults with ADHD.

Design of Studies Included in Analyses

The short-term safety and tolerability of atomoxetine in children and adolescents with ADHD were evaluated in 342 patients assigned to atomoxetine compared with 208 patients assigned to placebo during short-term treatment periods of up to 9 weeks in three double-blind studies. In study 1[3] (65 patients randomised to atomoxetine and 62 to placebo) and study 2[3] (64 patients randomised to atomoxetine and 62 to placebo), atomoxetine doses were titrated based upon clinical response and tolerability (starting dosage of approximately 0.5 mg/kg/day and maximum dosage of 2 mg/kg/day administered in two divided doses. Placebo was titrated similarly in a blinded manner. These studies also included a 1-week study drug discontinuation phase where atomoxetine was stopped abruptly. Data pertaining to the cardiovascular effects of drug discontinuation in children and adolescents were gathered in these trials. Study 3[1] incorporated randomisation to one of three fixed atomoxetine target dosage levels (0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day) [n = 213] or placebo (n = 84). The majority of the atomoxetine-treated patients received total daily doses between 1.2 mg/kg/day and 2.0 mg/kg/day, administered in two divided doses. Patients in all studies had the option to continue into long-term treatment in an open-labelled extension (for studies 1 and 2) or a blinded continuation period (study 3).

Long-term cardiovascular safety in the child/adolescent population (n = 169) was assessed in patients who entered an open-label extension or a blinded continuation following short-term treatment trials. These patients were treated with atomoxetine for at least 1 year.

Short-term safety and tolerability of atomoxetine in adult ADHD patients was assessed in two identical double-blind, randomised, 10-week, placebo-controlled studies (270 patients were randomised to atomoxetine; 266 to placebo).[5] The dose of atomoxetine was titrated for each individual based upon efficacy and tolerability with a starting dosage of 60 mg/day (30mg twice daily) and a maximum dosage of 120 mg/day (60mg twice daily). These studies included a 4-week blinded study drug discontinuation phase where atomoxetine was tapered or stopped abruptly. Long-term safety studies in adults are underway and no data are available.

Patients with clinically significant electrocardiogram abnormalities or current or past history of clinically significant elevation of blood pressure were excluded in all trials.

Methods

Measured Parameters

Adverse cardiovascular events were assessed by vital sign measurement and open-ended patient questioning at each visit and upon study discontinuation and periodic ECG. Blood pressure and sitting pulse were measured at each visit in all trials. In some, but not all studies, sitting and standing measurements were taken. For this pooled analysis, only measurements common to all studies were considered. Two blood pressure and pulse measurements were obtained at least 3 minutes apart, and the average value was used in analyses. Electrocardiograms (ECGs) were collected at baseline and throughout each trial. ECG tracings were interpreted either by a board-certified paediatric cardiologist at Riley Hospital for Children, Indianapolis, Indiana, USA, or were collected and processed by Biomedical Systems Corporation, St. Louis, Missouri, USA.

Statistical Analyses

Data were pooled after a statistical analysis confirmed that there was no treatment-by-study interaction. For each variable (heart rate, diastolic and systolic blood pressure, and corrected QT interval [QTc]) the following analyses were performed:

1. Treatment differences in mean change from baseline to endpoint were assessed using an analysis of variance (ANOVA) model with terms for study and treatment.
2. Treatment differences in percentages of patients meeting categorical criteria at endpoint were assessed using Fisher's exact test. Criteria for categorical changes are shown in table I and are based upon age, gender and height-adjusted National Institutes

Table I. Criteria for categorical analyses of change in vital signs and QTc[a]

Change from baseline to endpoint	Children and adolescents	Adults
Heart rate (beats/min)		
Pulse – high	Increase ≥25 to a value of ≥110	Increase ≥15 to a value of >120
Pulse – low	Decrease ≥20 to a value ≤65	Decrease ≥15 to a value <50
ECG heart rate – high	Increase ≥20 to a value of ≥100	Value ≥120
ECG heart rate – low	Decrease ≥15 to a value ≤60	Value ≤40
Blood pressure (mm Hg)		
Systolic – high	Value >95th percentile	Increase ≥20 to a value ≥180
Systolic – low	Not analysed	Decrease ≥20 to a value ≤90
Diastolic – high	Value >95th percentile	Increase ≥15 to a value ≥105
Diastolic – low	Not analysed	Decrease ≥15 to a value ≤50
QTc (data-corrected) – high (msec)	Increase ≥30	Increase ≥30
	Increase ≥60	Increase ≥60
	Increase to ≥500	Increase to ≥500

a Based upon age, gender, and height-adjusted National Institutes of Health norms,[13] Committee for Proprietary Medicinal Products (CPMP) guidelines,[14] or placebo data.

QTc = corrected QT interval.

Table II. Patient characteristics: short-term treatment

Characteristics	Children/adolescents			Adults		
	atomoxetine (n = 342)	placebo (n = 208)	p-value	atomoxetine (n = 270)	placebo (n = 266)	p-value
Age in years (SD)	10.7 (2.2)	10.3 (1.8)	0.082	41.5 (11.1)	40.7 (11.4)	0.393
No. of males (%)	250 (73.1)	163 (78.4)		174 (64.4)	174 (65.4)	
No. of females (%)	92 (26.9)	45 (21.6)	0.187	96 (35.6)	92 (34.6)	0.856
Ethnicity						
no. of Caucasian (%)	269 (78.7)	163 (78.4)		248 (91.9)	239 (89.8)	
no. of other (%)	73 (21.3)	45 (21.6)	0.887	22 (8.1)	27 (10.2)	0.397

of Health norms (blood pressure for children and adolescents[13]), Committee for Proprietary Medicinal Products (CPMP) guidelines (QTc[14]), or placebo data.

3. Treatment differences in mean change from baseline to endpoint of the withdrawal period were assessed with an ANOVA model as described above.

4. Long-term effects were assessed by examining summary statistics by visit on an observed case basis.

5. Dose response relationships were assessed using a general linear model with baseline and prescribed dose included as continuous effects using only patients with at least one year of atomoxetine exposure. Analyses of treatment effect were performed using F-tests for prescribed dose from this model.

Incidences of treatment-emergent adverse events were compared between treatment groups using the Fisher's exact test.

All patients with a baseline and at least one post-baseline measurement were included in each analysis.

Results

Patient Population

Demographic variables for participants in the child/adolescent and adult studies are shown in table II. Patient characteristics were similar between treatment groups.

Heart Rate

Heart rate was reported as a pulse measurement. Mean values and changes from baseline to endpoint for short-term treatment studies in child/adolescent and adult studies are shown in table III. In children/adolescents and adults, mean pulse increased by 5 beats/min to 9 beats/min during short-term treatment. These changes were statistically significantly different from those observed in the placebo group. Only in the child and adolescent studies was the percentage of patients with changes to 'high' values statistically significantly greater in the atomoxetine than in the placebo group.

In children and adolescents, mean pulse decreased by 3.8 beats/min (49% of the short-term phase increase) within 1 week of drug discontinuation. In the adult studies, double-blind therapy was followed by a 4-week blinded discontinuation phase, where atomoxetine was either tapered or stopped abruptly. With each discontinuation paradigm, drug-induced increases in pulse were essentially reversed by the end of the second week, with a mean overall reversal of about 4.6 beats/min (87% of the short-term phase pulse increase).

For children and adolescents (adult long-term data are not yet available), long-term effects of atomoxetine on pulse are illustrated in figure 1 for patients treated for at least 1 year. Mean pulse increased less than 10 beats/min and tended to occur during the initial titration period and then stabilised.

The relationship between atomoxetine dosage and change in pulse rate is illustrated in figure 2. There was a trend toward a statistically significant relationship between atomoxetine dose and pulse. However, between patient variability was large relative to the dose-response effect.

Table III. Baseline and change to endpoint in pulse and blood pressure: short-term treatment

Characteristics	Children/adolescents			Adults		
	atomoxetine (n = 335)[a]	placebo (n = 204)[a]	p-value[b]	atomoxetine (n = 258)[a]	placebo (n = 258)[a]	p-value[b]
Pulse (beats/min)						
Baseline mean (SD)	82.7 (10.4)	83.9 (10.4)		73.5 (9.8)	73.0 (9.9)	
Mean change at endpoint (SD)	+7.8 (12.0)	+1.5 (11.5)	<0.001	+5.3 (11.0)	−0.3 (9.4)	<0.001
Change to 'high' [no. (%)]	12 (3.6)	1 (0.5)	0.022	0	0	NA
Change to 'low' [no. (%)]	2 (0.6)	1 (0.5)	1.00	0	0	NA
Systolic blood pressure (mm Hg)						
Baseline mean (SD)	103.9 (9.9)	102.7 (9.5)		118.5 (10.2)	120.5 (11.6)	
Mean change at endpoint (SD)	+2.8 (10.2)	+1.2 (9.0)	0.148	+2.9 (10.8)	0 (10.4)	0.002
Change to 'high' [no. (%)]	22 (6.8)	6 (3.0)	0.073	0	0	NA
Change to 'low' [no. (%)]	0	0	NA	0	0	NA
Diastolic blood pressure (mm Hg)						
Baseline mean (SD)	64.5 (8.3)	63.3 (8.2)		76.6 (8.4)	76.3 (8.1)	
Mean change at endpoint (SD)	+2.1 (9.6)	−0.5 (9.0)	0.002	+1.8 (8.5)	+0.5 (7.7)	0.083
Change to 'high' [no. (%)]	9 (2.8)	1 (0.5)	0.098	0	1 (0.4)	1.0
Change to 'low' [no. (%)]	0	0	NA	0	0	NA

a Patient numbers per treatment group are lower than the totals because baseline and treatment data were not available for all patients.

b p-Values for mean changes were determined by analysis of variance or by Fisher's Exact test for categorical changes.

NA = not applicable.

Blood Pressure

Baseline and change to endpoint data for blood pressure recorded during short-term studies are shown in table III. Atomoxetine treatment in adults was associated with a modest but statistically significant mean increase in systolic blood pressure and a marginal increase in diastolic blood pressure compared with the placebo control group. There were no differences in the percentage of patients found to have categorical changes in blood pressure to values considered as 'high' or 'low' by defined study criteria.

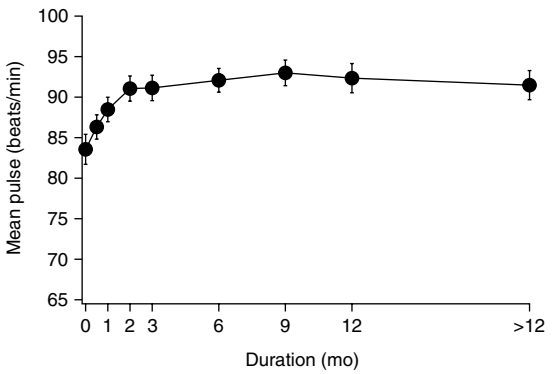

Fig. 1. Change in mean pulse (beats/min) ± 2 standard errors of the mean over time in children and adolescents with attention-deficit/hyperactivity disorder treated with atomoxetine for at least 1 year (n = 169) [>12 month group had an average duration of treatment of 20 months].

Systolic blood pressure decreased upon discontinuation of atomoxetine therapy by an average of 0.5mm Hg (17% of the short-term phase increase) within 2 weeks. Mean diastolic blood pressure decreased upon discontinuation by 0.6mm Hg (33%). These findings suggest that atomoxetine-related blood pressure changes in adults tend to subside gradually.

In contrast to adults, children and adolescents in the atomoxetine treatment group developed a statistically significant mean increase in diastolic blood pressure (+2.1mm Hg) compared with the placebo control group. As compared with placebo, a greater percentage of atomoxetine patients had at least one diastolic and systolic blood pressure measurement above the 95th percentile of the National Institutes of Health values[13] but these differences did not

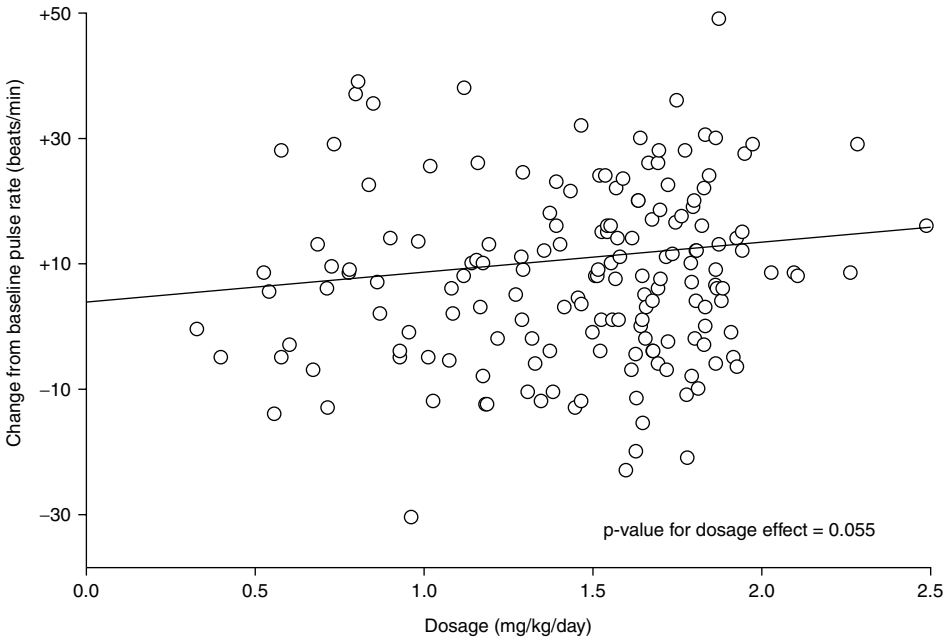

Fig. 2. Change from baseline to final pulse rate versus prescribed dosage in children and adolescents with attention-deficit/hyperactivity disorder treated with atomoxetine for at least 1 year (n = 169). The line was generated by least squares from a general linear model.

reach statistical significance. Mean diastolic blood pressure decreased by 1mm Hg (48% of the short-term phase increase) and systolic blood pressure decreased an average of 0.4mm Hg (14% of the short-term phase increase) within 1 week of atomoxetine discontinuation. This observation was similar to that seen in adult studies and indicated that reversal of drug-related blood pressure increases lagged behind reversal of pulse increases.

Long-term effects of atomoxetine on systolic and diastolic blood pressure for children and adolescents treated with atomoxetine for at least one year are shown in figure 3. In the child/adolescent population, increases of mean diastolic and systolic blood pressure were observed over the first few months as the dosage was increased and then tended to stabilise. Mean increases were small and not clinically significant. Further long-term exposure data are needed to determine if mean systolic blood pressure values stabilise.

The relationship of systolic and diastolic blood pressure to atomoxetine dosage in children and adolescents receiving at least one dose of drug is illustrated in figure 4 and figure 5. Blood pressure did not increase with increasing dosages of atomoxetine. In fact, systolic blood pressures often decreased with dosage. The pattern of scatter in the data sug-

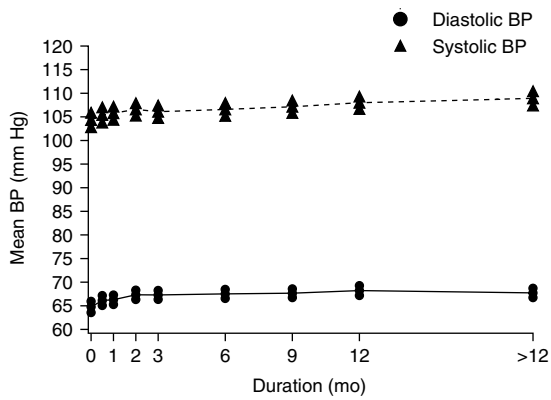

Fig. 3. Mean change (± 2 standard errors of the mean) in systolic and diastolic blood pressure (BP) over time in child/adolescent patients with attention-deficit/hyperactivity disorder treated with atomoxetine for at least 1 year (n = 169) [>12 month group had an average duration of treatment of 20 months].

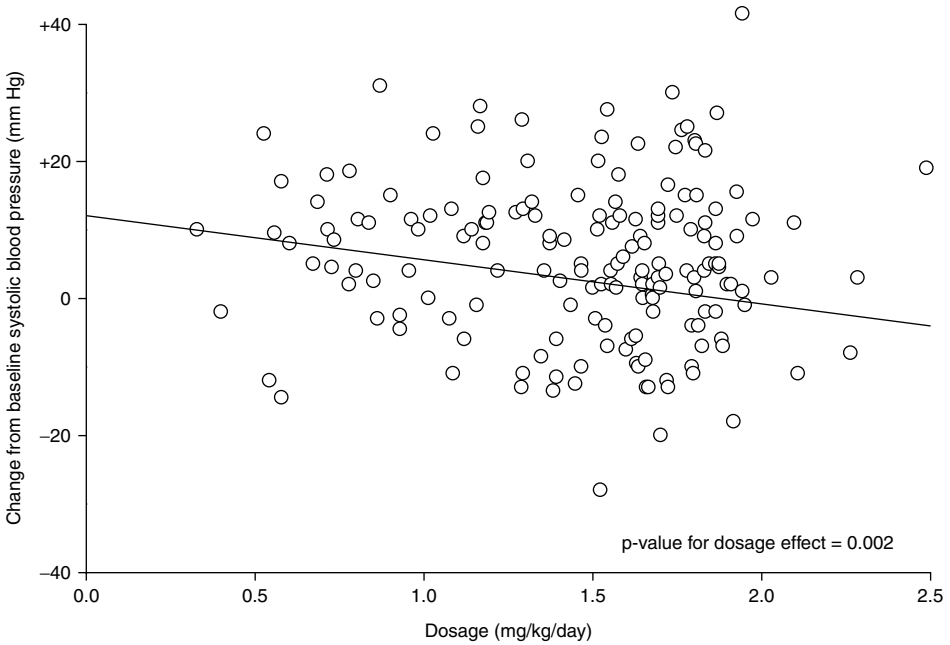

Fig. 4. Changes from baseline to final systolic blood pressure versus dosage in child/adolescent patients with attention deficit/hyperactivity disorder treated with atomoxetine for at least 1 year (n = 169). The line was generated by least squares from a general linear model.

gests that such observations have no clinical significance, and dosage cannot be used to predict changes in blood pressure for individual patients treated with atomoxetine.

QT Interval

The purpose of correcting the QT interval is to compensate for heart rate. While there is no universally accepted method for QT correction, the methods of Bazett, and to a lesser extent that of Fridericia, are most commonly used to correct the QT interval for heart rate effects. Other correction methods have been proposed, but none are entirely satisfactory.[15] With the Bazett formula, the QT interval is divided by the square root of the RR interval. This method overcorrects for heart rate effects, thereby erroneously suggesting a prolongation of the QTc interval. The method of Fridericia, in which the QT interval is divided by the cube root of the RR interval, is more appropriate for drugs associated with heart rate increases. However, the Fridericia method appears to slightly under-correct for heart rate effects, and could mask a true QT prolongation. Although no optimum method of QT correction exists, the best approach appears to be application of a factor based on the patient population being studied.

In this report, QT intervals were corrected for heart rate by data-specific factors. Baseline data were used to determine the optimal correction factor, which yielded the formula (equation 1):

$$QTcD = QT / RR^{0.39}$$

for children and adolescents. The best exponent for the RR interval in the denominator was found to be 0.4 for adults. Since correction factors based on the method of Bazett (exponent of 0.5) and Fridericia (exponent of 0.33) are in common use and usually reported by ECG machines, QTc determined by these methods are also reported here. These values are shown only for comparative purposes, and should not be considered as indicative of true QT changes. Categorical changes (increases of at least 30, 60, or to at least 500 msec) are those

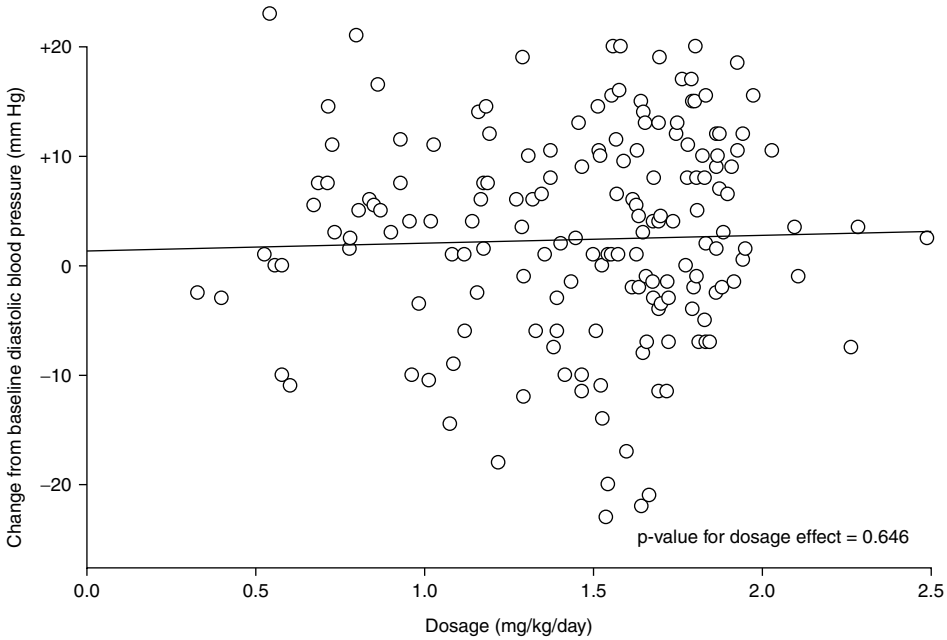

Fig. 5. Changes from baseline to final diastolic blood pressure versus dosage in child/adolescent patients treated with atomoxetine for at least 1 year (n = 169). The line was generated by least squares from a general linear model.

proposed by the European CPMP. Table IV contains only patients for whom baseline and treatment data are available.

Treatment with atomoxetine was not associated with QT prolongation by any commonly accepted criteria, as assessed by baseline to endpoint changes or categorical increases. Apparent increases revealed by application of the Bazett correction are an artefact related to inadequate correction for heart rate, since the appropriate correction factor based on baseline data did not reveal a change in QTc.

Figure 6 illustrates the relationship of change in QTcD from baseline to endpoint as a function of total daily atomoxetine dose for children and adolescents treated with atomoxetine for at least 1 year (n = 169). There is no evidence of an increase in QTc with increasing dosage of atomoxetine as indicated by the lack of a dose effect (p = 0.792).

Adverse Event Reports and Discontinuation

In the short-term studies, no paediatric patient discontinued treatment due to a cardiovascular adverse event, and four adult patients treated with atomoxetine were discontinued because of cardiovascular events (two for palpitation, one for hypertension, one for hypotension).

Adverse events attributable to the cardiovascular system are shown in table V. No cardiovascular adverse event was reported statistically significantly ($p < 0.05$) more often by atomoxetine patients than by placebo-treated patients for the child and adolescent population. A significant difference between atomoxetine and placebo-treated patients was only detected for palpitation (3.7% vs 0.8%, $p = 0.037$) in the adult study population. These were subjective reports of palpitations experienced since the last weekly visit. Since Holter monitoring was not part of these studies, the cardiac electrophysiology associated with these events is not known. It is interesting to note that palpitations were not reported in the

Table IV. Baseline and changes in corrected QT (QTc) intervals: short-term treatment

Characteristics	Children/adolescents			Adults		
	atomoxetine (n = 325)[a]	placebo (n = 202)[a]	p-value[b]	atomoxetine (n = 257)[a]	placebo (n = 257)[a]	p-value[b]
QTcD						
Baseline mean (SD)	406 (15.9)	407 (15.8)		410 (17.8)	409 (15.9)	
Mean change at endpoint (SD)	−3.1 (16.9)	−4.4 (18.7)	0.578	+0.6 (15.3)	+0.8 (14.2)	0.913
Increase ≥30 msec [no. (%)]	7 (2.2)	9 (4.5)	0.190	6 (2.3)	9 (3.5)	0.602
Increase ≥60 msec [no. (%)]	0	0	NA	0	0	NA
Increase ≥500 msec [no. (%)]	0	0	NA	0	0	NA
QTcB						
Baseline mean (SD)	417 (18.2)	418 (18.2)		414 (19.3)	413 (16.9)	
Mean change at endpoint (SD)	+1.5 (19.8)	−4.5 (22.8)	0.004	+5.7 (17.1)	+0.6 (16.0)	<0.001
Increase ≥30 msec [no. (%)]	20 (6.2)	15 (7.4)	0.592	16 (6.2)	12 (4.7)	0.561
Increase ≥60 msec [no. (%)]	1 (0.3)	2 (1.0)	0.562	0	0	NA
Increase ≥500 msec [no. (%)]	0	0	NA	0	0	NA
QTcF						
Baseline mean (SD)	400 (16.0)	401 (15.7)		407 (17.9)	406 (16.8)	
Mean change at endpoint (SD)	−5.3 (16.5)	−4.4 (17.4)	0.369	−2.7 (15.2)	+0.9 (14.4)	0.008
Increase ≥30 msec [no. (%)]	6 (1.8)	5 (2.5)	0.756	3 (1.2)	7 (2.7)	0.339
Increase ≥60 msec [no. (%)]	0	0	NA	0	0	NA
Increase ≥500 msec [no. (%)]	0	0	NA	0	0	NA

a Patient number per treatment group are lower than the totals because baseline and treatment data were not available for all patients.

b p-Values for mean changes were determined by analysis of variance, or by Fisher's Exact test for categorical changes.

NA = not applicable; **QTcB** = QT interval corrected using the Bazett formula; **QTcD** = QT interval corrected using derived data; **QTcF** = QT interval corrected using the Fridericia formula.

younger population. If these subjective experiences occurred, children and adolescents did not consider them bothersome enough to report as an adverse event.

Conclusions

Atomoxetine is associated with a mild but persistent increase in heart rate and blood pressure. In the short term, these increases were well tolerated, but the impact of long-term effects is not known, and risks in patients with hypertension or other forms of cardiovascular disease may be different. These effects tend to be sustained for the duration of therapy, but subside once atomoxetine is discontinued. Since the discontinuation phases of the studies were fairly brief (1 week in children/adolescents, and 4 weeks in adults), it is not known how long it would take for blood pressure and pulse to return to baseline. There is no evidence of a rebound effect, and none was expected. These vital sign changes were well tolerated as assessed by the low rate of discontinuation of atomoxetine treatment due to adverse cardiovascular events. Long-term consequences of mild elevations in heart rate and blood pressure are unknown and must be weighed against the known benefits of treating ADHD.

At clinically relevant doses, atomoxetine has no effect on cardiac repolarisation, as measured by the QTc interval. An apparent prolongation suggested by application of the Bazett correction method was found to be an artefact. When a correction factor based on pre-treatment data from the subject population was applied, no evidence for QTc prolongation was found.

Data suggest that atomoxetine is virtually devoid of cardiovascular toxicity during short-term treatment in all patient populations and during long-term treatment in the child/adolescent population. Long-term treatment studies in adults with ADHD are underway, and no conclusions can be made regard-

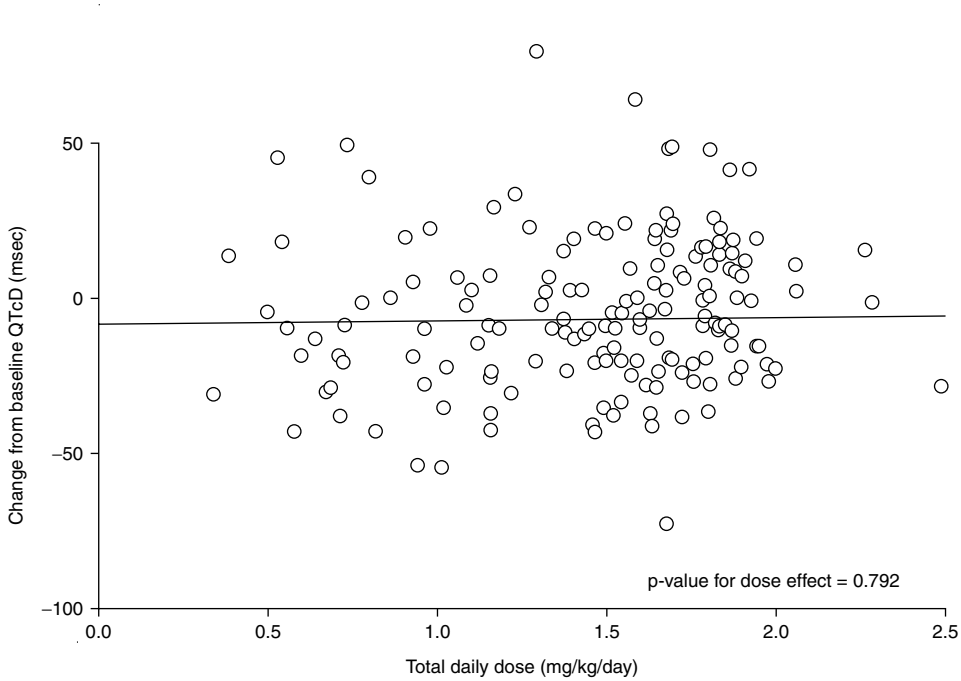

Fig. 6. Changes from baseline to final data-derived corrected QT interval (QTcD) versus prescribed dosage in child/adolescent patients with attention-deficit/hyperactivity disorder treated with atomoxetine for at least 1 year (n = 169). The line was generated by least squares from a general linear model.

ing cardiovascular effects with long-term treatment in adult patients. Interpretation of the long-term data in the child/adolescent population may be somewhat limited by the sample size but these initial results are encouraging and provide information out to 78 weeks of treatment. Additional studies of the long-term safety of atomoxetine are ongoing in the child/adolescent population as well and should provide additional information on long-term cardiovascular effects.

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Table V. Number of patients with treatment-emergent cardiovascular adverse events (%)

Event	Children/adolescents			Adults		
	atomoxetine (n = 340)[a]	placebo (n = 207)[a]	p-value[b]	atomoxetine (n = 269)[a]	placebo (n = 263)[a]	p-value[b]
Palpitations	1 (0.3)	0	1.00	10 (3.7)	2 (0.8)	0.037
Tachycardia	3 (0.9)	0	0.293	4 (1.5)	2 (0.8)	0.686
Cardiac murmur	2 (0.6)	0	0.529	0	0	NA
Extrasystoles	0	0	NA	1 (0.4)	1 (0.4)	1.00
Sinus tachycardia	2 (0.6)	0	0.529	1 (0.4)	0	1.00
Ventricular extrasystole	1 (0.3)	0	1.00	0	0	NA
Atrial hypertrophy	0	0	NA	0	1 (0.4)	0.494
Sinus bradycardia	0	0	NA	0	1 (0.4)	0.494

a Patient number per treatment group are lower than the totals because baseline and treatment data were not available for all patients.

b p-Values for comparing atomoxetine with placebo are based on Fisher's exact test.

NA = not applicable.

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