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An Evaluation of the Cardiovascular Safety Profile of Duloxetine

Findings from 42 Placebo-Controlled Studies

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Abstract

Background and objective: In recent years, new classes of medication, such as the serotonin-noradrenaline reuptake inhibitors (SNRIs), have been developed for use in the treatment of major depressive disorder (MDD). For many years, treatment options were largely limited to the use of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). However, there have been published reports of orthostatic hypotension, arrhythmias and corrected QT (QTc) interval changes in patients treated with TCAs. As new medications become available, it is important to understand how their cardiovascular safety profile compares with that of more established agents to aid clinicians and patients in choosing the best treatment options. This study was designed to evaluate the cardiovascular safety profile of the SNRI duloxetine through evaluation of cardiovascular-related parameters and adverse events (AEs).

Methods: The cardiovascular safety of duloxetine was assessed using all placebo-controlled duloxetine clinical trial data as of December 2005. This consisted of data from 42 placebo-controlled clinical trials of 8504 patients who were treated with duloxetine. Additional information from a high-dose clinical pharmacology study and postmarketing safety surveillance are also presented. Of the placebo-controlled trials included in this analysis, clinical indications under investigation included MDD (15 studies), diabetic peripheral neuropathic pain (3 studies), fibromyalgia (2 studies), generalised anxiety disorder (3 studies) and lower urinary tract disorders (19 studies, all related to incontinence). Cardiovascular safety was evaluated based on vital signs, ECGs and the incidence of treatment-emergent AEs potentially related to cardiovascular safety. These safety parameters were analysed across all indications. To identify both serious and non-serious cardiovascular-related AEs, as well as AEs reported as the reason for discontinuation, a comprehensive list of terms derived from the Medical Dictionary for Regulatory Activities (version 8.0) was generated and used to search the duloxetine databases for cardiovascular-related events.

Results: Calculation of change from baseline to maximum in ECG parameters showed significant differences between treatment groups for all parameters, with decreases from baseline in RR, QRS and QT intervals for patients receiving

duloxetine and increases from baseline for patients treated with placebo. These shifts were related to small heart rate changes, but the mean differences were not considered clinically relevant. Categorical analyses of shifts from normal to abnormal (or abnormal to normal) for heart rate and QT corrected for heart rate using Fridericia's formula (QTcF) values showed that most patients did not shift from their baseline category. Patients with MDD who were treated for up to 1 year with duloxetine had blood pressure changes early in treatment that then stabilised. Even in patients with elevated blood pressure at baseline in these clinical trials, no increased risk of sustained blood pressure elevation with duloxetine treatment was found.

Conclusion: Overall, the findings presented here support our conclusions that use of duloxetine does not appear to be associated with significant cardiovascular risks in patients with conditions for which the drug has been approved or studied.

Background

Options for the pharmacological treatment of major depressive disorder (MDD) in the past have been largely limited to the use of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). There are published reports of arrhythmias, orthostatic hypotension and corrected QT (QTc) interval changes in patients treated with TCAs and SSRIs, as well as hypertensive crisis and hypotension in patients treated with MAOIs; however, TCAs appear to be associated with more frequent reports of these effects than SSRIs.[1-3] Newer medications have recently appeared as alternatives to these traditional treatments, including serotonin-noradrenaline reuptake inhibitors (SNRIs) such as duloxetine. The purpose of this review is to describe data relevant to the cardiovascular effects of duloxetine.

Duloxetine is an SNRI with clinically proven efficacy in the treatment of MDD,[4-7] the management of diabetic peripheral neuropathic pain (DPNP)[8-10] and the treatment of incontinence in women.[11-13] Furthermore, duloxetine is being studied for other indications, including generalised anxiety disorder and fibromyalgia. The cardiovascular effects of duloxetine have been evaluated in preclinical and clinical trials over the past decade. *In vitro* studies of human atrial myocytes showed that duloxetine has no adverse effect on any of the human cardiac ion channels tested, including cardiac sodium current, transient outward potassium current, sustained current, inwardly-rectifying potassium current or human ether-a-go-go related gene (hERG), which predicts prolongation of the QT interval.[14] Repeat-dose evaluation of duloxetine in conscious rodent and canine models showed no significant alterations in blood pressure or heart rate.[15] Canine cardiac rhythm, conduction and heart rate were also unaffected after 1 year of treatment with duloxetine 3, 10 or 30 mg/kg/day.[16]

In this review, we present the cardiovascular findings from an extensive set of placebo-controlled studies of duloxetine; in these studies, data were collected from >8500 patients treated with duloxetine and >6100 patients treated with placebo. The findings from an additional study of healthy volunteers performed to evaluate the cardiovascular effects of high-dose duloxetine (up to 200mg twice daily, compared with the usual recommended therapeutic dose of 60mg once daily) are also discussed.[17,18] We also present findings from a 52-week open-label study in MDD[19] and the extension phases from three studies in DPNP.[8,20,21] Relevant findings from spontaneously reported adverse event (AE) reports are also included.

Table I. Summary of the 42 randomised, double-blind, placebo-controlled studies evaluated in the analyses

Study identifier	Phase	Duloxetine [n (dosage; mg/day)]	Placebo (n)	Treatment duration (weeks)	Primary disclosure
Major depressive disorder					
HMAG	Ib/II	53 (10–30)	52	10	Unpublished
HMAH	II	89 (20–30)	88	10	Unpublished
HMAI	II	390 (5, 10, 20)	126	8	Unpublished
HMAQ (a)	II	70 (40–80)	70	8	Goldstein et al.,[7] 2002
HMAQ (b)	II	82 (40–80)	75	8	Nemeroff et al.,[22] 2002
HMAT (a)	III	175 (40, 80)	90	8	Nemeroff et al.,[22] 2002
HMAT (b)	III	177 (40, 80)	89	8	Goldstein et al.,[6] 2004
HMAY (a)	III	188 (80, 120)	93	8	Detke et al.,[23] 2004
HMAY (b)	III	196 (80, 120)	99	8	Perahia et al.,[24] 2006
HMBH (a)	III	123 (60)	122	9	Detke et al.,[4] 2002
HMBH (b)	III	128 (60)	139	9	Detke et al.,[5] 2002
HMBV	IV	207 (60)	104	8	Raskin et al.,[25] in press
HMCB	IIIb	141 (60)	141	7	Brannan et al.,[26] 2005
HMCR	IIIb	273 (60–120)	137	8	Nierenberg et al.,[27] 2007
HQAC	II	35 (60, 120)	35	4	Mundt et al.,[28] 2007
Diabetic peripheral neuropathic pain					
HMAV (a)	III	226 (60–120)	108	12	Wernicke et al.,[29] 2006
HMAV (b)	III	232 (60, 120)	116	12	Raskin et al.,[9] 2005
HMAW	II	342 (20, 60, 120)	115	12	Goldstein et al.,[10] 2005
Generalised anxiety disorder					
HMBR	III	338 (60, 120)	175	9	Koponen et al.,[30] in press
HMDT	III	168 (60, 120)	159	10	Rynn et al.,[31] in press
HMDU	III	162 (60–120)	161	10	Hartford et al.,[32] in press
Fibromyalgia					
HMBO	II	104 (120)	103	12	Arnold et al.,[33] 2004
HMCA	III	234 (60, 120)	120	12	Arnold et al.,[34] 2005
Lower urinary tract disorder[a]					
SAAA	II	55 (20)	37	3	Unpublished
SAAB	II	221 (20, 30, 40)	67	6	Unpublished
SAAH	II	16 (40)	16	1	Unpublished
SAAI	II	47 (30, 40)	44	8	Unpublished

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Table I. Contd

Study identifier	Phase	Duloxetine [n (dosage; mg/day)]	Placebo (n)	Treatment duration (weeks)	Primary disclosure
SAAL	II	34 (30, 40)	16	9	Unpublished
SAAW	II	415 (20, 40, 80)	138	12	Norton et al.,[11] 2002
SBAB	II	34 (80)	31	4	Unpublished
SBAF	II	104 (80)	97	12	Ghoniem et al.,[35] 2005
SBAM	II	55 (80–120)	54	8	Cardozo et al.,[36] 2004
SBAT	III	247 (80)	247	12	Van Kerrebroeck et al.,[12] 2004
SBAV	III	344 (80)	339	12	Dmochowski et al.,[37] 2003
SBAX	III	227 (80)	231	12	Millard et al.[13] 2004
SBBA	III	224 (80)	227	36	Kinchen et al.,[38] 2005
SBBL	II	153 (80–120)	153	12	Unpublished
SBBO	IIIb	300 (80)	288	8	Unpublished
SBBR	IIIb	396 (80)	120	8	Castro-Diaz et al.,[39] in press
SBBT	III	60 (80)	61	8	Unpublished
SBBU	III	61 (80)	60	8	Mah et al.,[40] 2006
SBCC	IIIb	1378 (80)	1380	6	Unpublished

a 'Lower urinary tract disorder' includes studies in urinary incontinence, stress urinary incontinence, genuine stress incontinence and mixed urinary incontinence.

Methods

Patient Population

The cardiovascular safety of duloxetine was assessed using all placebo-controlled, randomised duloxetine clinical trial data available as of December 2005 (table I). To obtain these data, the PubMed database was searched using the terms 'duloxetine' and 'placebo' and 'randomised' and 'double-blind'. As of that time, 14 627 patients had participated in 42 placebo-controlled duloxetine studies, of which 6123 patients had been treated with placebo and 8504 were exposed to duloxetine. Of the 42 placebo-controlled trials included in this analysis, clinical indications under investigation included MDD (15 studies), DPNP (3 studies), fibromyalgia (2 studies), generalised anxiety disorder (3 studies) and lower urinary tract disorders (19 studies, all related to incontinence). The placebo-controlled duration of these studies ranged from 4 to 12 weeks.

No investigator-initiated or ongoing independent trials were included. We do not know of any studies, not sponsored by Eli Lilly and Company, that have been published that include cardiovascular data for patients treated with duloxetine. Studies lacking a placebo arm were not included in the pooled 42 studies but are discussed herein and include the high-dose study,[17,18] an open-label study in MDD[19] and three DPNP studies with uncontrolled long-term extension phases of the three placebo-controlled DPNP studies.[8,20,21]

In the supratherapeutic study[17,18] including healthy volunteers, subjects were randomised to receive duloxetine in escalating doses of 60mg twice daily, 160mg twice daily and 200mg twice daily, with each dose given for 4 days before being uptitrated to the next level, or placebo. Moxifloxacin, a fluoroquinolone antibacterial known to prolong the QTc interval, was selected as a positive control to demonstrate assay sensitivity.

AE data, derived from spontaneous reports, the literature and regulatory bodies, were evaluated to identify signals suggestive of adverse drug reactions of duloxetine.

Evaluated Data

Cardiovascular safety was evaluated based on vital signs, ECG findings, and incidences of treatment-emergent AEs potentially related to cardiovascular safety. To reduce variability in ECG data collection and analysis in these studies, all ECGs were evaluated by central facilities using calibrated machines. These safety parameters were analysed across all indications and by demographic subgroups including age (<65 years or ≥65 years). To identify both serious and non-serious cardiovascular-related AEs, as well as AEs reported as a reason for discontinuation, a comprehensive list of terms derived from the Medical Dictionary for Regulatory Activities (MedDRA®, version 8.0) was generated and used to search the duloxetine databases for cardiovascular-related events. Similar methods were used to determine potential QTc prolongation-related events.

Statistical Methods

The changes from baseline to both endpoint and maximum readings in vital signs and ECG measures were analysed using an ANOVA model that included main effects for therapy and study. Baseline was defined as the last non-missing value obtained during the pre-randomisation phase of each study; the endpoint was the last non-missing value in the treatment phase. Categorical data were analysed using the Cochran-Mantel-Haenszel test, controlling for study, or Fisher's exact test when cell sizes were very small. Statistical hypotheses were tested at a significance level of 0.05; treatment-by-subgroup interactions were tested at a significance level of 0.1.

Results

Patient Demographics and Drug Exposure

Table II presents the population demographics for the placebo-controlled trials included in this report. Overall, the majority of patients were female (82% of the duloxetine-treated group; 85% of the placebo-treated group), Caucasian (71% of the duloxetine group; 66% of the placebo group) and each treatment group's mean age was 51 years. The demographics were consistent with the general disease population for each indication under study. The duration of exposure to duloxetine by indication, as well as for all patients, is presented in table III.

Effects on ECG Parameters

Changes from baseline to endpoint in ECG parameters were noted, with heart rate increases being reflected in ECG interval (PR, RR, QRS and QT) decreases. There were significant differences between treatment groups for all parameters (table IV), but these findings were not considered clinically relevant by the Lilly clinical research physician and study team responsible for analysis and interpretation of safety data. Calculation of change from baseline to maximum in ECG parameters showed significant differences between treatment groups for all parameters, with decreases from baseline in RR, QRS and QT intervals for the patients receiving duloxetine and increases from baseline for patients treated with placebo. Again, these shifts were related to small heart rate changes (increased for duloxetine-treated patients and decreased for placebo-treated patients), but the mean differences were not considered clinically relevant by the Lilly study team. Demographic subgroup analyses showed that there was no increased risk in patients <65 years of age or in patients ≥65 years of age (table V).

Categorical analyses of shifts from lower category values to higher category values (or higher category values to lower category values) for heart rate and QT corrected for heart rate using Fridericia's formula (QTcF) values showed that most patients did not shift from their baseline category.[1] As expected, duloxetine-treated patients were more likely than their placebo-treated counterparts to demonstrate an increase in heart rate and a decrease in

1 Heart rate (bpm) categories were <50, ≥50 to ≤59, ≥60 to ≤79, ≥80 to ≤100, ≥101 to ≤120; QTcF (msec) categories were <390, ≥391 to ≤419, ≥420 to ≤449, ≥450 to ≤479, ≥480 to ≤500, >500.

Table II. Patient demographics by indication for the placebo-controlled studies

	Duloxetine	Placebo	p-Value[a]
Pooled population			
Number of patients	8504	6123	
Sex: male : female [n (%)]	1576 : 6928 (18.5 : 81.5)	935 : 5188 (15.3 : 84.7)	0.671
Race [n (%)]			0.001
African American	323 (3.8)	245 (4.0)	
Asian Pacific[b]	42 (0.5)	10 (0.2)	
Caucasian	6049 (71.1)	4032 (65.9)	
East Asian[c]	177 (2.1)	138 (2.3)	
Hispanic	437 (5.1)	270 (4.4)	
Native American	0 (0.0)	1 (<0.1)	
unknown	1476 (17.4)	1427 (23.3)	
Age (y); mean (SD) [range]	50.8 (13.5) [17.8–91.8]	50.8 (13.6) [18.0–91.9]	0.873
Major depressive disorder			
Number of patients	2327	1460	
Sex: male : female [n (%)]	819 : 1508 (35.2 : 64.8)	515 : 945 (35.3 : 64.7)	0.910
Race [n (%)]			0.139
African American	134 (5.8)	91 (6.2)	
Asian Pacific[b]	15 (0.6)	4 (0.3)	
Caucasian	1993 (85.6)	1244 (85.2)	
East Asian[c]	14 (0.6)	8 (0.5)	
Hispanic	134 (5.8)	103 (7.1)	
Native American	0 (0.0)	0 (0.0)	
unknown	37 (1.6)	10 (0.7)	
Age (y); mean (SD) [range]	44.6 (14.5) [17.8–89.7]	43.8 (14.7) [18.3–88.8]	0.734
Diabetic peripheral neuropathic pain			
Number of patients	800	339	
Sex: male : female [n (%)]	466 : 334 (58.3 : 41.8)	181 : 158 (53.4 : 46.6)	0.210
Race [n (%)]			0.381
African American	32 (4.0)	16 (4.7)	
Asian Pacific[b]	8 (1.0)	0 (0.0)	
Caucasian	670 (83.8)	291 (85.8)	
East Asian[c]	7 (0.9)	2 (0.6)	
Hispanic	76 (9.5)	29 (8.6)	
Native American	0 (0.0)	0 (0.0)	
unknown	7 (0.9)	1 (0.3)	
Age (y); mean (SD) [range]	59.8 (10.8) [20.4–88.8]	60.1 (10.3) [23.9–80.6]	0.589
Fibromyalgia			
Number of patients	338	223	
Sex: male : female [n (%)]	12 : 326 (3.6 : 96.4)	11 : 212 (4.9 : 95.1)	0.728
Race [n (%)]			0.865
African American	7 (2.1)	7 (3.1)	
Asian Pacific[b]	1 (0.3)	0 (0.0)	
Caucasian	302 (89.3)	195 (87.4)	

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Table II. Contd

	Duloxetine	Placebo	p-Value[a]
East Asian[c]	2 (0.6)	2 (0.9)	
Hispanic	24 (7.1)	16 (7.2)	
Native American	0 (0.0)	0 (0.0)	
unknown	2 (0.6)	3 (1.3)	
Age (y); mean (SD) [range]	49.8 (11.0) [19.1–79.6]	48.8 (11.5) [18.8–79.6]	0.380
Generalised anxiety disorder			
Number of patients	668	495	
Sex: male : female [n (%)]	230 : 438 (34.4 : 65.6)	180 : 315 (36.4 : 63.6)	0.695
Race [n (%)]			0.134
African American	56 (8.4)	47 (9.5)	
Asian Pacific[b]	9 (1.3)	2 (0.4)	
Caucasian	574 (85.9)	410 (82.8)	
East Asian[c]	7 (1.0)	3 (0.6)	
Hispanic	21 (3.1)	32 (6.5)	
Native American	0 (0.0)	1 (0.2)	
unknown	1 (0.1)	0 (0.0)	
Age (y); mean (SD) [range]	42.5 (13.3) [18.4–78.7]	42.4 (14.0) [18.0–83.5]	0.725
Lower urinary tract disorder			
Number of patients	4371	3606	
Sex: male : female [n (%)]	49 : 4322 (1.1 : 98.9)	48 : 3558 (1.3 : 98.7)	0.341
Race [n (%)]			0.013
African American	94 (2.2)	84 (2.3)	
Asian Pacific[b]	9 (0.2)	4 (0.1)	
Caucasian	2510 (57.4)	1892 (52.5)	
East Asian[c]	147 (3.4)	123 (3.4)	
Hispanic	182 (4.2)	90 (2.5)	
Native American	0 (0.0)	0 (0.0)	
unknown	1429 (32.7)	1413 (39.2)	
Age (y); mean (SD) [range]	54.0 (11.5) [18.6–91.9]	53.7 (11.5) [19.0–91.8]	0.894

a Frequencies were analysed using the Cochran-Mantel-Haenszel test for general association, controlling for study. Means were analysed using a type III sum of squares ANOVA.

b Asian Pacific includes: Australian, Cambodian, Fijian, Indonesian, New Zealander, New Guinean, Filipino descent, Samoan (Micronesian), Thai, Vietnamese.

c East Asian includes: Japanese, Cambodian, Chinese, Filipino descent, Guamanian, Hawaiian, Korean, Laotian, Malay, Melanesian descent (Pacific Islanders), Mongolian, Polynesian, Samoan, Thai, Vietnamese, Burmese, Indonesian.

QTcF. However, none of the reported changes were considered clinically relevant. One duloxetine-treated patient and two placebo-treated patients had changes in QTcF from ≤500 msec to >500 msec. The duloxetine-treated patient had a baseline QTcF value of 499 msec and a maximum post-baseline value of 514 msec. There was also one duloxetine-treated patient with QTcF values of >500 msec at both baseline (516 msec) and post-baseline (536 msec). In both of these patients, observed changes were well within variability expected within patients and there was no evidence that duloxetine was associated with QTcF increases to values >500 msec.

Effects on Vital Signs

Changes from baseline to endpoint in systolic blood pressure, diastolic blood pressure and pulse readings are presented in table VI. Minimal mean systolic and diastolic blood pressure increases were noted in duloxetine-treated patients (0.65mm Hg

Table III. Extent of drug exposure by indication for the placebo-controlled studies

	Duloxetine	Placebo
Pooled population		
Number of patients	8504	6123
Mean exposure (days ± SD)	61.47 ± 40.53	65.20 ± 43.69
Minimum-maximum exposure (days)	0–336	0–350
Patient-years	1430.92	1093.01
Duration of exposure; days [n (%)]		
≥7	8311 (97.7)	6088 (99.4)
≥14	7916 (93.1)	5962 (97.4)
≥28	7330 (86.2)	5629 (91.9)
≥42	6471 (76.1)	4920 (80.4)
≥56	4877 (57.3)	3476 (56.8)
Major depressive disorder		
Number of patients	2327	1460
Mean exposure (days ± SD)	49.60 ± 18.04	49.95 ± 17.06
Minimum-maximum exposure (days)	0–181	0–106
Patient-years	315.99	199.67
Duration of exposure; days [n (%)]		
≥7	2287 (98.3)	1449 (99.2)
≥14	2163 (93.0)	1399 (95.8)
≥28	1997 (85.8)	1260 (86.3)
≥42	1819 (78.2)	1117 (76.5)
≥56	1377 (59.2)	822 (56.3)
Diabetic peripheral neuropathic pain		
Number of patients	800	339
Mean exposure (days ± SD)	76.68 ± 27.73	79.58 ± 23.66
Minimum-maximum exposure (days)	1–189	6–125
Patient-years	167.96	73.86
Duration of exposure; days [n (%)]		
≥7	787 (98.4)	338 (99.7)
≥14	736 (92.0)	327 (96.5)
≥28	701 (87.6)	313 (92.3)
≥42	676 (84.5)	303 (89.4)
≥56	669 (83.6)	291 (85.8)
Fibromyalgia		
Number of patients	338	223
Mean exposure (days ± SD)	64.85 ± 31.24	66.04 ± 26.99
Minimum-maximum exposure (days)	1–191	4–97
Patient-years	60.01	40.32
Duration of exposure; days [n (%)]		
≥7	328 (97.0)	220 (98.7)
≥14	301 (89.1)	209 (93.7)
≥28	269 (79.6)	196 (87.9)
≥42	248 (73.4)	172 (77.1)

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Table III. Contd

	Duloxetine	Placebo
≥56	236 (69.8)	159 (71.3)
Generalised anxiety disorder		
Number of patients	668	495
Mean exposure (days ± SD)	51.99 ± 24.12	57.71 ± 20.41
Minimum-maximum exposure (days)	0–98	0–116
Patient-years	95.09	78.21
Duration of exposure; days [n (%)]		
≥7	608 (91.0)	489 (98.8)
≥14	571 (85.5)	472 (95.4)
≥28	524 (78.4)	428 (86.5)
≥42	487 (72.9)	395 (79.8)
≥56	467 (69.9)	366 (73.9)
Lower urinary tract disorder		
Number of patients	4371	3606
Mean exposure (days ± SD)	66.19 ± 50.64	71.00 ± 53.05
Minimum-maximum exposure (days)	0–336	0–350
Patient-years	791.87	700.96
Duration of exposure; days [n (%)]		
≥7	4301 (98.4)	3592 (99.6)
≥14	4145 (94.8)	3555 (98.6)
≥28	3839 (87.8)	3432 (95.2)
≥42	3241 (74.1)	2933 (81.3)
≥56	2128 (48.7)	1838 (51.0)

and 0.88mm Hg, respectively). Analysis of changes from baseline to the maximum in vital sign readings showed significant differences between treatment groups for all parameters. All mean changes to maximum values were greater than the mean changes to endpoint values, pointing to the transient nature of blood pressure data.

Consideration of persistent changes allows for evaluation of long-term effects. Sustained elevated blood pressure in these studies was defined as diastolic blood pressure ≥90mm Hg and an increase from baseline of ≥10mm Hg for three consecutive visits or systolic blood pressure ≥140mm Hg and an increase from baseline in ≥10mm Hg for three consecutive visits (studies with less than three visits were excluded from this analysis). When these criteria were taken into consideration, no significant differences between duloxetine-treated and placebo-treated groups were detected, as shown in table VII. Within the time frame covered by these studies, there was no evidence that duloxetine was associated with an emergence of sustained elevations in blood pressure.

Patient age is often a consideration when evaluating the cardiovascular effects of drugs. Table V shows the effects on vital sign measurements following treatment with duloxetine for patients <65 and ≥65 years of age. Similar changes in vital sign measurements were observed between the two age groups.

To address the issue of elevated blood pressure and cardiovascular risk with long-term duloxetine treatment, two additional sets of study data were reviewed. These data were obtained from an open-label, long-term study in MDD[19] and from three controlled studies of patients with DPNP[8,20,21] treated with duloxetine for up to 1 year. Patients with MDD who were treated for up to 1 year with duloxetine had blood pressure changes early in treatment that then stabilised.[19] Data from patients in this study suggested that a slight elevation in blood pressure may develop after 9–12 months of treat-

Table IV. Change from baseline to endpoint and maximum readings in ECG parameters in placebo-controlled studies

Parameter	Treatment	n	Baseline	Change to endpoint		Change to maximum	
			mean (SD)	mean (SD)	p-Value[a]	mean (SD)	p-Value[a]
Heart rate	Duloxetine	2727	69.48 (11.28)	+3.20 (9.86)	<0.001	+4.05 (10.19)	<0.001
(bpm)	Placebo	1979	69.13 (11.08)	−0.67 (8.87)		−0.01 (8.93)	
ECG interval (msec)							
PR	Duloxetine	2698	158.68 (24.77)	−3.58 (13.21)	<0.001	−2.37 (13.44)	<0.001
	Placebo	1967	157.92 (25.63)	+0.15 (14.37)		+1.30 (13.85)	
RR	Duloxetine	2727	886.43 (144.54)	−39.60 (119.51)	<0.001	−30.99 (119.22)	<0.001
	Placebo	1979	890.39 (143.93)	+8.11 (111.36)		+17.06 (111.38)	
QRS	Duloxetine	2727	90.35 (13.91)	−0.73 (6.96)	<0.001	−0.05 (7.08)	<0.001
	Placebo	1979	89.82 (13.40)	+0.22 (7.16)		+0.83 (7.06)	
QT	Duloxetine	2727	394.55 (31.92)	−6.94 (25.26)	<0.001	−5.01 (25.33)	<0.001
	Placebo	1977	396.10 (30.62)	+1.86 (24.15)		+3.78 (24.12)	
QTcB	Duloxetine	2727	420.68 (22.58)	+2.01 (18.32)	<0.001	+3.59 (18.46)	<0.001
	Placebo	1977	421.41 (21.53)	−0.03 (17.51)		+1.39 (17.60)	
QTcF	Duloxetine	2727	411.72 (21.10)	−1.11 (16.45)	0.001	+0.26 (16.63)	<0.001
	Placebo	1977	412.74 (19.70)	+0.65 (16.06)		+1.93 (16.06)	

a Comparisons are based on an ANOVA model containing main effects for treatment and study.

bpm = beats per minute; **QTcB** = QT interval corrected for heart rate using Bazett's formula; **QTcF** = QT corrected for heart rate using Fridericia's formula.

ment, but this could not be confirmed because of the absence of an untreated control group. Furthermore, the diabetic population has a well known predisposition to hypertension.[41] This fact, along with the effect of duloxetine on blood pressure, warranted a review of the cardiovascular effects of duloxetine in the DPNP studies.[8,20,21] As opposed to the overall population, where an increase in mean blood pressure was detected, patients treated with duloxetine in the DPNP studies were found to show a mean decrease. Mean changes in systolic blood pressure were similar for placebo and duloxetine without clinically important differences. There was an approximately 2mm Hg difference in the change in mean diastolic blood pressure over time (statistically significant for placebo vs duloxetine), which was attributed to a mean 1.7mm Hg decrease in the placebo group from baseline to endpoint.

Even for patients with elevated blood pressure at baseline in these clinical trials, no increased risk of sustained blood pressure elevation was found. In both duloxetine- and placebo-treated patients with pre-existing hypertension, individuals with hypertension at baseline were more likely to have sustained elevations than were patients without this condition (2.0% of hypertensive duloxetine-treated patients vs 0.9% of normotensive duloxetine-treated patients; 1.9% of hypertensive placebo-treated patients vs 0.9% of normotensive placebo patients). Thus, although treatment with duloxetine does result in a slight elevation in blood pressure, there is no evidence to suggest that duloxetine-treated patients with pre-existing elevated blood pressure are more likely to sustain persistent elevations in their blood pressure compared with placebo patients.

Shifts from baseline states to minimum or maximum values were examined based on predefined categories.[2] Shifts to minimum values were considered here as evaluating the possibility of patients becoming hypotensive while taking duloxetine. Although not anticipated, this could be a paradoxical reaction in some patients. For systolic blood pressure and heart rate, most patient values remained in their baseline categories. For diastolic blood pres-

2 Diastolic pressure (mm Hg) categories were <50, ≥50 to ≤59, ≥60 to ≤69, ≥70 to ≤79, ≥80 to ≤89, ≥90 to ≤99, ≥100; systolic pressure (mm Hg) categories were <80, ≥80 to ≤99, ≥100 to ≤119, ≥120 to ≤139, ≥140 to ≤159, ≥160 to ≤179, ≥180

Table V. Effect of age on vital signs and the ECG in placebo-controlled studies

Parameter	Treatment	<65 years of age				≥65 years of age			
		n	baseline mean (SD)	endpoint mean (SD)	p-value[a]	n	baseline mean (SD)	endpoint mean (SD)	p-value[a]
Systolic BP (mm Hg)	Duloxetine	6875	122.93 (15.40)	+0.84 (13.00)	<0.001	1331	134.02 (15.91)	−0.34 (15.30)	0.630
	Placebo	5029	123.17 (15.36)	−0.57 (13.12)		957	133.82 (16.00)	−0.42 (15.24)	
Diastolic BP (mm Hg)	Duloxetine	6875	76.80 (9.59)	+0.90 (9.02)	<0.001	1331	76.99 (9.51)	+0.75 (9.69)	0.238
	Placebo	5029	76.80 (9.50)	−0.27 (8.81)		957	76.91 (9.07)	+0.29 (9.04)	
Heart rate (bpm)	Duloxetine	6866	73.74 (9.77)	+1.34 (10.04)	<0.001	1328	72.41 (9.75)	+1.67 (10.08)	<0.001
	Placebo	5026	73.44 (9.68)	−0.13 (9.59)		955	72.25 (9.42)	−0.30 (8.96)	
ECG interval (msec)									
PR	Duloxetine	2107	155.94 (21.98)	−3.79 (12.60)	<0.001	591	168.47 (30.93)	−2.83 (15.19)	0.003
	Placebo	1587	155.40 (23.39)	+0.15 (14.15)		380	168.43 (31.34)	+0.15 (15.30)	
RR	Duloxetine	2113	881.95 (143.80)	−41.41 (116.97)	<0.001	614	901.81 (146.13)	−33.37 (127.77)	<0.001
	Placebo	1590	884.92 (140.35)	+9.40 (109.67)		389	912.75 (155.95)	+2.82 (118.01)	
QRS	Duloxetine	2113	89.79 (11.67)	−0.57 (6.75)	<0.001	614	92.29 (19.66)	−1.29 (7.64)	0.061
	Placebo	1590	89.69 (12.15)	+0.36 (7.24)		389	90.34 (17.63)	−0.34 (6.77)	
QT	Duloxetine	2113	392.03 (30.80)	−6.76 (24.17)	<0.001	614	403.21 (34.12)	−7.57 (28.73)	<0.001
	Placebo	1590	393.95 (29.61)	+2.28 (23.81)		387	404.91 (33.05)	+0.14 (25.46)	
QTcB	Duloxetine	2113	419.11 (22.22)	+2.68 (18.43)	<0.001	614	426.10 (22.96)	−0.30 (17.73)	0.537
	Placebo	1590	420.37 (21.06)	+0.09 (17.60)		387	425.66 (22.89),	−0.50 (17.15)	
QTcF	Duloxetine	2113	409.83 (20.30)	−0.61 (16.14)	0.006	614	418.24 (22.48)	−2.81 (17.38)	0.055
	Placebo	1590	411.32 (19.09)	+0.88 (16.07)		387	418.54 (21.07)	−0.31 (16.01)	

a Comparisons are based on an ANOVA model containing main effects for therapy and study.

BP = blood pressure; **bpm** = beats per minute; **QTcB** = QT interval corrected for heart rate using Bazett's formula; **QTcF** = QT corrected for heart rate using Fridericia's formula.

Table VI. Change from baseline to endpoint and maximum values in vital sign readings

Treatment	n	Baseline	Change to endpoint		Change to maximum	
		mean (SD)	mean (SD)	p-value[a]	mean (SD)	p-value[a]
Systolic blood pressure (mm Hg)						
Duloxetine	8206	124.73 (16.02)	+0.65 (13.41)	<0.001	+6.87 (13.02)	<0.001
Placebo	5986	124.88 (15.95)	−0.55 (13.48)		+5.43 (13.13)	
Diastolic blood pressure (mm Hg)						
Duloxetine	8206	76.83 (9.58)	+0.88 (9.13)	<0.001	+4.98 (8.63)	<0.001
Placebo	5986	76.81 (9.43)	−0.18 (8.85)		+3.91 (8.53)	
Pulse (bpm)						
Duloxetine	8194	73.53 (9.78)	+1.39 (10.04)	<0.001	+6.11 (9.84)	<0.001
Placebo	5981	73.25 (9.65)	−0.16 (9.49)		+4.53 (9.53)	

a Comparisons are based on an ANOVA model containing main effects for treatment and study.

bpm = beats per minute.

sure, approximately the same number of duloxetine-treated patient values remained unchanged (42%) compared with those that shifted to a lower value (43%); however, similar changes were also seen for the placebo-treated patients (42% unchanged category values and 45% shifting to a lower category value). Shifts to maximum values were also considered here as evaluating the possibility of patients becoming hypertensive while taking duloxetine. Again, for systolic blood pressure, most patient values remained in their baseline categories. However, for diastolic blood pressure, slightly more duloxetine-treated patient values increased to a higher value (47%) compared with those that remained unchanged (42%). For placebo-treated patients, approximately the same number of patients remained unchanged (44%) as did those who shifted to a higher category value (43%). For heart rate, duloxetine- and placebo-treated patients had similar percentages of patients remaining within their category (59% and 64%, respectively) and shifting from a lower category value to a higher category value (35% and 29%, respectively).

Supratherapeutic Dosage Study

The additional study of supratherapeutic doses of duloxetine escalating from 60mg twice daily to 200mg twice daily in healthy volunteers showed that blood pressure elevation was associated with administration of supratherapeutic doses of duloxetine.[18] A total of 92 subjects completed the 160mg twice daily dosage period and 84 subjects completed the 200mg twice daily dosage period. Initiation of duloxetine at 60mg twice daily resulted in a mean 5–7mm Hg elevation in both systolic and diastolic blood pressures that subsequently remained stable over the remainder of the dose-escalation periods. During the stepwise-tapering period, mean supine

Table VII. Incidence of sustained elevations in blood pressure

Parameter	Duloxetine		Placebo		p-Value[a]
	N	n (%)	N	n (%)	
Sustained elevation in blood pressure[b]	6345	72 (1.1)	4091	42 (1.0)	0.631
Sustained elevation in systolic blood pressure[c]	6342	54 (0.9)	4090	32 (0.8)	0.740
Sustained elevation in diastolic blood pressure[d]	6342	24 (0.4)	4090	15 (0.4)	1.00

a p-Value based on Fisher's exact test.

b Diastolic blood pressure ≥90mm Hg and an increase from baseline of ≥10mm Hg for three consecutive visits or systolic blood pressure ≥140mm Hg and an increase from baseline in ≥10mm Hg for three consecutive visits.

c Systolic blood pressure ≥140mm Hg and an increase from baseline in ≥10mm Hg for three consecutive visits.

d Diastolic blood pressure ≥90mm Hg and an increase from baseline of ≥10mm Hg for three consecutive visits.

N = total patients with a baseline and a post-baseline measurement; **n** = number of patients with sustained blood pressure.

Table VIII. Incidences of cardiovascular-related treatment-emergent adverse events occurring at statistically significantly different frequencies in the treatment groups

Event	Duloxetine (N = 8504) [n (%)]	Placebo (N = 6123) [n (%)]	Cochran-Mantel-Haenszel test p-value[a]	Fisher's exact test p-value[a]
Arrhythmias				
palpitations	126 (1.5)	58 (0.9)	0.008	0.004
tachycardia	48 (0.6)	16 (0.3)	0.010	0.007
atrioventricular block (1st degree)	3 (<0.1)	8 (0.1)	0.014	0.062
right bundle branch block	2 (<0.1)	4 (0.1)	0.038	0.244
Orthostatic hypotension	15 (0.2)	1 (<0.1)	0.010	0.004
Hypertension				
increased blood pressure	46 (0.5)	12 (0.2)	<0.001	<0.001
increased systolic blood pressure	5 (0.1)	0 (0.0)	0.035	0.079
Cardiac structural disease	7 (0.1)	11 (0.2)	0.033	0.149
Other cardiac conditions				
peripheral oedema	42 (0.5)	51 (0.8)	0.002	0.015
increased blood total cholesterol	10 (0.1)	1 (<0.1)	0.024	0.031
swelling (primarily in, but not confined to, the extremities)	1 (<0.1)	5 (0.1)	0.037	0.089
Other vascular conditions				
peripheral coldness	17 (0.2)	4 (0.1)	0.030	0.044
varicose veins	0 (0.0)	4 (0.1)	0.020	0.031

a Statistical significance between treatment groups was defined as $p \leq 0.05$.

blood pressure decreased and reached normal values within 1–2 days of discontinuation of the drug. Mean supine heart rate also increased after administration of duloxetine 60mg twice daily and exhibited a continued, dose-dependent increase, reaching 10–12 beats per minute above baseline at the end of the 200mg twice daily dosage period. Heart rate also returned to normal within 1–2 days of discontinuation of duloxetine.

In this study, ECG measurements were collected at five time points to provide QTcF intervals for comparison with time-matched QTcF intervals obtained during the placebo and duloxetine treatment periods.[18] Compared with placebo, the mean change in QTcF interval decreased at each time point with duloxetine 200mg twice daily. The upper limit of the two-sided 90% CI was <10 msec at each time point, indicating no clinically relevant increase in QTcF interval following duloxetine 200mg twice daily compared with placebo. No individual QTcF exceeded 470 msec with either duloxetine or placebo treatment and only two subjects receiving duloxetine had categorical QTcF increases >30 msec at either 160mg twice daily or 200mg twice daily dosages, compared with six subjects receiving placebo. No subject had a maximum QTcF interval >450 msec based on the average of replicate QTcF values after 4 days of duloxetine 200mg twice daily. There was no evidence that duloxetine treatment adversely affected ventricular repolarisation as assessed by mean changes or outliers in the QT interval corrected for heart rate using Fridericia's formula. There was no discernible concentration effect of duloxetine with regard to QTcF and there was no increase from baseline in QTcF with increasing duloxetine concentration.

Treatment-Emergent Adverse Events

In addition to consideration of ECGs and vital signs data, AEs were evaluated. Events were classified by general cardiovascular-related categories, and those incidents occurring at statistically significantly different frequencies between the duloxetine-treated and placebo-treated groups are shown in table VIII. Treatment-emergent AEs reported in the duloxetine-treated group at a statistically signifi-

cantly higher rate compared with placebo were palpitations, tachycardia, orthostatic hypotension, increased blood pressure, increased blood total cholesterol and peripheral coldness. Patients taking placebo reported atrioventricular block (1st degree), swelling (primarily in, but not confined only to, the extremities), peripheral oedema and varicose veins more often than patients receiving duloxetine; statistically significant increases versus duloxetine treatment were noted for peripheral oedema and varicose veins. It should be noted that reports of peripheral oedema were thought by the study investigators to be possibly not cardiovascular-related.

Cardiovascular-related AEs reported as the reason for discontinuation from study participation were statistically significantly different for tachycardia (four duloxetine-treated vs no placebo-treated patients; p = 0.044) and peripheral oedema (no duloxetine-treated vs three placebo-treated patients; p = 0.041). There were no significant differences between patients receiving duloxetine and those receiving placebo in the occurrence of QT prolongation-related treatment-emergent AEs, as shown in table IX. Cardiovascular-related serious AEs were uncommon (0.3% [18/6123] in the placebo-treated group and 0.2% [21/8504] in the duloxetine-treated group), with no significant differences between the groups.

The proportion of patients reporting at least one treatment-emergent cardiovascular-related AE by age group was 6.9% and 5.8% for duloxetine and placebo, respectively, among patients <65 years of age and 7.6% and 8.2%, respectively, among patients ≥65 years of age. However, there were no significant differences between treatment groups in the older subgroup. Among patients <65 years of age, significantly more patients in the duloxetine group reported palpitations (1.7% vs 1.0% with placebo, p = 0.002), tachycardia (0.6% vs 0.2% with placebo, p = 0.002) and increased blood pressure (0.5% vs 0.2% with placebo, p = 0.004). Significantly more placebo-treated patients (0.8%) reported peripheral oedema compared with duloxetine-treated patients (0.4%, p = 0.019). No significant differences were noted between treatment groups with respect to cardiovascular AEs leading to discontinuation of study drug or cardiovascular-related deaths or serious AEs within either age group.

Discussion

The cardiovascular profile of duloxetine has been previously investigated in eight clinical studies conducted as part of the clinical development plan for duloxetine in trials of MDD.[14] The analysis reported here includes data from >8500 patients treated with duloxetine and >6100 patients treated with placebo in studies of depression, DPNP and other indications. In these studies, the incidence of treatment-emergent abnormal ECGs in patients taking duloxetine at 40 mg/day, 80 mg/day or 120 mg/day did not differ significantly from that in patients taking placebo. Although duloxetine treatment can result in small changes in blood pressure, few patients receiving this drug developed clinically relevant high blood pressure. The possibility of sustained elevation in blood pressure was found to be very slight, with both the placebo-treated and duloxetine-treated patients presenting with similar incidences of this adverse event during study participation. In the clinical setting, such changes in diastolic

Table IX. Incidence of potential QT prolongation-related treatment-emergent adverse events

Event	Duloxetine (N = 8504) [n (%)]	Placebo (N = 6123) [n (%)]	p-Value[a]
Syncope	15 (0.2)	11 (0.2)	1.000
Vasovagal syncope	3 (<0.1)	0 (0.0)	0.270
Prolonged QTc interval	1 (<0.1)	1 (<0.1)	1.000
Prolonged QT interval	2 (<0.1)	0 (0.0)	0.513
Loss of consciousness	1 (<0.1)	1 (<0.1)	1.000

a p-Value based on Fisher's exact test.

QTc = corrected QT interval.

blood pressure would be clinically unremarkable. Furthermore, in contrast to findings reported for other treatments for depression,[42-48] patients with pre-existing hypertension included in the placebo-controlled trials discussed in this analysis showed no increased risk of sustained elevations in blood pressure with duloxetine treatment.

Since US FDA approval of the drug, duloxetine has been used by >3 million patients. Rare reports of 'hypertensive crisis' in patients taking duloxetine have been received by the manufacturer and many of these have been in patients with known hypertension. Duloxetine produces a modest mean increase in blood pressure, but clinical trial data do not indicate that underlying hypertension is exacerbated by this drug. Nevertheless, because of the known adrenergic pharmacology and the fact that isolated cases of severe blood pressure elevation have been reported, the term 'hypertensive crisis' has been added to the section of the duloxetine package insert, which deals with postmarketing event reports.

The cardiovascular effects of other antidepressants have been well documented. TCAs have been studied in the depressed population without concomitant cardiovascular disease[49-52] and in those with pre-existing cardiac conditions.[42,43] The most common cardiovascular effects of TCAs include orthostatic hypotension and slowing of intraventricular conduction, as identified by prolonged PR, QRS and QT intervals during a standard ECG, or by sudden death as a result of torsade de pointes.[44-47] The venous and arterial dilation associated with TCA treatment are due to the anticholinergic and adrenergic effects of these drugs.[42,43,49-51] Sodium channel blockade leads to QRS prolongation, potassium channel blockade leads to QT prolongation and the anticholinergic effects of these drugs also result in cardiac changes.

SSRIs have been found to produce mild bradycardia (observed during long-term treatment with fluoxetine, fluvoxamine or paroxetine)[43,48] and to reduce heart rate (with citalopram treatment).[53] This effect is in opposition to the tachycardia associated with TCAs. Citalopram treatment is associated with a nonspecific, clinically insignificant prolongation of QT interval, irrespective of patient age.[43] The citalopram single isomer, escitalopram, appears to have similar effects to those seen with citalopram treatment.[54] There have also been a number of case reports of dysrhythmia and syncope associated with fluoxetine, and a study of elderly patients with depression showed a significant risk of syncope and orthostatic hypotension associated with use of this drug.[55,56] Results of a study in rats dosed with fluoxetine suggested that a central action of the drug on the vasomotor centre may be responsible for the blood pressure decrease observed with this drug;[57] however, further investigation is needed to clarify the cause of this effect.

Antidepressants that inhibit reuptake of both noradrenaline and serotonin may be more effective than SSRIs.[58-61] A recently completed meta-analysis including a number of duloxetine studies showed superiority of duloxetine versus single reuptake inhibition.[62] Data comparing TCAs with fluoxetine, paroxetine and escitalopram and presented as a meta-analysis have shown that dual reuptake TCAs are superior to SSRIs.[63] Two other papers have shown advantages for clomipramine over paroxetine and citalopram.[64,65] Unfortunately, the latest Cochrane review of antidepressants[66] did not include duloxetine data and therefore was unable to address the superiority of duloxetine versus single reuptake inhibition. However, the finding that dual-action antidepressants might have increased efficacy is likely to be applicable to duloxetine. Indeed, meta-analytic data have shown that venlafaxine has proven superiority over SSRIs.[58]

However, venlafaxine has a dose-dependent effect on blood pressure, and a significant incidence of hypertension (>10%) has been reported with use of this drug in clinical trials when patients were treated with the maximum recommended therapeutic dose of 375 mg/day.[67] Treatment with reboxetine showed a tendency toward orthostatic changes in systolic blood pressure and related symptoms.[68,69] TCAs have been known to have antihistaminic and adrenergic effects that can lead to decreases in blood pressure and orthostatic collapse.[41] Duloxetine lacks any effect on α-adrenergic or histaminergic

receptors, and because it is highly protein-bound, a lower proportion of this drug is free in the periphery to exert effects on blood pressure.[70,71] Hypotension was of limited concern in the current analysis of placebo-controlled trial data, with <1% of duloxetine-treated patients experiencing orthostatic hypotension (vs 0.1% of placebo-treated patients).

Treatment-emergent cardiovascular AEs were also limited, with palpitations not associated with ECG changes being the only event reported for >1% of duloxetine-treated patients. Tachycardia, increased blood pressure, and hypotension were seen more frequently in duloxetine-treated patients, while peripheral oedema, swelling (primarily in, but not confined to, the extremities), and varicose veins were noted more often by patients treated with placebo. Cardiovascular-related serious AEs were uncommon in duloxetine-treated patients and were not significantly different in either number or type of event when compared with the placebo-treated study population.

Although SNRIs are similar in some ways and appear as a group to be more efficacious in the treatment of depression than SSRIs,[59] they do not necessarily share the same pharmacology or adverse effects. At therapeutically relevant doses, duloxetine displays both serotonin reuptake inhibition and noradrenaline reuptake inhibition; in contrast, venlafaxine affects both transmitter transporters only at higher doses.[70] Venlafaxine has been shown to be dual acting at higher doses (150–225 mg/day), and indirect evidence suggests that it selectively inhibits serotonin uptake at low doses.[72] The affinity of duloxetine for the serotonin uptake transporter has been found to be about nine times greater than for the noradrenaline uptake transporter, while venlafaxine is less potent at inhibiting both serotonin and noradrenaline reuptake.[70]However, not all pharmacological properties and adverse effects can be explained by the primary pharmacology of these drugs. The cardiac effects of venlafaxine are thought to be caused by binding of the drug to cardiac sodium channels,[73] whereas *in vitro* studies of the effects of duloxetine on human atrial myocytes showed no adverse effect on the cardiac ion channels tested.[74]

When evaluating the patients by age during treatment, no significant differences were noted between these groups for vital signs, ECG results or AE profiles. Thus, the concern frequently raised when planning treatment regimens for elderly patients – that they are more likely to have cardiovascular complaints that could be affected by addition of new drugs to their current treatment regimens – may be less of an issue when considering treating these patients with duloxetine than with many other drugs.

Concerns have also been raised in the past regarding QT prolongation.[43] When healthy volunteers were treated with duloxetine doses up to 200mg twice daily, ECG findings showed no drug effect on QT prolongation.[17] This dose results in a duloxetine plasma concentration that would be achieved in patients devoid of cytochrome P450 (CYP) 2D6 activity, either due to maximal enzyme inhibition or genotypic deficiency, and maximal CYP1A2 inhibition. Thus, QTc prolongations resulting from drug interactions based on inhibition of either CYP2D6 or CYP1A2 are not anticipated. It is important to note when reviewing table IV that measuring the QT interval using Bazett's formula for correction for heart rate (QTcB) is problematic when there are drug-related heart rate changes such as occur with duloxetine, because the results may incorrectly suggest that duloxetine is prolonging the QTc interval. In particular, QTcB overcorrects when heart rates increase; thus, Fridericia's correction (QTcF) is more accurate than Bazett's in patients with altered heart rates.[75] Findings from this large dataset show that the AEs typically associated with QT prolongation (syncope, vasovagal syncope, prolonged QTc interval, prolonged QT interval, or loss of consciousness) occurred in similar frequencies in both patients receiving placebo and those receiving duloxetine treatment. These data and the direct QTc measurements support the conclusion that duloxetine has no adverse effect on cardiac repolarisation.

This clinical trial data review is limited by use of only double-blind, placebo-controlled studies, which do not include patient populations representa-

tive of the typical clinic setting (i.e. a wide range of patients and treatment regimens). In most studies, patients with unstable cardiovascular disease or significant pre-existing ECG abnormalities were excluded; furthermore, as per the study protocols, patients with cardiovascular disease had to be stable and taking stable medications. The doses of duloxetine used in these trials, ranging from 10 mg/day to 120 mg/day, varied from indication to indication, with patients often being treated with flexible dosage regimens. Treatment durations were not typical of what would be seen in clinical practice as the effect of duloxetine was generally evaluated within a 4- to 12-week treatment window for patients with MDD, DPNP, generalised anxiety disorder or fibromyalgia. Comparative trials against other treatments for these conditions would be useful for further defining the cardiovascular effects of these products in similar patient populations. Additional information regarding concomitant medications and their possible combined cardiovascular effects would also be applicable in the clinical setting. In addition, the results could have been presented by indication; however, the cardiovascular data have been remarkably similar in other duloxetine studies presented by indication.

Conclusion

Overall, the findings presented in this review support the conclusion that duloxetine across a wide dose range is a cardiovascular-safe treatment option for patients with depression, diabetic neuropathic pain and other conditions, although the duration of treatment was generally no longer than 56 days and many patients will require treatment for longer periods. In contrast to many drugs used to treat conditions for which duloxetine is approved, the risk of serious cardiovascular-related adverse effects appears to be minimal with duloxetine.

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