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The cardiovascular safety profile of escitalopram

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Abstract
The cardiovascular effects of escitalopram were examined in a large group of participants in double-blind, randomized, placebo-controlled studies. Escitalopram (n=3298) was administered at doses between 5 and 20 mg/day. Patients were treated in acute (8–12 weeks) and long-term (24 weeks) studies. Assessment of cardiovascular safety included heart rate, blood pressure (BP), treatment-emergent adverse events (TEAEs) and electrocardiograms (ECGs). In the short-term, there was a small, but statistically significant 2 beats per minute decrease in heart rate with escitalopram compared with placebo. The difference compared to placebo in systolic or diastolic BP was not clinically or statistically significant. Valid ECG assessments at both baseline and last assessment were available for 2407 escitalopram patients and 1952 placebo patients. Escitalopram-placebo differences in mean changes in ECG values were not clinically meaningful. The mean difference to placebo in the corrected QT [Fridericia's (QTcF)] interval was 3.5 ms (all escitalopram doses); 1.3 ms (escitalopram 10 mg) and 1.7 ms (escitalopram 20 mg) (p=0.2836 for 10 versus 20 mg). One out of 2407 escitalopram patients had a QTcF interval >500 ms and a change from baseline >60 ms. The incidence and types of cardiac-associated adverse events were similar between patients treated for 8–12 weeks with placebo (2.2%) or escitalopram (1.9%) and for 24 weeks with placebo (2.7%) or escitalopram (2.3%). Analyses of data from long-term studies and studies of the elderly showed similar results. In conclusion, these data demonstrate that escitalopram, like other SSRIs, has a statistically significant effect on heart rate and no clinically meaningful effect on ECG values, BP, with a placebo-level incidence of cardiac-associated adverse events.

1. Introduction

Escitalopram oxalate [S-(+)-1-[3-(dimethylamino)propyl]-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile] is the therapeutically active enantiomer of the racemic

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antidepressant citalopram. Like other selective serotonin reuptake inhibitors (SSRIs) and the serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine, escitalopram has a high affinity for the primary binding site on the serotonin transporter protein. Escitalopram also binds to the allosteric site on serotonin transporter (Chen et al., 2005a, 2005b), which decreases the dissociation rate of escitalopram from the primary site and may have a stabilising, or self-potentiating, effect on the escitalopram-transporter complex. Such allosteric binding has led to escitalopram being described as an allosteric serotonin reuptake inhibitor (Sánchez, 2006; Ali and Lam, 2011).

The cardiovascular safety of antidepressants has been the subject of recent debate and, in particular, the prescribing information and recommended dosing for citalopram have been modified to address concerns about the risk of QTc prolongation (Beach et al., 2013; Vieweg et al., 2012). Therefore, the present analysis of patient-level data was undertaken to evaluate the effect of escitalopram on cardiovascular safety measures in more than 3000 patients from randomised, double-blind placebo-controlled clinical studies in major depressive disorder (MDD), social anxiety disorder (SAD), generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), and panic disorder (PD).

2. Experimental procedures

2.1. Patients

The individual patient data come from all randomised placebo-controlled studies sponsored by H. Lundbeck A/S or Forest Laboratories, Inc in which ECGs were performed at baseline and at last assessment. Escitalopram was dosed once daily using a fixed dose or flexible dose design to a maximum of 20 mg/day. Patients treated with 20 mg/day were administered 10 mg/day for the first week. All protocols were approved by institutional review boards/independent ethics committees at each study site in accordance with the principles of the Declaration of Helsinki, and all patients provided signed informed consent before study participation. For each of the studies, medically qualified personnel were responsible for ensuring that the treatment-emergent adverse events (TEAEs) were coded using the lowest level term (LLT).

A TEAE is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. TEAEs are presented by the preferred term corresponding to the LLT.

An integrated safety database included all clinical studies with a design allowing for pooling and comparison of safety data, which are the basis for the present analyses. A resting 12-lead electrocardiograms (ECG) was recorded at both baseline and at least at last assessment for 5 of the 6 short-term (8 weeks) placebo-controlled studies in major depressive disorder (MDD), for both of the elderly placebo-controlled MDD studies, and 6 of the 9 placebo-controlled studies of 'other indications' [generalised anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder (PD)] studies (Table 1).

2.2. Heart rate (ventricular rate)

A supine heart rate of >120 beats per minute (bpm) and an increase of ≥ 15 bpm from baseline was prospectively defined as a potentially clinically significant (PCS) high value. A supine heart rate of <50 bpm and a decrease of ≥ 15 bpm from baseline was prospectively defined to be a PCS low value. Sensitivity analyses were performed using >120 bpm and an increase of ≥ 10 bpm and <50 bpm and a decrease of ≥ 10 bpm from baseline.

2.3. Blood pressure (BP)

PCS limits were prospectively defined to be as follows: low supine systolic BP (≤ 90 and a decrease of ≤ 20 mmHg from baseline), high systolic BP (≥ 180 and an increase of ≥ 20 mmHg from baseline), low diastolic BP (≤ 50 and a decrease of ≥ 15 mmHg from baseline), and high diastolic BP (≥ 105 and an increase of ≥ 15 mmHg from baseline). In addition, sensitivity analyses were performed for high systolic BP using ≥ 160 and an increase of ≥ 10 mmHg from baseline and ≥ 150 and an increase of ≥ 10 mmHg from baseline.

2.4. ECG interval assessments

ECGs were obtained at baseline and at last assessment and quantitative assessments of RR, PR, QRS, and corrected QT [Fridericia's (QTcF)] intervals were performed by a central laboratory using the formula: $QTcF = QT/RR^{1/3}$. Limits for PCS values for QTcF intervals were prospectively defined as a post-baseline value >500 ms or an increase in QTcF >60 ms from baseline. Sensitivity analyses using QTcF values >480 and >450 ms were made, together with an increase in QTcF >30 ms from baseline.

2.5. Statistical analyses

All analyses of safety and tolerability were based on the all-patients-treated set (APTS or safety population), which comprised all patients who took at least one dose of escitalopram or placebo. For most analyses, all escitalopram dosage groups were pooled. Last assessment analyses used the last observation carried forward method (LOCF) while end of study used observed cases (OC). The change in heart rate, blood pressure, and ECG intervals from baseline to Week 8/10/12 in acute studies and to Weeks 8 and 24 in long-term studies was compared between escitalopram and placebo using a fixed-effects analysis of variance model with treatment and study as main effects. Both LOCF and OC methods were used in these comparisons. The treatment variable was either placebo/escitalopram or placebo/escitalopram dose regimen. The 95% confidence interval (95% CI) for difference to placebo is presented where relevant. Treatment-emergent adverse events (TEAEs) are presented for the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) *for Cardiac Disorders*.

3. Results

3.1. Short-term data

There are 17 randomised placebo-controlled studies (14 short-term and 3 long-term) (Table 1). ECGs were performed at baseline and at end of study or at last assessment in 12 of these studies [7 studies in MDD (8 or 12-weeks duration), 3 in GAD (8-weeks duration), 1 in PD (10-weeks duration) and 1 in SAD (12-weeks duration)], in which 2164 patients were treated with escitalopram and 2050 patients with placebo. Patients treated with escitalopram had a mean age of 42.2 years, 60.5% were women, and 89.7% were Caucasian. There were no differences between escitalopram and placebo in patient baseline characteristics including mean BP, heart rate (HR) and ECG intervals (Table 2). The overall withdrawal rate was 19.9% (escitalopram) and

Table 1 Summary data for clinical studies included in the analyses (APTS).

Study	Indication	Duration and reference	Dose (mg/day)	Number of patients[a]	Reference
1[c]	MDD	8 weeks	PBO	122	Burke et al., 2002
			ESC 10	119	
			ESC 20	125	
2[c]	MDD	8 weeks	PBO	127	Rapaport et al., 2004
			ESC 10-20	125	
3[c]	MDD	8 weeks	PBO	153	Ninan et al., 2003,
			ESC 10-20	147	
4[c]	MDD[b]	8 weeks	PBO	132	Alexopoulos et al., 2004
			ESC 10-20	134	
5	MDD	8 weeks	PBO	189	Wade et al., 2002
			ESC 10	191	
6	MDD	8 weeks	PBO	154	Lepola et al., 2003
			ESC 10-20	155	
7[c]	MDD (elderly)	12 weeks	PBO	134	Bose et al., 2008b
			ESC 10-20	130	
8	MDD (elderly)	8 weeks	PBO	180	Kasper et al., 2005a
			ESC 10	173	
9[c]	GAD	8 weeks	PBO	128	Goodman et al., 2005
			ESC 10-20	126	
10[c]	GAD	8 weeks	PBO	142	Goodman et al., 2005
			ESC 10-20	145	
11[c]	GAD	8 weeks	PBO	157	Davidson et al., 2004
			ESC 10-20	158	
12[c]	GAD[b]	8 weeks	PBO	136	Bose et al., 2008a
			ESC 10-20	127	
13	GAD	24 weeks	PBO	166	Lader et al., 2004
			ESC 5	167	
			ESC 10	167	
			ESC 20	170	
14	GAD[b]	24 weeks	PBO	139	Baldwin et al., 2006
			ESC 5	134	
			ESC 10	136	
			ESC 20	133	
15[c]	PD	10 weeks	PBO	119	Stahl et al., 2003
			ESC 5-20	128	
16	SAD	12 weeks	PBO	177	Kasper et al., 2005b
			ESC 10-20	181	
17	OCD[b]	24 weeks	PBO	114	Stein et al., 2007
			ESC 10	113	
			ESC 20	114	

[a]APTS.
[b]Excluded—ECG measurements not taken at screening and last visit.
[c]US studies, ESC: escitalopram, GAD; generalised anxiety disorder, OCD: obsessive-compulsive disorder, PD: panic disorder, PBO: placebo, SAD=social anxiety disorder. [MDD: PBO=877, ESC=996; elderly: PBO=314, ESC=303; other indications (GAD, PD, SAD, OCD): PBO=1278, ESC=1999].

19.4% (placebo), with 7.4% (escitalopram) and 3.8% (placebo) withdrawing due to TEAEs.

The heart rate (mean±SEM) was statistically significantly reduced (−2.0±0.4 bpm at end of treatment and −1.8±0.3 bpm at last assessment, $p<0.0001$ for both) in the escitalopram group compared to the placebo group (Table 1, Supplementary materials). The reduction in HR was not dose-related and similar in the escitalopram 10 mg, 20 mg or 10/20 mg flexible dose groups. The incidence of patients with PCS low heart rate was 0.3% in both the escitalopram and placebo groups (Table 3). Sensitivity analyses using >120 bpm and an increase of ≥10 bpm and <50 bpm and a decrease of ≥10 bpm from baseline showed no patients with a PCS high heart rate and a slight increase in the incidence of PCS low heart rate in both placebo- and escitalopram-treated groups (Table 3, Supplementary materials). For the PR and QRS intervals, there were more outliers (PCS high) in the escitalopram groups versus placebo. The incidence of patients with a PR interval ≥250 ms was 3.4% for escitalopram and 0.1% in the placebo group.

Table 2 Patient baseline characteristics.

	Short-term studies		Long-term studies*	
	PBO ($n=2050$)	ESC ($n=2164$)	PBO ($n=280$)	ESC ($n=730$)
Age, mean (SD)	43.6±16.0	42.2±14.9	37.2±11.7	37.2±11.2
Women (*n*, %)	1246 (60.8%)	1307 (60.5%)	148 (52.9%)	404 (55.3%)
Caucasian (*n*, %)	1801 (87.9%)	1941 (89.7%)	274 (97.8%)	717 (98.2%)
Black	129 (5.2%)	144 (4.4%)	-	-
Asian	122 (4.9%)	127 (3.9%)	-	-
Systolic bp (mm Hg)	124.4±15.4	124.7±15.6	128.0±15.4	127.8±15.7
Diastolic bp (mm Hg)	77.7±9.6	77.8±9.7	80.2±10.0	79.6±10.1
			PBO ($n=163$)	ESC ($n=502$)**
Heart rate (bpm)	68.1±11.4	67.8±11.5	71.4±12.5	70.7±12.9
QTcF (ms)	391.3±25.2	391.3±25.2	389.4±18.0	390.7±19.3
PR (ms)	156.1±22.8	156.6±23.4	158.4±20.2	158.3±21.5
QRS (ms)	87.9±11.8	87.7±11.2	88.6±8.3	89.0±9.2

*From Lader et al. (2004) and Stein et al. (2007).
**From Lader et al. (2004).

Table 3 Potentially clinically significant (PCS) ECG parameters (short-term, APTS).

	PBO		ESC		ESC 10 mg		ESC 20 mg		ESC flex	
Assessment and PCS criterion	*n*	PCS *n* (%)	*n*	PCS *n* (%)	*n*	PCS *n* (%)	*n*	PCS *n* (%)	*n*	PCS *n* (%)
Patients treated	1786		1903		483		125		1295	
Heart Rate (bpm)										
High: >120 bpm with increase ≥15	1776	0 (0.0%)	1898	0 (0.0%)	483	0 (0.0%)	125	0 (0.0%)	1290	0 (0.0%)
Low: <50 bpm with decrease ≥15	1770	5 (0.3%)	1895	6 (0.3%)	483	1 (0.2%)	125	0 (0.0%)	1287	5 (0.4%)
PR Interval (ms)										
High: ≥250 ms (end)	1416	2 (0.1%)	1715	58 (3.4%)	390	3 (0.8%)	93	0 (0.0%)	1232	55 (4.5%)
High: ≥250 ms (last assessment)	1761	2 (0.1%)	1798	3 (0.2%)	471	3 (0.6%)	93	0 (0.0%)	1234	0 (0.0%)
QRS Interval (ms)										
High:≥150 ms (end)	1100	2 (0.2%)	1175	5 (0.4%)	398	4 (1.0%)	93	0 (0.0%)	684	1 (0.1%)
High:≥150 ms (last assessment)	1349	2 (0.1%)	1437	6 (0.4%)	483	4 (0.8%)	93	0 (0.0%)	861	2 (0.2%)
QTcF Interval (ms)										
High: >500 ms (end)	1428	0 (0.0%)	1510	0 (0.0%)	398	0 (0.0%)	93	0 (0.0%)	1019	0 (0.0%)
Increase >60 ms (end)	1340	4 (0.3%)	1466	3 (0.2%)	397	1 (0.3%)	93	0 (0.0%)	976	2 (0.2%)
High: >500 ms (last assessment)	1776	0 (0.0%)	1898	2 (0.1%)	483	1 (0.2%)	125	0 (0.0%)	1290	1 (0.1%)
Increase >60 ms (last assessment)	1707	4 (0.2%)	1839	4 (0.2%)	482	2 (0.4%)	125	0 (0.0%)	1232	2 (0.2%)

The difference in the mean (95% confidence interval) change in QTcF interval between the escitalopram group and the placebo group was 3.5 ms (95% CI: 2.1 to 4.8) at end of treatment and 3.3 ms (95% CI: 2.1 to 4.4) at last assessment (Table 4). The difference to placebo in the mean change in the QTcF interval between escitalopram 10 mg and 20 mg was not significant at end of study ($p=0.8869$) or at last assessment ($p=0.9038$) (Table 4).

There were few outliers and no meaningful difference in reported incidence of outliers of the QTcF interval absolute values or in change from baseline in QTcF between the escitalopram and placebo groups. At end of treatment, there were no patients (placebo or escitalopram) with a QTcF interval >500 ms and 4 placebo and 3 escitalopram patients with a change from baseline in the QTcF interval >60 ms (Table 3). At last assessment, there were no placebo patients and 2 escitalopram patients with a QTcF interval >500 ms and 4 placebo and 4 escitalopram patients with a change from baseline in the QTcF interval >60 ms (Table 3). One placebo patient had a QTcF interval >500 ms at baseline, but not at last assessment. Of the 2 escitalopram patients with a QTcF interval >500 ms at last assessment, 1 patient (flexible dosing) had at QTcF interval of 535 ms at baseline and at last assessment. At last assessment, 1 patient had both a QTcF interval >500 ms and a

Table 4 Mean changes in QTcF interval (short- and long-term studies, APTS).

QTcF (ms)	PBO[b]	ESC	ESC 5 mg[c]	ESC 10 mg	ESC 20 mg	ESC flex
Short-term studies						
Patients treated	1786	1903	-	483	125	1295
Mean change from baseline (end)[a]	−0.3±0.5 (1370)	3.1±0.5 (1466)	-	2.4±1.0 (397)	3.4±2.0 (93)	3.4±0.5 (976)
Mean change from baseline (last)[a]	−0.5±0.4 (1707)	2.7±0.4 (1839)	-	2.6±0.9 (482)	2.9±1.6 (125)	2.8±0.5 (1232)
Mean change versus placebo (end)	-	3.5 (2.1 to 4.8)	-	1.3 (−1.2 to 3.9)	1.7 (−1.2 to 3.9)	4.5 (2.7 to 6.0)
Mean change versus placebo (last)	-	3.3 (2.1 to 4.4)	-	1.7 (−0.5 to 3.9)	1.9 (−2.0 to 5.8)	3.9 (2.6 to 5.3)
Long-term studies						
Patients treated	166	504	170	167	170	-
Mean change from baseline (end)	0.4±1.5 (109)	1.2±0.8 (354)	0.5±1.4 (122)	0.4±1.6 (111)	2.6±1.3 (121)	-
Mean change from baseline (last)	0.5±1.1 (163)	0.9±0.7 (499)	0.6±1.1 (165)	0.1±1.2 (166)	2.1±1.1 (168)	-
Mean change versus placebo (end)	-	0.8 (−2.6 to 4.2)	0.2 (−3.9 to 4.2)	0.0 (−4.1 to 4.1)	2.2 (−1.9 to 6.3)	-
Mean change versus placebo (last)	-	0.4 (−2.1 to 3.0)	0.1 (−3.0 to 3.3)	−0.4 (−3.5 to 2.8)	1.6 (−1.6 to 4.7)	-

[a] The mean change from baseline versus placebo was based on the placebo mean change from baseline from the corresponding studies.
[b] Values are means±SEM (number of patients).
[c] Values are means (95% CI).

change from baseline in the QTcF interval >60 ms (432 ms at baseline and 522 ms at last assessment). This patient, an 88-year old man with a history of heart failure, was withdrawn due to asthenia after 14 days of treatment with escitalopram 10 mg (study 8). Sensitivity analyses revealed more patients with a QTcF >450 ms and 480 ms or increase in QTcF >30 ms from baseline in both placebo- and escitalopram-treated patients (Table 4, Supplementary materials).

Blood pressure (mean±SEM) was measured in all 17 studies included in this analysis at baseline and after 8–12 weeks. The mean systolic and diastolic pressure was slightly reduced in the escitalopram and placebo groups at end of 8–12 weeks treatment and at last assessment (Table 2, Supplementary materials). There were no differences in systolic or diastolic mean values (<0.3 mmHg) in the escitalopram group compared to the placebo group (Table 2, Supplementary materials). At last assessment, the number of patients with PCS blood pressure after placebo treatment (n=2453) was 7 (0.3%) with PCS high systolic values, and 6 (0.2%) with PCS high diastolic values, and 6 (0.3%) with PCS low systolic values and 4 (0.2%) with PCS low diastolic values. After escitalopram treatment (n=3279), the number of patients with PCS blood pressure was 6 (0.2%) with PCS high systolic values, and 2 (0.1%) with PCS high diastolic values, and 6 (0.2%) with PCS low systolic values and 3 (0.1%) with PCS low diastolic values. Sensitivity analyses revealed more patients with high systolic BP using ≥160 and an increase of ≥10 mmHg from baseline and ≥150 and an increase of ≥10 mmHg from baseline in both placebo- and escitalopram-treated patients (Table 5, Supplementary materials).

There were 41 (1.9%) escitalopram-treated patients (total=2164) and 45 (2.2%) placebo-treated patients (total=2050) who reported a cardiac-associated TEAE (Table 5). The incidence of cardiac-associated TEAEs was similar between patients taking 10 mg, 20 mg and flexibly-dosed escitalopram and placebo.

3.2. Long-term data

In the 3 placebo-controlled long-term studies, escitalopram patients had a mean age of 37.2 years, 55.3% were women, and 98.2% were Caucasian. There were no differences between escitalopram and placebo in patient baseline characteristics including mean BP, HR and ECG intervals (Table 2). Overall withdrawal rates were 24.1% (escitalopram) and 25.3% (placebo), with 8.7% (escitalopram) and 5.7% (placebo) withdrawing due to TEAEs. One placebo-controlled long-term study recorded ECGs at baseline and end of study/last assessment (Table 1, study 13, and Table 5).

The heart rate (mean±SEM) was slightly reduced, but not statistically significant [−1.8±1.2 bpm at end of treatment (p=0.1469) and −1.4±0.9 bpm at last assessment (p=0.1157)] in the escitalopram group compared to the placebo group (Table 1, Supplementary materials). Sensitivity analyses showed no patients with a PCS high heart rate and a slight increase in the incidence of PCS low heart rate in both placebo- and escitalopram-treated groups (Table 3, Supplementary materials). BP decreased in both the escitalopram and placebo group; however, there were no differences in either systolic or diastolic mean BP values (<0.5 mmHg) in the escitalopram group compared to the placebo group (Table 6, Supplementary materials). At last

Table 5 Incidence of all TEAEs within the SOC *Cardiac Disorders* (short- and long-term studies, APTS).

Preferred term	Short-term					Long-term[c]				
	PBO *n* (%)	ESC *n* (%)	ESC 10 mg *n* (%)	ESC 20 mg *n* (%)	ESC flex *n* (%)	PBO *n* (%)	ESC *n* (%)	ESC 5 mg *n* (%)	ESC 10 mg *n* (%)	ESC 20 mg *n* (%)
Patients treated	2050	2164	483	125	1556	419	1134	301	416	417
Patients with cardiac TEAEs	45 (2.2%)	41 (1.9%)	5 (1.0%)	3 (2.4%)	33 (2.1%)	11 (2.6%)	31 (2.7%)	7 (2.3%)	12 (2.9%)	12 (2.9%)
Palpitations	28 (1.4%)	24 (1.1%)	3 (0.6%)	3 (2.4%)	18 (1.2%)	4 (1.0%)	13 (1.1%)	3 (1.0%)	4 (1.0%)	6 (1.4%)
Tachycardia	7 (0.3%)	9 (0.4%)	1 (0.2%)	-	8 (0.5%)	6 (1.4%)	13 (1.1%)	2 (0.7%)	7 (1.7%)	4 (1.0%)
Angina pectoris	2 (<0.1%)	1 (<0.1%)	-	-	1 (<0.1%)	1 (0.2%)	1 (0.1%)	1 (0.3%)	-	-
Angina unstable	1 (<0.1%)	-	-	-	-	-	-	-	-	-
Atrial fibrillation	1 (<0.1%)	-	-	-	-	-	-	-	-	-
AV block first degree[a]	1 (<0.1%)	1 (<0.1%)	-	-	1 (<0.1%)	-	-	-	-	-
Bradycardia	1 (<0.1%)	1 (<0.1%)	-	-	1 (<0.1%)	-	1 (0.1%)	-	-	1 (0.2%)
Bundle branch block right	1 (<0.1%)	-	-	-	-	-	-	-	-	-
Extra systoles	1 (<0.1%)	-	-	-	-	-	1 (0.1%)	1 (0.3%)	-	-
Myocardial infarction	1 (<0.1%)	-	-	-	-	-	1 (0.1%)	-	1 (0.2%)	-
Nodal rhythm	1 (<0.1%)	1 (<0.1%)	-	-	1 (<0.1%)	-	-	-	-	-
Sinus bradycardia	1 (<0.1%)	3 (0.1%)	-	-	3 (0.2%)	-	-	-	-	-
Tachycardia paroxysmal	1 (<0.1%)	-	-	-	-	-	-	-	-	-
WPW syndrome[b]	1 (<0.1%)	-	-	-	-	-	-	-	-	-
Arrhythmia	-	1 (<0.1%)	-	-	1 (<0.1%)	-	-	-	-	-
Myocarditis	-	1 (<0.1%)	1 (0.2%)	-	-	-	-	-	-	-
Sinus tachycardia	-	1 (<0.1%)	-	-	1 (<0.1%)	-	-	-	-	-
Myocardial ischaemia	-	-	-	-	-	-	1 (0.1%)	-	-	1 (0.2%)

[a]AV: atrioventricular.
[b]WPW syndrome: Wolff–Parkinson–White syndrome.
[c]SAD study (Lader et al., 2004).

Table 6 Potentially clinically significant (PCS) ECG parameters (long-term, APTS).

	PBO		ESC		ESC 5 mg		ESC 10 mg		ESC 20 mg	
Assessment and PCS criterion	***n***	**PCS *n* (%)**	***n***	**PCS *n* (%)**	***n***	**PCS *n* (%)**	***n***	**PCS *n* (%)**	***n***	**PCS *n* (%)**
Patients treated	166		504		167		167		170	
Heart rate (bpm)										
High: >120 bpm with increase ≥15	165	0 (0.0%)	499	0 (0.0%)	165	0 (0.0%)	166	0 (0.0%)	168	0 (0.0%)
Low: <50 bpm with decrease ≥15	165	0 (0.0%)	499	3 (0.6%)	165	2 (1.2%)	166	1 (0.6%)	168	0 (0.0%)
PR interval (ms)										
High: ≥250 ms (end)	111	0 (0.0%)	354	0 (0.0%)	122	0 (0.0%)	111	0 (0.0%)	121	0 (0.0%)
High: ≥250 ms (last assessment)	164	1 (0.6%)	499	0 (0.0%)	165	0 (0.0%)	166	0 (0.0%)	168	0 (0.0%)
QRS interval (ms)										
High:≥150 ms (end)	111	0 (0.0%)	354	0 (0.0%)	122	0 (0.0%)	111	0 (0.0%)	121	0 (0.0%)
High:≥150 ms (last assessment)	165	0 (0.0%)	500	0 (0.0%)	165	0 (0.0%)	167	0 (0.0%)	168	0 (0.0%)
QTcF interval (ms)										
High: >500 ms (end)	111	0 (0.0%)	354	0 (0.0%)	122	0 (0.0%)	111	0 (0.0%)	121	0 (0.0%)
Increase >60 ms (end)	109	0 (0.0%)	354	1 (0.3%)	122	0 (0.0%)	111	1 (0.9%)	121	0 (0.0%)
High: >500 ms (last assessment)	165	0 (0.0%)	499	0 (0.0%)	165	0 (0.0%)	166	0 (0.0%)	168	0 (0.0%)
Increase >60 ms (last assessment)	163	0 (0.0%)	499	1 (0.2%)	165	0 (0.0%)	166	1 (0.6%)	168	0 (0.0%)

assessment, the incidence of PCS high systolic BP values was 0.7% (2/278) in placebo patients. After escitalopram treatment (n=723), 1 patient (0.1%) had a PCS high systolic BP value, 1 patient (0.1%) had a PCS low systolic BP value and 1 patient (0.1%) had a PCS low diastolic BP value. Sensitivity analyses revealed more patients with high systolic BP using ≥160 and an increase of ≥10 mmHg from baseline and ≥150 and an increase of ≥10 mmHg from baseline in both placebo- and escitalopram-treated patients (Table 5, Supplementary materials).

The difference in the mean (95% confidence interval) change in QTcF interval between escitalopram and placebo groups was 0.8 ms (95% CI: −2.6 to 4.2) at end of treatment and 0.4 ms (95% CI: −2.1 to 3.0) at last assessment (Table 4). There were no patients with a QTcF interval >500 ms and 1 escitalopram patient with a change from baseline in the QTcF interval >60 ms (Table 6). Sensitivity analyses revealed no patients with a QTcF >450 ms and 480 ms in either placebo- and escitalopram-treated patients more patients with increase in QTcF >30 ms from baseline in both treatment groups (Table 4, Supplementary materials). The difference to placebo in the mean change in the QTcF interval between escitalopram 10 mg and 20 mg was not significant at end of study (p=0.2836) or at last assessment (p=0.2243) (Table 4).

There were 31 (2.7%) escitalopram-treated patients (total=1134) and 11 (2.6%) placebo-treated patients (total=419) who reported at least one cardiac-associated TEAE (Table 5). The incidence of cardiac-associated TEAEs was similar between patients taking 5 mg, 10 mg, and 20 mg escitalopram; no differences were observed in comparison to the placebo-treated group.

3.3. Data from studies of older adults

Two of the short term randomised placebo-controlled studies (above) (Table 1 - studies 7 and 8) enrolled older adults (≥60 years cut off used in one study and ≥65 years used in the other study) MDD patients. In both studies, ECG data were collected at baseline and last assessment (Table 1). In these studies, 303 patients were treated with escitalopram and 314 patients were treated with placebo. The studies enrolled subjects with a mean age of 72.1±7.5 years; 68.7% were women, and 95.3% were Caucasian. Withdrawal rates were 20.8% for escitalopram and 14.3% for placebo, with 10.2% (escitalopram) and 4.1% (placebo) withdrawing due to TEAEs.

At end of treatment (Week 8 or 12), the heart rate (mean±SD) was slightly reduced in escitalopram-treated patients (−1.8±9.4 bpm, n=197) compared to placebo-treated patients (+0.7±11.2 bpm, n=208). At last assessment, the mean heart rate in escitalopram-treated patients had decreased by −1.4±9.7 bpm (n=250) as compared to placebo-treated patients (+0.8±10.8 bpm, n=247). The difference to placebo for escitalopram-treated patients in the change from baseline in heart rate (mean±SEM) was −2.6±1.0 bpm at end of treatment (p=0.0074) and −2.3±0.9 bpm at last assessment (p=0.0218). At last assessment, there were no patients with a high PCS heart rate and no placebo and 2 (0.7%) escitalopram patients with a PCS low heart rate. There was no difference in systolic mean BP values (<0.5 mmHg) and a slight increase (1.1±0.8 mmHg) in diastolic pressure (mean±SEM) in the escitalopram group compared to the placebo group. At last assessment, no placebo patients (n=311) had a PCS high diastolic BP value, 5 patients (1.6%) had a PCS high systolic BP value, 1 patient (0.3%) had a PCS low systolic BP value and no patients had a PCS low diastolic BP value. After escitalopram treatment (n=302), no patients had a PCS high diastolic BP value, 4 patients (1.3%) had a PCS high systolic BP value, no patients had a PCS low systolic BP value and no patients had a PCS low diastolic BP value.

Changes from baseline in the QTcF interval were similar between treatment groups: +3.1±19.2 ms (escitalopram,

$n=197$) versus $+1.0\pm18.3$ ms (placebo, $n=208$). At last assessment, the QTcF values were $+3.0\pm19.4$ ms (escitalopram, $n=250$) versus $+0.9\pm17.7$ ms (placebo, $n=247$). The difference in the mean (95% confidence interval) change from baseline in QTcF interval between escitalopram-treated patients and placebo-treated patients was +2.1 ms (95% CI: −1.5 to 5.8) at end of treatment and +2.2 ms (95% CI: −1.0 to 5.5) at last assessment. At last assessment, there was 1 escitalopram patient with a QTcF interval >500 ms and 2 escitalopram patients with a change from baseline in the QTcF interval >60 ms (one of whom is described above).

There were 7 (2.3%) escitalopram-treated patients ($n=303$) and 12 (3.8%) placebo-treated patients ($n=314$) who reported a cardiac associated TEAE. Two patients in each group (escitalopram vs placebo) had cardiac-associated TEAEs that were considered by the investigator as related to treatment.

3.4. Tolerability summary

In short term studies, a similar proportion of patients in all treatment groups experienced at least one event within the SOC *Cardiac Disorders* −2.3% (placebo) and 1.0-2.4% for the escitalopram dosage groups. In long-term studies, a similar proportion of patients in all treatment groups reported at least one event within the SOC *Cardiac Disorders*, with an incidence ranging from 2.6% in the placebo group to 2.3-2.9% for the escitalopram dose groups.

In both short-term and long-term treatment, the most frequently reported TEAEs were palpitations and tachycardia; however, there were no differences in their rates of occurrence between escitalopram and placebo. Of the 3279 patients treated with escitalopram, one was withdrawn due to a cardiac-associated TEAE.

4. Discussion

The present analysis of placebo-controlled clinical trials of escitalopram assessed the effects of escitalopram on heart rate, blood pressure, and ECGs in a large group of patients. Central autonomic dysfunction associated with MDD can lead to changes in vagal or sympathetic modulation, resulting not only in symptoms such as hyperhydrosis, but also in changes in heart rate or blood pressure regulation. Cardiac vagal control, as measured by the beat-to-beat variability in the timing of heart beats (or heart rate variability), is a prognostic indicator of risk for cardiac disease and death from both coronary heart disease and congestive heart failure (Rottenberg, 2007). In a study of 75 unmedicated patients with MDD, there was an overall shift of autonomic balance toward sympathetic predominance as compared with matched healthy controls, with MDD patients having a higher heart rate, greater heart rate variability, and an increase in sympathetically influenced QT variability. This autonomic dysfunction was exacerbated by SNRI and to a lesser degree by SSRI treatment (Koschke et al., 2009).

In the present analysis, 2407 escitalopram patients had valid ECG assessments at both baseline and last assessment. For all doses of escitalopram, including flexible dosing (10 or 20 mg), the mean difference from placebo was 3.5 ms, which is slightly lower than reported in a thorough QT study conducted with healthy subjects (Forest Pharmaceuticals, Inc, 2011). There was no evidence of dose dependence in the mean difference from placebo in the QTcF interval in short-term (1.3 ms for escitalopram 10 mg and 1.7 ms for escitalopram 20 mg) or long-term studies (0.0 ms for escitalopram 10 mg and 2.2 ms for escitalopram 20 mg). The lower QTcF values after 8 weeks (1.3 ms) and 24 weeks (0.0 ms) of treatment with escitalopram 10 mg/day compared to the thorough QT study (4.5 ms), in which healthy subjects were treated for only 9 days, might indicate that the QTcF interval increase was transitory in the thorough QT study. One escitalopram-treated patient had QTcF >500 ms and a QTcF increase >60 ms.

Escitalopram treatment resulted in a slight decrease in blood pressure in both short-term (−1.7 mmHg) and long-term studies (−3.9 mmHg), with no indication of a dose effect. The differences in mean systolic (0 mmHg) or diastolic values (<0.5 mmHg) between escitalopram and placebo were small and not clinically meaningful. Nine (0.3%) patients treated with escitalopram ($n=3279$) had elevated blood pressure values considered to be PCS, compared to 15 (0.6%) of patients treated with placebo ($n=2453$).

The incidence of cardiac-associated TEAEs was similar between adult patients treated for 8-12 weeks with placebo (2.2%) or escitalopram (1.9%) and for 24 weeks with placebo (2.7%) or escitalopram (2.3%). In elderly patients, the incidence of cardiac-associated events was similar for the groups treated with escitalopram (2.3%) and placebo (3.8%).

In a recent Danish case-time-control study of out-of-hospital cardiac arrests (OHCA) from 2001 to 2007, defined as patients who received cardio-pulmonary resuscitation or defibrillation, the odds ratio of an OHCA following treatment with escitalopram was 1.10 (95% CI: 0.64 to 1.87) compared to age- and gender-matched controls from the entire Danish population (Weeke et al., 2012). These results are consistent with those from the escitalopram clinical development programme, in which escitalopram is considered safe and well tolerated, when used at the recommended doses.

If escitalopram were associated with adverse cardiovascular reactions, it would be expected that these would be detected in cases of accidental or intentional overdose. A review of 28 cases of accidental ingestion or overdose of escitalopram (at doses ranging from 5 to 300 mg) showed no adverse sequelae (LoVecchio et al., 2006). In a review of 1179 cases of ingestion of escitalopram alone, with doses ranging from 5 mg to >600 mg, dysrhythmia was reported in 1.3% and conduction disturbance in 0.4% of serious outcomes, none of which were fatal (Forrester, 2007). Gorp et al. (2009) reviewed 79 cases of escitalopram overdose, ranging from 20 to 560 mg, in which escitalopram was the only drug or the co-ingested drugs were non-toxic; 11 patients had QT interval prolongation, but there were no deaths, seizures or arrythmias. In a review of 421 escitalopram overdose cases, ranging from 5 to 1800 mg, conduction disturbances were noted in 7 patients (1.3%), as evidenced by QTc prolongation on ECG, with a maximum QTc interval of 549 ms (Hayes et al., 2010). In a review of 63 escitalopram overdose cases ranging from 40 to 1860 mg, mild QTc interval prolongation was seen in four cases and

moderate in one case, with one case of seizure and no deaths (Yilmaz et al., 2010).

A meta-analysis (van Melle et al., 2004) found a 2–2.5 fold increased risk of impaired cardiovascular outcome in post-acute myocardial infarction patients with depression. In a placebo-controlled, randomised, controlled study of 240 patients with acute coronary syndrome treated prophylactically with escitalopram 10 mg/daily or placebo for 12 months, there was a significantly better effect on preventing depression in the escitalopram-treated patients, and there were no differences in the incidence and type of adverse events between the treatment groups (Hansen et al., 2012). Furthermore, there was no difference between treatment groups in the mean QTc interval, nor in the incidence of patients with a QTc interval >450 ms after 6 or 12 months (Hanash et al., 2012). Depression is not only a major problem in patients with acute coronary syndrome, with a negative impact on survival, but depressive symptoms themselves can increase the risk of sudden cardiac death. In an 8-year study of 915 elderly ($\geq$70 years) people in Northern Finland, a high score on depressive symptoms was a significant predictor of subsequent sudden cardiac death (univariate hazard ratio of 2.67 [95% CI: 1.06 to 2.63]), but not non-fatal myocardial infarction (Luukinen et al., 2003).

The results of this systematic review of individual patient data are limited by the exclusion from the clinical trials of patients with a serious comorbid illness for safety reasons. Thus, further studies are needed of higher risk patient groups with more complex medical histories, including more complex medication regimens.

5. Conclusion

A systematic review of individual patient data from a large group of patients participating in placebo-controlled studies indicates that escitalopram appears to have a benign cardiovascular profile, both in short-term and longer-term studies, as well as two studies that included old adults. This is further supported from epidemiological analysis and clinical trials in patients with cardiac diseases.

Role of the funding source

H. Lundbeck A/S sponsored the study. Lundbeck was involved in the study design, in the collection, analysis and interpretation of data, in the writing of the study reports, and in the decision to submit the paper for publication.

Contributors

Authors Thase and Kennedy wrote the first draft of the manuscript. Larsen undertook the statistical analysis. All authors (Thase, Larsen, Reines and Kennedy) contributed to and have approved the final manuscript.

Conflicts of interest

ME Thase is an advisor/consultant for H. Lundbeck A/S. During the past 5 years, he has had similar relationships with Alkermes; AstraZeneca; Bristol-Myers Squibb Company; Cephalon, Inc.; Eli Lilly & Co.; Forest Laboratories, GlaxoSmithKline; Janssen Pharmaceutica; MedAvante, Inc.; Merck; Mylan Laboratories; Neuronetics; Novartis; Organon Inc.; Otsuka; PamLab; Pfizer, Inc.; PharmaNeuroboost; Rexahn; Roche Laboratories; Sanofi Aventis; Schering-Plough; Shire US, Inc.; Sunovion; Takeda; Teva; Transcept; and Wyeth Pharmaceuticals. During this same timeframe, Dr. Thase has received honoraria for talks from: AstraZeneca; Bristol-Myers Squibb; Eli Lilly & Co.; GlaxoSmithKline; Merck; Mylan Laboratories; Pfizer; and Wyeth Pharmaceuticals. Dr. Thase has received research funding from the Agency for Healthcare Research and Quality and the National Institute of Mental Health, as well as Alkermes; AstraZeneca; Eli Lilly & Co.; Forest Laboratories; GlaxoSmithKline; Otsuka; PharmaNeuroboost; and Sepracor, Inc. He has equity holdings in MedAvante, Inc., and has received income from royalties from American Psychiatric Publishing, Inc., Guilford Publications and Herald House.

S.H. Kennedy has received grant funding and consulting honoraria from H. Lundbeck A/S. He has also received grant funding or consulting honoraria within the past 5 years from AstraZeneca, Biovail, Boehringer-Ingelheim, Eli Lilly & Co, GlaxoSmithKline, Janssen-Otrho, Merck-Frosst, Organon, Pfizer, Servier, and St. Jude Medical.

EH Reines and KG Laursen (*statistician*) are employed by H. Lundbeck A/S.

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Appendix A. Supplementary materials

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References

Alexopoulos, G.S., Gordon, J., Zhang, D. 2004. A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder. Neuropsychopharmacology 29(suppl), S87. See also ⟨http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-27_final.pdf⟩ (accessed September, 2012).

Ali, M.K., Lam, R.W., 2011. Comparative efficacy of escitalopram in the treatment of major depressive disorder. Neuropsychiatr. Dis. Treat. 7, 39–49.

Baldwin, D.S., Huusom, A.K.T., Mæhlum, E., 2006. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. Br. J. Psychiatry 189, 264–272.

Beach, S.R., Celano, C.M., Noseworthy, P.A., Januzzi, J.L., Huffman, J.C., 2013. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics 54 (1). http://dx.doi.org/10.1016/j.psym.2012.11.001 Jan-Feb 1-13.

Bose, A., Korotzer, A., Gommoll, C., Li, D., 2008a. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in

the treatment of generalized anxiety disorder. Depress. Anxiety 25, 854–861.
Bose, A., Li, D., Gandhi, C., 2008b. Escitalopram in the acute treatment of depressed patients aged 60 years or older. Am. J. Geriatr. Psychiatry 16, 14–20.
Burke, W.J., Gergel, I., Bose, A., 2002. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J. Clin. Psychiatry 63, 331–336.
Chen, F., Larsen, M.B., Neubauer, H.A., Sánchez, C., Plenge, P., Wiborg, O., 2005a. Characterization of an allosteric citalopram-binding site at the serotonin transporter. J. Neurochem. 92, 21–28.
Chen, F., Larsen, M.B., Sánchez, C., Wiborg, O., 2005b. The S-enantiomer of R,S-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors. Eur. Neuropsychopharmacol. 15, 193–198.
Davidson, J.R., Bose, A., Korotzer, A., Zheng, H., 2004. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress. Anxiety 19, 234–240.
Forest Pharmaceuticals, Inc, 2011. Evaluation of the effects of sequential multiple-dose regimens of escitalopram on cardiac repolarization in healthy subjects. Available from: ⟨http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-PK-21_final.pdf⟩ (accessed September, 2012).
Forrester, M.B., 2007. Escitalopram ingestions reported to Texas poison control centers, 2002–2005. Hum. Exp. Toxicol. 26, 473–482.
Goodman, W.K., Bose, A., Wang, Q., 2005. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J. Affect. Disord. 87, 161–167.
Gorp, F., van, Whyte, I.M., Isbister, G.K., 2009. Clinical and ECG effects of escitalopram overdose. Ann. Emerg. Med. 54, 404–408.
Hanash, J.A., Hansen, B.H., Hansen, J.F., Nielsen, O.W., Rasmussen, A., Birket-Smith, M., 2012. Cardiovascular safety of 1-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome. J. Cardiovasc. Pharmacol. 60, 397–405.
Hansen, B.H., Hanash, J.A., Rasmussen, A., Hansen, J.F., Andersen, N.L.T., Nielsen, O.W., et al., 2012. Effects of escitalopram in prevention of depression in patients with acute coronary syndrome (DECARD). J. Psychosom. Res. 72, 11–16.
Hayes, B.D., Klein-Schwartz, W., Clark, R.F., Muller, A.A., Miloradovich, J.E., 2010. Comparison of toxicity of acute overdoses with citalopram and escitalopram. J. Emerg. Med. 39, 44–48.
Kasper, S., de Swart, H., Andersen, H.F., 2005a. Escitalopram in the treatment of depressed elderly patients. Am. J. Geriatr. Psychiatry 13, 884–891.
Kasper, S., Stein, D., Loft, H., Nil, R., 2005b. Escitalopram in the treatment of social anxiety disorder. Randomised, placebo-controlled, flexible-dosage study. Br. J. Psychiatry 186, 222–226.
Koschke, M., Boettger, M.K., Schulz, S., Berger, S., Terhaar, J., Voss, A., et al., 2009. Autonomy of autonomic dysfunction in major depression. Psychosom. Med. 71, 852–860.
Lader, M., Stender, K., Burger, V., Nil, R., 2004. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. Depress. Anxiety 19, 241–248.
Lepola, U.M., Loft, H., Reines, E.H., 2003. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int. Clin. Psychopharmacol. 18, 211–217.
LoVecchio, F., Watts, D., Winchell, J., Knight, J., McDowell, T., 2006. Outcomes after supratherapeutic escitalopram ingestions. J. Emergency Med. 30, 17–19.
Luukinen, H., Laippala, P., Huikuri, H.V., 2003. Depressive symptoms and the risk of sudden cardiac death among the elderly. Eur. Heart J. 24, 2021–2026.
Ninan, P.T., Ventura, D., Wang, J., 2003. Escitalopram is effective and well tolerated in the treatment of severe depression. Poster presented at the Congress of the American Psychiatric Association, May 17-22, San Francisco, CA. See also ⟨http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-26_final.pdf⟩. (accessed September, 2012).
Rapaport, M.H., Bos, A., Zheng, H. 2004. Escitalopram continuation treatment prevents relapse of depressive episodes. J. Clin. Psychiatry65, 44–49. See also : ⟨http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-02_final.pdf⟩ (accessed September, 2012).
Rottenberg, J., 2007. Cardiac vagal control in depression: a critical analysis. Biol. Psychol. 74, 200–211.
Sánchez, C., 2006. The pharmacology of citalopram enantiomers: the antagonism by R-citalopram on the effect of S-citalopram. Basic Clin. Pharmacol. Toxicol. 99, 91–95.
Stahl, S.M., Gergel, I., Li, D., 2003. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 64, 1322–1327.
Stein, D.J., Andersen, E.W., Tonnoir, B., Fineberg, N., 2007. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed dose, 24-week study. Curr. Med. Res. Opin. 23, 701–711.
van Melle, J.P., de Jonge, P., Spijkerman, T.A., Tijssen, J.G., Ormel, J., van Veldhuisen, D.J., et al., 2004. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom. Med. 66, 22–814.
Vieweg, W.V., Hasnain, M., Howland, R.H., Hettema, J.M., Kogut, C., Wood, M.A., Pandurangi, A.K., 2012. Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? Am. J. Med. 125, 68–859.
Wade, A., Lemming, O.M., Hedegaard, K.B., 2002. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int. Clin. Psychopharmacol. 17, 95–102.
Weeke, P., Jensen, A., Folke, F., Gislason, G.H., Olesen, J.B., Andersson, C., et al., 2012. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case–time–control study. Clin. Pharmacol. Ther. 92, 72–79.
Yilmaz, Z., Ceschi, A., Rauber-Lüthy, C., 2010. Escitalopram causes fewer seizures in human overdose than citalopram. Clin.Toxicol. 48, 207–212.